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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

23-26 April 2019

Opinions on paediatric investigation plans

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

- Lentiviral vector containing the human ABCA4 gene, EMEA-002407-PIP01-18, from Sanofi-Aventis Recherche & Développement, for the treatment of inherited retinal disorders;
- Adeno-associated viral vector serotype 5 containing a B domain deleted variant of human coagulation factor VIII gene, EMEA-002427-PIP01-18, from BioMarin International Limited, for the treatment of haemophilia A

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

- Dexamethasone, EMEA-002423-PIP01-18, from Ocular Therapeutix, Inc., for the treatment of postoperative pain and inflammation associated with ophthalmic surgery

  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 for paediatric patients.

The PDCO adopted an Opinion on the **refusal** of a PIP for:

- Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII, EMEA-002472-PIP02-19, from Krystal Biotech, Inc., for the treatment of dystrophic epidermolysis bullosa

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 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.

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Adoption of an Opinion following re-examination

The PDCO adopted Opinions for the following products:

- Following the re-examination of the positive Opinion on a modification to an agreed PIP with deferral and waiver adopted on 1 March 2019 for *Neisseria meningitidis* serogroup A polysaccharide conjugated to tetanus toxoid / *N. meningitides* serogroup C polysaccharide conjugated to tetanus toxoid / *N. meningitidis* serogroup Y polysaccharide conjugated to tetanus toxoid / *N. meningitidis* serogroup W polysaccharide conjugated to tetanus toxoid (MenACYW), EMEA-001930-PIP01-16-M01, from Sanofi Pasteur Inc., for prevention of invasive meningococcal disease, the PDCO adopted a revised positive opinion and agreed to the changes regarding the measures of the paediatric investigation plan in the scope set out in Annex I of the opinion;
- Following the re-examination of the positive Opinion on a PIP with deferral adopted on 1 March 2019 for Ofatumumab, EMEA-002397-PIP01-18, from Novartis Europharm Limited, for the treatment of multiple sclerosis, the PDCO adopted a revised positive Opinion and

  - agreed the paediatric investigation plan in accordance with Article 17(1) of Regulation (EC) No 1901/2006 as amended,

  - granted a deferral in accordance with Article 21 of said Regulation;

  - granted a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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.

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:

- Glu-NH-CO-NH-Lys-(Ahx)-[N,N9-bis[2-hydroxy-5-(carboxyethyl) benzyl]ethylenediamine-N,N9-diacetic acid, EMEA-002503-PIP01-18, from Trasis S.A., for the visualisation of prostate specific membrane antigen in prostate cancer;
- Tisotumab vedotin, EMEA-002522-PIP01-18, from Genmab A/S, for the treatment of cervical cancer;
- Emiplacel, EMEA-002539-PIP01-18, from Pluristem Ltd., for the treatment of peripheral ischaemia;
- Ramipril / bisoprolol, EMEA-002531-PIP01-18, from Midas Pharma GmbH, for the treatment of heart failure, treatment of coronary artery disease and treatment of hypertension;
- Abemaciclib, EMEA-002342-PIP03-18, from Eli Lilly and Company Limited, for the treatment of breast cancer;
- Sutimlimab, EMEA-002542-PIP01-18, from Bioverativ USA, Inc., for the treatment of primary cold

agglutinin disease;

- Capivasertib, EMEA-002551-PIP01-18, from AstraZeneca AB, for the treatment of breast cancer and treatment of prostate cancer

The PDCO adopted an Opinion on the **refusal** of a request for waiver for:

- 2-(2-(3-Butoxy-phenyl)-ethylamino)-N,N-dimethyl-acetamide hydrochloride, EMEA-002519-PIP02-18, from Newron Pharmaceuticals SpA, for the treatment of schizophrenia

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:

- Macrogol 3350 / sodium ascorbate / sodium sulfate / ascorbic acid / sodium chloride / potassium chloride, EMEA-001705-PIP02-15-M02, from Norgine Limited, for the bowel cleansing prior to clinical procedures;
- Rilpivirine (hydrochloride), EMEA-000317-PIP01-08-M11, from Janssen-Cilag International NV, for the treatment of human immunodeficiency virus (HIV-1) infection;
- *Dermatophagoides pteronyssinus and Dermatophagoides farinae* extracts 50%/50%, EMEA-000815-PIP01-09-M01, from Allergy Therapeutics (UK) Ltd, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Lenvatinib, EMEA-001119-PIP02-12-M05, from Eisai Europe Ltd, for the treatment of follicular thyroid cancer, treatment of osteosarcoma and treatment of papillary thyroid cancer;
- Birch, hazel and alder pollen extracts, EMEA-000808-PIP01-09-M01, from Allergy Therapeutics (UK) Ltd, for the treatment of allergic rhinitis / rhino-conjunctivitis;
- Obeticholic Acid, EMEA-001304-PIP02-13-M04, from Intercept Pharma Ltd., for the treatment of primary biliary cirrhosis and treatment of biliary atresia;
- Isatuximab, EMEA-002205-PIP01-17-M01, from Sanofi-Aventis Recherche & Développement, for the treatment of malignant neoplasms of the haematopoietic and lymphoid tissue;
- Semaglutide, EMEA-001441-PIP02-15-M02, from Novo Nordisk, for the treatment of type 2 diabetes mellitus;
- Atezolizumab, EMEA-001638-PIP01-14-M02, from Roche Registration GmbH, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms);
- Ravulizumab, EMEA-001943-PIP01-16-M02, from Alexion Europe SAS, for the treatment of atypical haemolytic uremic syndrome;
- Daratumumab, EMEA-002152-PIP01-17-M01, from Janssen-Cilag International NV, for the treatment of lymphoid malignancies (except mature B-cell neoplasms);

- Ibrutinib, EMEA-001397-PIP03-14-M04, from Janssen-Cilag International N.V., for the treatment of mature B-cell neoplasm;
- Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor, EMEA-001995-PIP01-16-M02, from Celgene Europe B.V., for the treatment of B-lymphoblastic leukemia/lymphoma and treatment of mature B-cell neoplasms;
- Perampanel, EMEA-000467-PIP01-08-M11, from Eisai Europe Limited, for the treatment of treatment-resistant epilepsies;
- Palbociclib, EMEA-002146-PIP01-17-M01, from Pfizer Europe MA EEIG, for the treatment of Ewing sarcoma

Opinion on compliance check

The PDCO adopted positive Opinions on full compliance check for:

- *N. meningitidis* serogroup A polysaccharide conjugated to tetanus toxoid / *N. meningitidis* serogroup C polysaccharide conjugated to tetanus toxoid / *N. meningitidis* serogroup W polysaccharide conjugated to tetanus toxoid / *N. meningitidis* serogroup Y polysaccharide conjugated to tetanus toxoid, EMEA-C-000429-PIP01-08-M04, from Pfizer Europe MA EEIG, for the prevention of meningococcal disease;
- Beclometasone (dipropionate) / formoterol (fumarate dihydrate), EMEA-C-000548-PIP01-09-M08, from Chiesi Farmaceutici S.p.A., for the treatment of asthma;
- Turoctocog alfa, EMEA-C-000428-PIP01-08-M03, from Novo Nordisk A/S, for the treatment of hereditary factor VIII deficiency;
- Split influenza virus, inactivated containing antigen equivalent to A/ California/7/2009(H1N1)-like strain (A/California/7/2009), adjuvanted, EMEA-C-000669-PIP01-09-M02, from Sanofi Pasteur SA, for the prevention of influenza;
- Sofosbuvir / ledipasvir, EMEA-C-001411-PIP01-12-M04, from Gilead Sciences Ireland UC, for the treatment of chronic hepatitis C;
- Emicizumab, EMEA-C-001839-PIP01-15, from Roche Registration Limited, for the treatment of hereditary factor VIII deficiency;
- Sofosbuvir, EMEA-C-001276-PIP01-12-M02, from Gilead Sciences Ireland UC, for the treatment of chronic hepatitis C;
- Anidulafungin, EMEA-C-000469-PIP01-08-M07, from Pfizer Limited, for the treatment of invasive candidiasis

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/measures 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.

Withdrawals

The PDCO noted that 8 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

Other matters

The next meeting of the PDCO will be held on 27-29 May 2019.

– END –

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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