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Human Medicines Division

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

12-15 October 2021

Opinions on paediatric investigation plans

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

- Peptide derivative of glucagon-like-peptide 1 and glucagon with fatty acid side chain (BI 456906), EMEA-002942-PIP01-20, from Boehringer Ingelheim International GmbH, for the treatment of non-alcoholic steatohepatitis;
- Marzeptacog alfa (activated), EMEA-002270-PIP03-20, from Catalyst Biosciences, Inc., for the treatment of haemophilia A;
- Marzeptacog alfa (activated), EMEA-002270-PIP04-20, from Catalyst Biosciences, Inc., for the treatment of haemophilia B;
- Satralizumab, EMEA-001625-PIP02-21, from Roche Registration GmbH, for the treatment of myasthenia gravis;
- Ravulizumab, EMEA-001943-PIP04-20, from Alexion Europe SAS, for the treatment of neuromyelitis optica spectrum disorders;
- Magrolimab, EMEA-002819-PIP01-20, from Gilead Sciences International Ltd, for the treatment of acute myeloid leukaemia and treatment of myelodysplastic syndromes (including juvenile myelomonocytic leukaemia);
- Lutetium (^{177}Lu) oxodotreotide, EMEA-002950-PIP01-20, from Advanced Accelerator Applications, for the treatment of gastroenteropancreatic neuroendocrine tumours;
- 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA (ATL1102), EMEA-002981-PIP01-21, from Antisense Therapeutics Limited, for the treatment of Duchenne muscular dystrophy;
- Evenamide, EMEA-002519-PIP03-21, from Newron Pharmaceuticals SpA, for the treatment of schizophrenia;

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- Neisseria meningitidis serogroup B Protein-based active substance / Recombinant Neisseria meningitidis serogroup B protein 1 / Recombinant Neisseria meningitidis serogroup B protein 3 / Recombinant Neisseria meningitidis serogroup B protein 2, EMEA-002954-PIP02-21, from Sanofi Pasteur, for the prevention of meningococcal disease;

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

- Human normal immunoglobulin, EMEA-003076-PIP01-21, from Octapharma Pharmazeutika Produktionsges.m.b.H, for treatment of primary immunodeficiency. 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.

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:

- Eplerenone / furosemide, EMEA-003065-PIP01-21, from Przedsiębiorstwo Farmaceutyczne LEK-AM Sp. z o.o., for the treatment of heart failure;
- Ramipril / amlodipine (besilate), EMEA-003070-PIP01-21, from 1A Pharma GmbH, for the treatment of hypertension;
- Verdiperstat, EMEA-002708-PIP02-21, from Biohaven Pharmaceutical Ireland DAC, for the treatment of amyotrophic lateral sclerosis;
- Ofranergene obadenovec, EMEA-003062-PIP01-21, from Vascular Biogenics Ltd. (VBL Therapeutics), for the treatment of fallopian tube cancer, treatment of ovarian cancer and treatment of peritoneal cancer;
- Vibostolimab / pembrolizumab, EMEA-003063-PIP01-21, from Merck, Sharp & Dohme Inc, for the treatment of all conditions included in the category of malignant neoplasms (except nervous system neoplasms, haematopoietic and lymphoid tissue neoplasms and melanoma) and treatment of malignant neoplasms of the central nervous system;
- Adagrasib, EMEA-003068-PIP01-21, from Mirati Therapeutics, Inc., for the treatment of all solid and haematological malignancies;
- Adavosertib, EMEA-003069-PIP01-21, from AstraZeneca AB, for the treatment of malignant endometrial neoplasms and treatment of pancreatic cancer;
- Otenaproxesul, EMEA-003061-PIP01-21, from Antibe Therapeutics Inc., for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);
- Benralizumab, EMEA-001214-PIP08-21, from AstraZeneca AB, for the treatment of non-cystic

fibrosis bronchiectasis with an eosinophilic phenotype;

- Human alpha1-proteinase inhibitor, EMEA-001525-PIP02-21, from Kamada Ireland Limited, for the treatment of emphysema secondary to congenital deficiency of alpha-1 antitrypsin;
- Diphtheria toxoid / Tetanus toxoid / Bordetella pertussis antigen: Pertussis toxoid / Bordetella pertussis antigen: Filamentous Haemagglutinin / Bordetella pertussis antigen: Pertactin / Inactivated poliovirus: type 1 (Mahoney strain) / Inactivated poliovirus: type 2 (MEF-1 strain) / Inactivated poliovirus: type 3 (Saukett strain), EMEA-003066-PIP01-21, from Vakzine Projekt Management GmbH, for the prevention of infectious diseases caused by Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, Poliovirus types 1, 2 and 3;
- Pamrevlumab, EMEA-002979-PIP03-21, from FibroGen, Inc, for the treatment of pancreatic cancer;

The PDCO adopted 0 opinions on the **refusal** of a request for waiver.

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:

- Azilsartan medoxomil, EMEA-000237-PIP01-08-M10, from Takeda Development Centre Europe Ltd, for the treatment of hypertension;
- Macitentan, EMEA-001032-PIP01-10-M04, from Janssen-Cilag International NV, for the treatment of pulmonary arterial hypertension, treatment of systemic sclerosis and treatment of idiopathic pulmonary fibrosis;
- Vericiguat, EMEA-001636-PIP01-14-M02, from Bayer AG, for the treatment of left ventricular failure;
- Deferoxamine (mesylate) / histidine / tryptophan / aspartic acid / n-acetyl-histidine (monohydrate) / glycine / alfa-ketoglutaric acid / arginine / potassium chloride / magnesium chloride (hexahydrate) / calcium chloride (dihydrate) / sodium chloride / alanine / 3,4-dimethoxy-N-methylbenzohydroxamic acid, EMEA-002735-PIP03-20-M01, from Dr. Franz Köhler Chemie GmbH, for heart transplantation;
- Glycopyrronium bromide, EMEA-002383-PIP01-18-M01, from Dr. August Wolff GmbH & Co. KG - Arzneimittel, for the treatment of hyperhidrosis;
- Sodium zirconium cyclosilicate, EMEA-001539-PIP01-13-M05, from AstraZeneca AB, for the treatment of hyperkalaemia;
- Evinacumab, EMEA-002298-PIP01-17-M03, from Regeneron Ireland DAC, for the treatment of elevated cholesterol;
- Naloxegol, EMEA-001146-PIP01-11-M07, from Kyowa Kirin Pharmaceutical Development Limited, for the treatment of opioid-induced constipation;
- Vonicog alfa, EMEA-001164-PIP01-11-M05, from Baxalta Innovations GmbH, for the treatment of von Willebrand disease;

- Marstacimab, EMEA-002285-PIP02-19-M01, from Pfizer Europe MA EEIG, for the treatment of congenital haemophilia A and treatment of congenital haemophilia B;
- Upadacitinib, EMEA-001741-PIP01-14-M05, from AbbVie Ltd, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, spondyloarthritis and juvenile idiopathic arthritis);
- Dalbavancin hydrochloride, EMEA-000016-PIP01-07-M08, from Allergan Pharmaceuticals International Limited, for the treatment of acute bacterial skin and skin structure infections;
- Ceftobiprole medocaril (sodium), EMEA-000205-PIP02-11-M05, from Basilea Pharmaceutica International Ltd., for the treatment of pneumonia;
- Oritavancin (diphosphate), EMEA-001270-PIP01-12-M04, from Menarini International Operations Luxembourg S.A., for the treatment of acute bacterial skin and skin structure infections;
- Isavuconazonium (sulfate), EMEA-001301-PIP02-12-M04, from Basilea Pharmaceutica International Ltd., for the treatment of invasive aspergillosis and treatment of mucormycosis;
- Rilpivirine / dolutegravir, EMEA-001750-PIP01-15-M05, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Tenofovir alafenamide / emtricitabine / bictegravir, EMEA-001766-PIP01-15-M04, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Pretomanid, EMEA-002115-PIP01-17-M04, from Global Alliance for TB Drug Development, for the treatment of multi-drug-resistant tuberculosis;
- Perampanel, EMEA-000467-PIP01-08-M15, from Eisai Europe Limited, for the treatment of treatment-resistant epilepsies;
- Erenumab, EMEA-001664-PIP02-15-M05, from Novartis Europharm Limited, for the prevention of migraine headaches;
- Soticlestat, EMEA-002572-PIP02-19-M01, from Takeda Pharma A/S, for the treatment of Dravet syndrome and treatment of Lennox-Gastaut syndrome;
- Ruxolitinib (phosphate), EMEA-000901-PIP04-17-M02, from Novartis Europharm Limited, for the treatment of chronic Graft versus Host Disease;
- Regorafenib, EMEA-001178-PIP01-11-M06, from Bayer AG, for the treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue);
- Larotrectinib, EMEA-001971-PIP02-16-M04, from Bayer AG, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms);
- Cyclophosphamide, EMEA-002644-PIP01-19-M01, from Accord Healthcare S.L.U., for the treatment of all malignant neoplasms;
- Inotuzumab ozogamicin, EMEA-001429-PIP01-13-M04, from Pfizer Europe MA EEIG, for the treatment of B cell acute lymphoblastic leukaemia;
- Vamorolone, EMEA-001794-PIP02-16-M04, from ReveraGen BioPharma Ltd, for the treatment of Duchenne muscular dystrophy;
- Methoxiflurane, EMEA-000334-PIP01-08-M10, from Medical Developments UK Ltd, for the treatment of acute pain;

- Molgramostim, EMEA-002282-PIP01-17-M01, from Savara Aps, for the treatment of pulmonary alveolar proteinosis;
- Lumasiran (ALN-GO1), EMEA-002079-PIP01-16-M02, from Alnylam UK Limited, for the treatment hyperoxaluria;
- Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) [QIVc], EMEA-002068-PIP01-16-M04, from Seqirus Netherlands, for the prevention of influenza;
- Bilastine, EMEA-000347-PIP02-16-M03, from Faes Farma S.A., for the treatment of allergic conjunctivitis;
- Cotadutide, EMEA-002287-PIP01-17-M03, from AstraZeneca AB, for the treatment of Type 2 Diabetes Mellitus;
- Baloxavir marboxil, EMEA-002440-PIP01-18-M02, from Roche Registration GmbH, for the treatment of influenza infection and prevention of influenza infection;
- Sotrovimab, EMEA-002899-PIP01-20-M01, from GlaxoSmithKline Trading Services Ltd, for the treatment of coronavirus disease 2019 (COVID-19);
- Tecovirimat (monohydrate), EMEA-001205-PIP02-19-M01, from SIGA Technologies, Inc., for the treatment of orthopoxvirus disease (smallpox, monkeypox, cowpox, and vaccinia);
- Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine/ matrix-M1 adjuvant (NVX-CoV2373), EMEA-002941-PIP01-20-M01, from Novavax CZ a.s., for the prevention of coronavirus disease 2019 (COVID-19).

Opinion on compliance check

The PDCO adopted positive opinions on (full) compliance check for:

- Dolutegravir, EMEA-C-000409-PIP01-08-M06, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Oseltamivir (phosphate), EMEA-C-000365-PIP01-08-M12, from Roche Registration GmbH, for the treatment and prevention of influenza;
- Aflibercept, EMEA-C-000236-PIP05-18, from Bayer AG, for the retinopathy of prematurity;
- Fosdenopterin, EMEA-C-001491-PIP01-13-M01, from Comharsa Life Sciences Limited, for the treatment of molybdenum cofactor deficiency type A;

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.

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. Opinions of the Paediatric Committee (PDCO) on PIPs and waivers lead to 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: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip

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