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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 July 2019

Opinions on paediatric investigation plans

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

- Liposomal ciclosporin A (L-CsA), EMEA-002344-PIP02-18, from Breath Therapeutics GmbH, for the treatment of bronchiolitis obliterans syndrome;
- Eptinezumab, EMEA-002243-PIP01-17, from Alder BioPharmaceuticals Limited, for the prevention of migraine headaches;
- Pegvorhyaluronidase alfa, EMEA-001883-PIP03-17, from Halozyme Inc, for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue neoplasms);
- Niraparib (tosylate monohydrate), EMEA-002268-PIP02-18, from Tesaro UK Ltd, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid malignancies);
- Baloxavir marboxil, EMEA-002440-PIP01-18, from Roche Registration GmbH, for the prevention of Influenza infection and treatment of Influenza infection;
- Bempegaldesleukin, EMEA-002492-PIP01-18, from Nektar Therapeutics, for the treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic, and lymphoid tissue neoplasms);
- Birch bark extract, EMEA-001299-PIP03-17, from Amryt Research Limited, for the treatment of epidermolysis bullosa;
- Tirzepatide, EMEA-002360-PIP01-18, from Eli Lilly and Company, for the treatment of type 2 diabetes mellitus;
- Dostarlimab, EMEA-002463-PIP01-18, from Tesaro UK Ltd, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid malignancies);

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- Levonorgestrel, EMEA-002474-PIP02-18, from Chemo Research, S.L., for the prevention of pregnancy;
- Fosmetpantotenate, EMEA-002036-PIP01-16, from Retrophin Europe Limited, for the treatment of Pantothenate Kinase associated neurodegeneration;
- Trifarotene cream HE1, EMEA-001492-PIP02-18, from Premier Research Group SLU, for the treatment of ichthyoses;
- Equine Immunoglobulin F(ab')2 fragments targeting Shiga toxin (NEAST), EMEA-002444-PIP02-18, from Chemo Research, S.L., for the prevention of haemolytic uremic syndrome;
- Recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein, EMEA-002435-PIP01-18, from PTC Therapeutics International Limited, for the treatment of aromatic L-amino acid decarboxylase deficiency;
- Pegylated-fibroblast growth factor 21, EMEA-002448-PIP01-18, from Bristol-Myers Squibb International Corporation, for the treatment of non-alcoholic steatohepatitis

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

- Recombinant Hepatitis B Vaccine, EMEA-002157-PIP01-17, from VBI Vaccines Inc., for the prevention of Hepatitis B virus infection

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:

- Atropine (sulfate) / obidoxime (chloride) /, EMEA-002570-PIP01-19, from Emergent Netherlands B.V., for the treatment of organophosphates poisoning;
- Zofenopril / nebivolol, EMEA-002593-PIP01-19, from Menarini Ricerche SpA , for the treatment of hypertension;
- Infigratinib, EMEA-002594-PIP01-19, from QED THERAPEUTICS, for the treatment of cholangiocarcinoma;
- Fexapotide (triflutate), EMEA-002598-PIP01-19, from FGK Representative Service GmbH, for the treatment of benign prostatic hyperplasia;
- Belantamab mafodotin, EMEA-002468-PIP04-19, from GlaxoSmithKline Trading Services, for the treatment of multiple myeloma;

- Rosuvastatin / ramipril, EMEA-002569-PIP01-19, from Egis Pharmaceuticals PLC, for the prevention of cardiovascular events, treatment of hypertension and treatment of lipid metabolism disorders;
- Influenza virus surface antigens (haemagglutinin) of strain A (H1N1) / influenza virus surface antigens (haemagglutinin) of strain A (H3N2) / influenza virus surface antigens (haemagglutinin) of strain B (Victoria lineage) / influenza virus surface antigens (haemagglutinin) of strain B (Yamagata lineage), EMEA-002027-PIP02-17-M01, from Adimmune Corporation, for the prevention of influenza infection;
- Botulinum toxin type A, EMEA-002628-PIP01-19, from Allergan Pharmaceuticals International Limited, for prevention of post-operative atrial fibrillation in patients undergoing open-chest cardiac surgery

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:

- Tisagenlecleucel, EMEA-001654-PIP02-17-M01, from Novartis Europharm Limited, for the treatment of mature B-cell neoplasms;
- Ferric maltol, EMEA-001195-PIP01-11-M04, from Norgine BV, for the treatment of iron deficiency;
- Risdiplam, EMEA-002070-PIP01-16-M03, from Roche Registration GmbH, for the treatment of spinal muscular atrophy;
- Sacubitril /valsartan, EMEA-000316-PIP02-11-M04, from Novartis Europharm Ltd., for the treatment of heart failure;
- Recombinant Neisseria meningitidis group B NHBA fusion protein / recombinant Neisseria meningitidis group B NadA protein / recombinant Neisseria meningitidis group B fHbp fusion protein / Outer Membrane Vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4, EMEA-000139-PIP01-07-M03, from GSK Vaccines S.r.l., for the prevention of meningococcal meningitis;
- Fevipiprant, EMEA-001315-PIP02-16-M02, from Novartis EuroPharm Limited, for the treatment of asthma;
- Pretomanid, EMEA-002115-PIP01-17-M01, from Global Alliance for TB Drug Development, for the treatment of multi-drug-resistant tuberculosis;
- Onasemnogene abeparvovec, EMEA-002168-PIP01-17-M02, from AveXis Netherlands B.V., for the treatment of spinal muscular atrophy;
- Empagliflozin, EMEA-000828-PIP04-16-M03, from Boehringer Ingelheim International GmbH, for the treatment of type 1 diabetes mellitus;
- Lonoctocog alfa, EMEA-001215-PIP01-11-M07, from CSL Behring GmbH, for the treatment of congenital factor VIII deficiency;
- Cabozantinib, EMEA-001143-PIP01-11-M02, from Ipsen Pharma, for the treatment of malignant solid tumours;
- Etrolizumab, EMEA-001434-PIP01-13-M02, from Roche Registration GmbH, for the treatment of

Crohn's disease and treatment of ulcerative colitis;

- Ataluren, EMEA-000115-PIP01-07-M10, from PTC Therapeutics International, Limited, for the treatment of dystrophinopathy;
- Pazopanib, EMEA-000601-PIP01-09-M06, from Novartis Europharm Limited, for the treatment of Ewing sarcoma family of tumours, treatment of non-rhabdomyosarcoma soft tissue sarcoma and treatment of rhabdomyosarcoma;
- 2-hydroxypropyl-ß-cyclodextrin (HP-ß-CD), EMEA-001866-PIP01-15-M04, from Mallinckrodt Pharmaceuticals Ireland Ltd, for the treatment of Niemann-Pick disease, type C;
- Purified antigen fractions of inactivated split virion Influenza A/Vietnam/1194/2004 (H5N1) like strain used / Purified antigen fractions of inactivated split virion Influenza A/Indonesia/05/2005 (H5N1) like strain used, EMEA-000160-PIP01-07-M05, from GlaxoSmithKline Biologicals S.A., for the prevention of influenza infection;
- Finerenone, EMEA-001623-PIP01-14-M03, from Bayer AG, for the treatment of chronic kidney disease;
- Anti-respiratory syncytial virus human IgG1κ monoclonal antibody, EMEA-001784-PIP01-15-M01, from AstraZeneca AB, for the prevention of lower respiratory tract infection caused by respiratory syncytial virus;
- Cobimetinib, EMEA-001425-PIP01-13-M04, from Roche Registration GmbH, for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue) with Ras, Raf or MEK pathway activation;
- (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-l]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid, EMEA-002054-PIP01-16-M01, from Albireo AB, for the treatment of Progressive Familial Intrahepatic Cholestasis;
- Dermatophagoides pteronyssinus / Dermatophagoides farinae, EMEA-001258-PIP01-11-M05, from ALK-Abelló A/S, for the treatment of allergic rhinitis and treatment of asthma;
- Brivaracetam, EMEA-000332-PIP01-08-M14, from UCB Pharma S.A., for the treatment of epilepsy with partial onset seizures and treatment of neonatal seizures;
- Lomitapide, EMEA-001124-PIP01-10-M04, from Amryt Pharmaceuticals DAC, for the treatment of (heterozygous and homozygous) familial hypercholesterolaemia;
- Upadacitinib, EMEA-001741-PIP01-14-M02, from AbbVie Ltd, for the treatment of chronic idiopathic arthritis (including rheumathoid arthritis, psoriatic arthritis, spondyloarthritis and juvenile idiopathic arthritis);
- Dolutegravir (DTG) / lamivudine (3TC), EMEA-001940-PIP01-16-M02, from ViiV Healthcare BV, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection;
- Liquid ethanolic extract 30 per cent (w/w) of Allium cepa L. (fresh bulb) and Citrus limon (L.) Burm. f. (fresh fruit), Paullinia cupana Kunth, Theobroma cacao L., EMEA-001835-PIP01-15-M04, from Legacy Healthcare, for the treatment of alopecia;
- Human fibrinogen / human thrombin /, EMEA-001149-PIP01-11-M05, from Omrix Biopharmaceuticals N.V., for the treatment of cerebrospinal fluid leakage resulting from a neurosurgical procedure and treatment of haemorrhage resulting from a surgical procedure;

- Semaglutide, EMEA-001441-PIP03-17-M01, from Novo Nordisk A/S, for the treatment of obesity;
- Larotrectinib, EMEA-001971-PIP02-16-M02, 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);

Opinion on compliance check

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

- Terbinafine (hydrochloride), EMEA-C-001259-PIP02-13-M02, from Polichem, S.A, for the treatment of onychomycosis;

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 by written procedure on 21–24 August 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: 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/human-regulatory/overview/paediatric-medicines/paediatric-regulation
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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