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Human Medicines Division

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

8-11 December 2020

Opinions on paediatric investigation plans

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

- Arimoclomol (citrate), EMEA-001748-PIP03-19, from Orphazyme A/S, for the treatment of amyotrophic lateral sclerosis;
- Autologous peripheral blood T cells CD4- and CD8-selected and CD3- and CD28-activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured (KTE-X19), EMEA-001862-PIP03-20, from Kite Pharma EU B.V., for the treatment of mature B-cell neoplasms;
- Lenacapavir, EMEA-002740-PIP01-19, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Allopurinol / verinurad, EMEA-002754-PIP01-19, from AstraZeneca AB, for the treatment of chronic kidney disease;
- Esketamine (hydrochloride), EMEA-002772-PIP01-20, from Celon Pharma S.A., for the treatment of bipolar depression and treatment of major depressive disorder;
- Retinol (Vitamin A), EMEA-002790-PIP01-20, from orphanix GmbH, for the prevention of bronchopulmonary dysplasia;
- Carfilzomib, EMEA-001806-PIP04-19, from Amgen Europe BV, for the treatment of acute lymphoblastic leukaemia;
- Autologous tumour-infiltrating lymphocytes (LN-144/LN-145), EMEA-002776-PIP01-20, from Iovance Biotherapeutics, Inc., for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms);
- (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (KH176), EMEA-002113-PIP01-16, from Khondrion BV, for the treatment of mitochondrial

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respiratory chain/oxidative phosphorylation defects;

- Obinutuzumab, EMEA-001207-PIP02-19, from Roche Registration GmbH, for the treatment of systemic lupus erythemathosus;
- Sparsentan, EMEA-001984-PIP03-20, from Travere Therapeutics Ireland Ltd., for the treatment of IgA nephropathy;
- Dexmedetomidine (hydrochloride), EMEA-002758-PIP01-19, from BioXcel Therapeutics, Inc., for the treatment of bipolar disorder and treatment of schizophrenia;
- Sparsentan, EMEA-001984-PIP02-20, from Travere Therapeutics Ireland Ltd., for the treatment of focal segmental glomerular sclerosis;
- 3-((1R,3s,5S)-3-((7-((5-methyl-1H-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile (TD-1473), EMEA-002757-PIP01-19, from Theravance Biopharma Ireland Limited, for the treatment of ulcerative colitis.

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

The PDCO adopted opinions for the following products:

- Following the re-examination of the positive opinion on a PIP with Deferral and waiver adopted on 16/10/2020 for adeno-associated viral vector serotype 9 containing the human mini-dystrophin gene (PF-06939926), EMEA-002741-PIP01-20, from Pfizer Europe MA EEIG, for the treatment of Duchenne muscular dystrophy, the PDCO recommended to maintain its opinion and to agree the paediatric investigation plan in accordance with Article 17(1) of said Regulation and to grant a deferral in accordance with Article 21 of said Regulation.

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:

- Umbralisib tosylate, EMEA-002890-PIP01-20, from CambPharma Solutions (CY) Ltd, for the treatment of mature B cell malignancies;
- 18-(p-[131I]-iodophenyl)octadecyl phosphocholine, EMEA-002745-PIP02-20, from Cellectar Biosciences, Inc., for the treatment of lymphoplasmacytic lymphoma;

- Ublituximab, EMEA-002889-PIP01-20, from CambPharma Solutions (CY) Ltd, for the treatment of mature B cell malignancies;
- Reldesemtiv, EMEA-002868-PIP01-20, from Cytokinetics, Inc., for the treatment of amyotrophic lateral sclerosis;
- Nefopam (hydrochloride) / paracetamol, EMEA-002877-PIP01-20, from Aptys Pharmaceuticals, for the treatment of acute pain;
- Eliapixant, EMEA-002882-PIP01-20, from Bayer AG, for the treatment of refractory and/or unexplained chronic cough;
- Heparin sodium, EMEA-002885-PIP01-20, from YES Pharmaceutical Development Services GmbH, for the prevention and treatment of thromboembolic events;
- Alpha1-Proteinase Inhibitor (Human), EMEA-002888-PIP01-20, from Baxalta Innovations GmbH , for the treatment of emphysema secondary to alpha 1-proteinase inhibitor deficiency;
- Acetylcysteine / Ibuprofen (sodium dihydrate), EMEA-002561-PIP02-20, from E-Pharma Trento S.p.A., for the treatment of upper respiratory tract infections;
- Recombinant humanised monoclonal immunoglobulin G4, with specificity for human tau (UCB0107) EMEA-002884-PIP01-20, from UCB Pharma S.A., for the treatment of progressive supranuclear palsy;
- Lorlatinib, EMEA-002669-PIP02-20, from Pfizer Europa MA EEIG, for the treatment of lung cancer;
- Catumaxomab, EMEA-002879-PIP01-20, from Lindis Biotech GmbH, for the treatment of malignant ascites;
- Rosuvastatin (calcium) / acetylsalicylic acid, EMEA-002891-PIP01-20, from Neopharmed Gentili S.p.A., for the prevention of cardiovascular events;

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:

- Cobicistat, EMEA-000969-PIP01-10-M05, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus type-1 (HIV-1) infection;
- Human fibrinogen / human thrombin, EMEA-001598-PIP01-13-M03, from Instituto Grifols, S.A., for the treatment of haemorrhage resulting from a surgical procedure;
- Lasmiditan, EMEA-002166-PIP01-17-M05, from Eli Lilly and Company Limited, for the treatment of migraine with and without aura;
- Darvadstrocel, EMEA-001561-PIP01-13-M02, from Takeda Pharma A/S, for the treatment of perianal fistula;

- Ceftazidime / avibactam, EMEA-001313-PIP01-12-M10, from Pfizer Europe MA EEIG, for the treatment of infections due to aerobic Gram-negative organisms, treatment of intra-abdominal infections, treatment of pneumonia and treatment of urinary tract infections;
- Aztreonam / avibactam, EMEA-002283-PIP01-17-M01, from Pfizer Europe MA EEIG, for the treatment of infections caused by aerobic gram-negative bacteria;
- Fosdenopterin, EMEA-001491-PIP01-13-M01, from Origin Biosciences, Inc., for the treatment of molybdenum cofactor deficiency type A;
- Split influenza virus, inactivated containing antigens equivalent to the A/H1N1-like strain, A/H3N2-like strain, B-like strain (Victoria lineage) and B-like strain (Yamagata lineage), EMEA-002359-PIP01-18-M02, from Sanofi Pasteur, for the prevention of influenza infection;
- 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1Hindol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-C]pyridin-2-one) (JNJ-53718678), EMEA-001838-PIP01-15-M03, from Janssen-Cilag International NV, for the treatment of lower respiratory tract disease caused by human respiratory syncytial virus;
- Human Thrombin / Human Fibrinogen, EMEA-001149-PIP01-11-M06, from Omrix Biopharmaceuticals N.V., for the treatment of cerebrospinal fluid leakage resulting from a neurosurgical procedure, treatment of haemorrhage resulting from a surgical procedure;
- Cannabidiol, EMEA-001964-PIP01-16-M03, from GW Pharma (International) B.V., for the treatment of seizures associated with Dravet syndrome, treatment of seizures associated with Lennox-Gastaut syndrome, treatment of seizures associated with infantile spasms and treatment of seizures associated with tuberous sclerosis complex;
- Luspatercept, EMEA-001521-PIP01-13-M05, from Celgene Europe B.V., for the treatment of beta-thalassaemia and treatment of myelodysplastic syndromes;
- Cobicistat / darunavir, EMEA-001280-PIP01-12-M03, from Janssen-Cilag International NV, for the treatment of HIV-1 infection;
- Obeticholic acid, EMEA-001304-PIP02-13-M05, from Intercept Pharma International Ltd., for the treatment of biliary atresia and treatment of primary biliary cirrhosis;
- Tofacitinib, EMEA-000576-PIP03-12-M05, from Pfizer Europe MA EEIG, for the treatment of ulcerative colitis;
- Emtricitabine / tenofovir alafenamide, EMEA-001577-PIP02-14-M04, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Daprodustat, EMEA-001452-PIP01-13-M03, from GlaxoSmithKline Trading Services Limited, for the treatment of anaemia due to chronic disorders;
- Brentuximab vedotin, EMEA-000980-PIP01-10-M07, from Takeda Pharma A/S, for the treatment of Hodgkin lymphoma and treatment of anaplastic large cell lymphoma;
- Siponimod (hemifumarate), EMEA-000716-PIP01-09-M03, from Novartis Europharm Ltd, for the treatment of multiple sclerosis;
- Vortioxetine, EMEA-000455-PIP02-10-M07, from H. Lundbeck A/S, for the treatment of major depressive disorder;
- Crizotinib, EMEA-001493-PIP03-18-M01, from Pfizer Europe MA EEIG, for the treatment of

inflammatory myofibroblastic tumour and treatment of anaplastic large cell lymphoma;

- Risankizumab, EMEA-001776-PIP02-17-M01, from AbbVie Ltd, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, spondylarthritis and juvenile idiopathic arthritis);
- Eribulin, EMEA-001261-PIP01-11-M06, from Eisai GmbH, for the treatment of soft tissue sarcoma;
- Denosumab, EMEA-000145-PIP02-12-M03, from Amgen Europe B.V., for the treatment of osteoporosis;
- Pitolisant, EMEA-001176-PIP01-11-M06, from Bioprojet Pharma for the treatment of narcolepsy;
- Bictegravir / emtricitabine / tenofovir alafenamide / /, EMEA-001766-PIP01-15-M03, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Ofatumumab, EMEA-002397-PIP01-18-M01, from Novartis Europharm Limited, for the treatment of multiple sclerosis;
- *In vitro* expanded autologous human articular chondrocytes, EMEA-001823-PIP01-15-M02, from TETEC Tissue Engineering Technologies AG, for the treatment of cartilage disorders;
- Betibeglogene autotemcel, EMEA-001665-PIP01-14-M04, from bluebird bio (Netherlands) B.V., for the treatment of β-thalassaemia;

Opinion on compliance check

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

- Elbasvir / grazoprevir, EMEA-C-001604-PIP01-13-M03, from Merck Sharp & Dohme B.V., for the treatment of chronic hepatitis C;
- Idursulfase, EMEA-C-000294-PIP02-12-M01, from Shire Human Genetic Therapies AB, for the treatment of mucopolysaccharidosis II (Hunter syndrome);
- Dapagliflozin, EMEA-C-000694-PIP01-09-M08, from Astrazeneca AB, for the treatment of type 2 diabetes mellitus;
- Riociguat, EMEA-C-000718-PIP01-09-M06, from Bayer AG, for the treatment of pulmonary hypertension;

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 PDCO welcomed the new alternate Michal Odermarsky who has been nominated by the EC as representatives from healthcare/patient organisation and Sara Vennberg as alternate from Sweden.

The next meeting of the PDCO will be held on 26-29 January 2021.

– 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: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip
3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website:

   https://www.ema.europa.eu/en/committees/paediatric-committee-pdco

   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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