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Inspections, Human Medicines Pharmacovigilance and Committees Division

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

13-16 December 2016

Opinions on paediatric investigation plans

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

- Ciprofloxacin Hydrochloride, EMEA-001563-PIP02-15, from Aradigm Limited, for the treatment of chronic pulmonary infections caused by P. aeruginosa;
- Abatacept, EMEA-000118-PIP03-15, from Bristol-Myers Squibb Pharma EEIG, for the treatment of systemic lupus erythematosus;
- 2-hydroxypropyl-ß-cyclodextrin (HP-ß-CD), EMEA-001866-PIP01-15, from Vtesse Europe Ltd, for the treatment of Niemann-Pick disease, type C;
- Fc- and CDR-modified humanized monoclonal antibody against C5, EMEA-001943-PIP01-16, from Alexion Europe SAS, for the treatment of atypical Haemolytic Uremic Syndrome;
- Esketamine (hydrochloride), EMEA-001428-PIP03-15, from Janssen-Cilag International NV, for the treatment of major depressive disorder;
- Anti-(human calcitonin gene-related peptide receptor) human monoclonal antibody, EMEA-001664-PIP02-15, from Amgen Europe B.V., for the prevention of migraine headaches;
- Autologous CD34+ cells transduced with lentiviral vector encoding the human beta-globin gene, EMEA-001933-PIP01-16, from Fondazione Telethon, for the treatment of beta-thalassemia;
- Varicella-zoster virus (inactivated), EMEA-001073-PIP02-14, from Merck Sharp & Dohme (Europe), Inc, for the prevention of Varicella Zoster Virus disease;
- pegvaliase, EMEA-001951-PIP01-16, from BioMarin International Limited, for the treatment of hyperphenylalaninaemia;
- Volanesorsen, EMEA-001915-PIP01-15, from Ionis Pharmaceuticals, Inc., for the treatment of familial chylomicronemia syndrome;
- Vadadustat, EMEA-001944-PIP01-16, from Akebia Therapeutics, Inc., for the treatment of anaemia

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due to chronic disorders;

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

- Ambrisentan / tadalafil, EMEA-002030-PIP01-16, from Glaxo Group Limited, for the treatment of pulmonary arterial hypertension.

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.

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:

- Apolipoprotein A-1 (ApoA-1), EMEA-002040-PIP01-16, from CSL Behring GmbH, for the treatment of acute myocardial infarction;
- (2-Hydroxyethyl)trimethylammonium 3-[2-fluoro-5-(2,3-difluoro-6-methoxybenzyloxy)-4-methoxyphenyl]-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-5-carboxylate, EMEA-002039-PIP01-16, from ObsEva Ireland Limited, for the treatment of endometriosis and treatment of leiomyoma of uterus;
- Candesartan cilexetil / Amlodipine besylate / Hydrochlorothiazide, EMEA-002024-PIP01-16, from Midas Pharma GmbH, for the treatment of hypertension;
- Mirvetuximab soravtansine, EMEA-001921-PIP01-16, from ImmunoGen Europe Limited, for the treatment of ovarian carcinoma, treatment of Fallopian tube carcinoma and treatment of peritoneal carcinoma;
- Doxorubicin (hydrochloride), EMEA-002043-PIP01-16, from ONXEO, for the treatment of hepatocellular carcinoma;
- (1S,3S,4R)-4-[(3aS,4R,5S,7aS)-4-(aminomethyl)-7a-methyl-1-methylidene-octahydro-1H-inden-5-yl]-3-(hydroxymethyl)-4-methylcyclohexan-1-ol; acetic acid salt, EMEA-002062-PIP01-16, from Aquinox Pharmaceuticals (Canada) Inc., for the treatment of interstitial cystitis.

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:

- Nanobody directed towards the fusion protein of human respiratory syncytial virus, EMEA-001553-PIP01-13-M01, from Ablynx NV, for the treatment of lower respiratory tract disease caused by human respiratory syncytial virus (RSV);
- Ipilimumab, EMEA-000117-PIP02-10-M07, from Bristol-Myers Squibb Pharma EEIG, for the treatment of melanoma;
- Ocrelizumab, EMEA-000310-PIP03-10-M02, from Roche Registration Ltd., for the treatment of multiple sclerosis;
- Potassium chloride / Sodium chloride / Citric acid (as citric acid anhydrous) / Sodium citrate / Simeticone / Sodium sulfate (as sodium sulfate anhydrous) / Macrogol 4000, EMEA-001356-PIP02-12-M01, from Alfa Wassermann S.p.A., for the bowel cleansing prior to clinical procedures;
- 4-amino-1-[5-chloro-2,5-dideoxy-2-fluoro-3-O-(2-methylpropanoyl)-4-[[(2-methylpropanoyl)oxy]methyl]-a- L-lyxofuranosyl]-2(1H)-pyrimidinone, EMEA-001758-PIP01-15-M01, from Janssen-Cilag International NV, for the treatment of lower respiratory tract disease caused by human respiratory syncytial virus;
- Paclitaxel, EMEA-001308-PIP01-12-M01, from Celgene Europe Limited, for the treatment of solid malignant tumours;
- ranibizumab, EMEA-000527-PIP04-13-M01, from Novartis Europharm Limited, for the treatment of retinopathy of prematurity;
- tenofovir alafenamide / emtricitabine, EMEA-001577-PIP02-14-M01, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Patiromer sorbitex calcium, EMEA-001720-PIP01-14-M01, from Vifor Fresenius Medical Care Renal Pharma France, for the treatment of hyperkalaemia;
- Nivolumab, EMEA-001407-PIP02-15-M01, from Bristol-Myers Squibb Pharma EEIG, for the treatment of malignant neoplasms of lymphoid tissue and treatment of malignant neoplasms of the central nervous system;
- Rilpivirine (RPV) / Dolutegravir (DTG), EMEA-001750-PIP01-15-M01, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Humanized anti-IL-6 receptor (IL-6R) monoclonal antibody, EMEA-001625-PIP01-14-M01, from CHUGAI PHARMA EUROPE LTD, for the treatment of neuromyelitis optica;
- budesonide, EMEA-001087-PIP02-12-M03, from Vectura Limited, for the treatment of asthma;
- Dupilumab, EMEA-001501-PIP02-13-M02, from sanofi-aventis recherche & développement, for the treatment of asthma;
- Idursulfase, EMEA-000294-PIP02-12-M01, from Shire Human Genetic Therapies AB, for the treatment of Mucopolysaccharidosis II (Hunter syndrome);

- *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily B; *Escherichia coli*) / *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily A; *Escherichia coli*), EMEA-001037-PIP02-11-M04, from Pfizer Ltd, for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroup B;
- Eltrombopag, EMEA-000170-PIP03-13-M02, from Novartis Europharm Limited, for the treatment of aplastic anaemia;
- midostaurin, EMEA-000780-PIP01-09-M03, from Novartis Europharm Ltd, for the treatment of acute myeloid leukaemia, treatment of malignant mastocytosis and treatment of mast cell leukaemia;
- elbasvir / grazoprevir, EMEA-001604-PIP01-13-M02, from Merck Sharp & Dohme (Europe), Inc., for the treatment of chronic hepatitis C;
- belatacept, EMEA-000157-PIP01-07-M03, from Bristol-Myers Squibb Pharma EEIG, for the prevention of rejection of transplanted kidney;
- CONCENTRATE OF PROTEOLYTIC ENZYMES ENRICHED IN BROMELAIN, EMEA-000142-PIP02-09-M05, from MediWound Germany GmbH, for the treatment of burns;
- Idelalisib, EMEA-001350-PIP02-13-M03, from Gilead Sciences International Ltd, for the treatment of mature B-cell neoplasm;
- Beclometasone (dipropionate) / formoterol (fumarate dihydrate), EMEA-000548-PIP01-09-M06, from Chiesi Farmaceutici S.p.A., for the treatment of asthma;
- Edoxaban (tosylate), EMEA-000788-PIP02-11-M05, from Daiichi Sankyo Europe GmbH, for the prevention of arterial thromboembolism, treatment of venous thromboembolism and prevention of venous thromboembolism;
- Bedaquiline (fumarate), EMEA-000912-PIP01-10-M03, from Janssen Infectious Diseases BVBA, for the treatment of multi-drug resistant tuberculosis;
- Terbinafine (hydrochloride), EMEA-001259-PIP02-13-M01, from Polichem SA, for the treatment of onychomycosis.

The PDCO adopted opinions on the **refusal** of modifications to an agreed PIP for the following applications:

- Bumetanide, EMEA-001303-PIP01-12-M01, from Neurochlore, for the treatment of autistic spectrum disorder;
- Methoxy polyethylene glycol- epoetin beta, EMEA-000172-PIP01-07-M02, from Roche Registration Limited, for the treatment of symptomatic anaemia associated with chronic kidney disease.

Opinion on compliance check

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

- Solifenacin (succinate), EMEA-C-000573-PIP02-13-M03, from Astellas Pharma Europe B.V., for the treatment of neurogenic detrusor overactivity;
- Dinutuximab, EMEA-C-001285-PIP01-12-M02, from United Therapeutics Europe Limited, for the treatment of neuroblastoma;
- Cobicistat / elvitegravir / tenofovir disoproxil fumarate / emtricitabine, EMEA-C-000970-PIP01-10-M01, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;

- Catridecacog, EMEA-C-000185-PIP01-08-M05, from Novo Nordisk A/S, for the treatment of congenital factor XIII A-subunit deficiency;
- tenofovir disoproxil fumarate / emtricitabine, EMEA-C-001091-PIP02-15, from Gilead Sciences International Ltd., for the prevention of human immunodeficiency virus (HIV-1) infection;
- Fibrinogen (human plasma-derived), EMEA-C-000457-PIP02-10-M02, from LFB Biotechnologies, for the treatment of congenital fibrinogen deficiency;
- Natalizumab, EMEA-C-001095-PIP02-12, from Biogen Idec Ltd, for the treatment of multiple sclerosis.

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/measured 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.

Adoption of an opinion following re-examination

The PDCO adopted an opinion for the following product:

- Following the re-examination of the positive opinion on a modification of an agreed Paediatric Investigation Plan adopted on 24 October 2016 for Methoxyflurane, EMEA-000334-PIP01-08-M05, for the treatment of acute pain, from Medical Developments UK Ltd, the PDCO adopted a revised positive opinion.

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.

Withdrawals

The PDCO noted that 4 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

The PDCO also noted that the application leading the opinion adopted during the PDCO 8-11 November 2016 meeting for Rubidium (82Rb) chloride, EMEA-000882-PIP03-11-M02, from Jubilant DraxImage Inc., for the visualisation of myocardial perfusion for diagnostic purposes was withdrawn before the adoption of the decision by the Agency.

Other matters

The next meeting of the PDCO will be held on 24-27 January 2017.

– 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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