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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

27-29 May 2019

Opinions on paediatric investigation plans

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

- (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide, EMEA-002310-PIP02-17, from Achillion Pharmaceuticals, Inc., for the treatment of C3 glomerulopathy;
- Tropifexor, EMEA-002471-PIP01-18, from Novartis Europharm Limited, for the treatment of non-alcoholic steatohepatitis;
- Tabelecleucel, EMEA-002025-PIP02-16, from Atara Biotherapeutics, Inc., for the treatment of Epstein-Barr virus associated post-transplant lymphoproliferative disorder;
- Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human βA-T87Q-globin gene, EMEA-001665-PIP02-17, from bluebird bio France, for the treatment of sickle cell disease;
- Emricasan, EMEA-002457-PIP01-18, from Novartis Europharm Limited, for the treatment of non-alcoholic steatohepatitis;
- Fentanyl (hydrochloride), EMEA-001509-PIP01-13-M02, from Incline Therapeutics Europe, Ltd., for the treatment of acute pain;
- Lonafarnib, EMEA-002516-PIP01-18, from Eiger BioPharmaceuticals Europe Limited, for the treatment of Hutchinson-Gilford Progeria Syndrome and treatment of progeroid laminopathies.

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

- Diphtheria toxoid / tetanus toxoid / pertussis toxoid / pertussis filamentous haemagglutinin / pertactin, EMEA-002343-PIP01-18, from Vakzine Projekt Management GmbH, for the prevention of infectious diseases caused by *Corynebacterium diphtheriae*, *Clostridium tetani* and *Bordetella pertussis*.

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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not represent a significant therapeutic benefit over existing treatments for paediatric patients.

- Dexamethasone (sodium phosphate) / levofloxacin, EMEA-002375-PIP02-18, from NTC srl, for the treatment of acute otitis externa.

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.

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.

Adoption of an Opinion following re-examination

No items

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:

- Rosuvastatin (calcium) / ezetimibe, EMEA-002541-PIP01-18, from Abbott Laboratories Limited, for the treatment of elevated cholesterol;
- Bempedoic acid, EMEA-001872-PIP02-19, from Esperion Therapeutics, Inc., for the treatment of mixed dyslipidaemia;
- Bempedoic acid / ezetimibe, EMEA-002200-PIP02-19, from Esperion Therapeutics, Inc., for the treatment of mixed dyslipidaemia;
- 5’-hydroxy-2’-deoxy-P-thiothymidylyl-(3’→5’)-2’-deoxy-P-thiocytidylyl-(3’→5’)-2’-deoxy-P-thio-7-deaza-guanylyl-(3’→5’)-2’-deoxy-P-thioadenylyl-(3’→5’)-2’-deoxy-P-thioadenylyl-(3’→5’)-2’-deoxy-P-thiocytidylyl-(3’→5’)-2’-deoxy-P-thio-7-deaza-guanylyl-(3’→5’)-2’deoxy-P-thiothymidylyl-(3’→5’)-2’-deoxy-P-thiothymidylyl-(3’→5’)-2’-deoxy-P-thiocytidylyl-(3’→5’)-2’-deoxy-P-thio-7-deaza-guanylyl-1-glycerol-3-thiophosphoryl-2’-deoxy-P-thio-7-deaza-guanylyl-(5’→3’)-2’-deoxy-P-thiocytidylyl-(5’→3’)-2’-deoxy-P-thiothymidylyl-(5’→3’)-2’-deoxy-P-thiothymidylyl-(5’→3’)-2’-deoxy-P-thio-7-deaza-guanylyl-(5’→3’)-2’-deoxy-P-thiocytidylyl-(5’→3’)-2’-deoxy-P-thioadenylyl-(5’→3’)-2’-deoxy-P-thioadenylyl-(5’→3’)-2’-deoxy-P-thio-7-deaza-guanylyl-(5’→3’)-2’-deoxy-P-thiocytidylyl-(5’→3’)-5’-hydroxy-2’-deoxythymidine docosasodium salt (tilsotolimod), EMEA-002318-PIP03-19, from Idera Pharmaceuticals Inc., for the treatment of malignant melanoma;
- Heparin (sodium), EMEA-002557-PIP01-19, from B. Braun Melsungen AG, for the prevention of thromboembolic events;
- Momelotinib, EMEA-001656-PIP02-19, from Sierra Oncology Inc., for the treatment of primary myelofibrosis;
- Moxetumomab pasudotox, EMEA-002525-PIP01-18, from AstraZeneca AB, for the treatment of hairy cell leukaemia;

- Bisoprolol fumarate / ramipril, EMEA-002560-PIP01-19, from Neopharmed Gentili S.p.A., for the treatment of heart failure and treatment of hypertension;
- Bemarituzumab, EMEA-002401-PIP01-18, from Five Prime Therapeutics, Inc., for the treatment of gastric and gastro-oesophageal junction cancer.

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:

- Durvalumab, EMEA-002028-PIP01-16-M01, from AstraZeneca AB, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue) and treatment of malignant neoplasms of haematopoietic and lymphoid tissue;
- Tocilizumab, EMEA-000309-PIP04-17-M02, from Roche Registration GmbH, for the treatment of cytokine release syndrome associated with chimeric antigen receptor (CAR) T cell therapy;
- Recombinant Influenza Hemagglutinin-strain A (H1N1 subtype) / Recombinant Influenza Hemagglutinin-strain A (H3N2 subtype) / Recombinant Influenza Hemagglutinin-strain B (Victoria lineage) / Recombinant Influenza Hemagglutinin-strain B (Yamagata lineage) (RIV4), EMEA-002418-PIP01-18-M01, from Sanofi Pasteur, for the prevention of influenza infection;
- Balovaptan, EMEA-001918-PIP01-15-M02, from Roche Registration GmbH, for the treatment of autism spectrum disorder;
- Humanised anti-IL-6 receptor (IL-6R) monoclonal antibody, EMEA-001625-PIP01-14-M03, from Roche Registration GmbH, for the treatment of neuromyelitis optica;
- Testosterone, EMEA-001529-PIP02-14-M02, from Acerus Biopharma Inc., for the treatment of male hypogonadism;
- Tremelimumab, EMEA-002029-PIP01-16-M01, from AstraZeneca AB, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue) and treatment of malignant neoplasms of haematopoietic and lymphoid tissue;
- Concentrate of proteolytic enzyme in bromelain, EMEA-000142-PIP02-09-M08, from MediWound Germany GmbH, for the treatment of burns;
- Lanadelumab, EMEA-001864-PIP01-15-M04, from Shire Pharmaceuticals Ireland Limited, for the treatment of hereditary angioedema attacks;
- Afatinib, EMEA-001596-PIP02-17-M01, from Boehringer Ingelheim International GmbH, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue neoplasms) and treatment of malignant neoplasms of the central nervous system;
- Galcanezumab, EMEA-001860-PIP03-16-M03, from Eli Lilly and Company Limited, for the prevention of migraine headaches;
- Pneumococcal polysaccharide serotype 1 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 3 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 4 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 5 – diphtheria CRM197

conjugate / pneumococcal polysaccharide serotype 6A – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 6B – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 7F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 9V – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 14 – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 18C – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 19A – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 19F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 22F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 23F – diphtheria CRM197 conjugate / pneumococcal polysaccharide serotype 33F – diphtheria CRM197 conjugate (15-valent pneumococcal polysaccharide conjugate vaccine [V114]), EMEA-002215-PIP01-17-M02, from Merck Sharp & Dohme (Europe), Inc., for the prevention of disease caused by *Streptococcus pneumoniae*;

- Baricitinib, EMEA-001220-PIP03-16-M01, from Eli Lilly and Company Limited, for the treatment of atopic dermatitis;
- Terbinafine (hydrochloride), EMEA-001259-PIP02-13-M02, from Polichem, S.A., for the treatment of onychomycosis;
- Posaconazole, EMEA-000468-PIP02-12-M05, from Merck Sharp & Dohme (Europe), Inc., for the prevention of invasive fungal infections and treatment of invasive fungal infections;
- Venetoclax, EMEA-002018-PIP02-16-M02, from AbbVie Ltd, for the treatment of malignant neoplasms of the haematopoietic and lymphoid tissue and treatment of solid malignant tumours;
- Eculizumab, EMEA-000876-PIP03-14-M03, from Alexion Europe SAS, for the treatment of neuromyelitis optica spectrum disorders;
- Eravacycline, EMEA-001555-PIP01-13-M03, from Tetraphase Pharmaceuticals, Inc., for the treatment of complicated intra-abdominal infection;
- Esketamine (hydrochloride), EMEA-001428-PIP03-15-M01, from Janssen-Cilag International NV, for the treatment of major depressive disorder;
- Human normal immunoglobulin, EMEA-001853-PIP01-15-M02, from Grifols Therapeutics LLC, for the treatment of primary immunodeficiency;
- 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide / ivacaftor, EMEA-001640-PIP01-14-M05, from Vertex Pharmaceuticals (Europe) Ltd., for the treatment of cystic fibrosis;
- Tedizolid (phosphate), EMEA-001379-PIP01-12-M04, from Merck Sharp & Dohme (Europe), Inc., for the treatment of acute bacterial skin and skin structure infections.

The following product was granted a product-specific waiver in replacement of an agreed PIP:

- Brimonidine (tartrate), EMEA-002558-PIP01-19, from Bausch Health Ireland Limited, for the treatment of conjunctival hyperaemia.

Opinion on compliance check

The PDCO adopted positive Opinions on full compliance check for:

- Ustekinumab, EMEA-C-000311-PIP01-08-M04, from Janssen-Cilag International NV, for the treatment of chronic plaque psoriasis;
- Rituximab, EMEA-C-000308-PIP01-08-M04, from Roche Registration GmbH, for the treatment of

diffuse large B-cell lymphoma and treatment of autoimmune arthritis;

- Peginterferon alfa-2a, EMEA-C-000298-PIP01-08-M06, from Roche Registration GmbH, for the treatment of chronic hepatitis B and treatment of chronic hepatitis C;
- Efmoroctocog alfa, EMEA-C-001114-PIP01-10-M03, from Swedish Orphan Biovitrum AB (publ), for the treatment of hereditary Factor VIII deficiency.

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 5 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 25-28 June 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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