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Procedure Management and Committees Support Division

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

11-13 November 2015

Opinions on paediatric investigation plans

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

- Emtricitabine / tenofovir disoproxil fumarate, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection and for the prevention of human immunodeficiency virus (HIV-1) infection;
- Ethosuximide, from Advicenne Pharma, for the treatment of childhood absence epilepsy;
- Emtricitabine / tenofovir alafenamide / GS-9883, from Gilead Sciences International Ltd, for the treatment of human immunodeficiency virus (HIV-1) infection.

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.

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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

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:

- Dupilumab, from Sanofi-Aventis Recherche & Développement, for the treatment of nasal polyposis;
- Ketoprofen, from Promo International S.r.l., for the treatment of musculoskeletal and connective tissue pain;
- Telotristat etiprate, from IPSEN PHARMA, for the treatment of carcinoid syndrome;
- Recombinant human monoclonal IgG1 antibody directed against Programmed Death Ligand-1 (anti-PD-L1) (MSB0010718C), from Merck KGaA, for the treatment of Merkel cell carcinoma;
- Inactivated poliovirus type 1 (Brunhilde), Inactivated poliovirus type 2 (MEF-1), Inactivated poliovirus type 3 (Saukett), from Statens Serum Institut, for the prevention of poliomyelitis.

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:

- Nilotinib, from Novartis Europharm Ltd, for the treatment of chronic myeloid leukaemia;
- Ticagrelor, from AstraZeneca AB, for the prevention of thromboembolic events;
- C1 inhibitor (human), from NPS Pharma Holdings Limited, for the treatment of C1 inhibitor deficiency;
- Apremilast, from Celgene Europe Limited, for the treatment of psoriasis;
- Ceftaroline fosamil, from AstraZeneca AB, for the treatment of complicated skin and soft tissue and infections and treatment of community acquired pneumonia;
- Edoxaban (tosylate), from Daiichi Sankyo Development Ltd, for the prevention of arterial thromboembolism, treatment of venous thromboembolism and prevention of venous thromboembolism;
- Human normal immunoglobulin, from Bio Products Laboratory Limited, for the treatment of primary immunodeficiency as model for replacement therapy and treatment of idiopathic thrombocytopenic purpura as model for immunomodulation;
- Lipegfilgrastim, from UAB ”Sicor Biotech“, for the treatment of chemotherapy-induced neutropenia and prevention of chemotherapy-induced febrile neutropenia;
- *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily A; Escherichia coli) / *Neisseria meningitidis* serogroup B recombinant lipoprotein (rLP2086; subfamily B; *Escherichia*

coli), from Pfizer Ltd, for the prevention of invasive meningococcal disease caused by *N. meningitidi*s serogroup B;

- Lorcaserin, from Eisai Limited UK, for the treatment of obesity;
- Delamanid, from Otsuka Europe Development and Commercialisation Ltd., for the treatment of multi drug resistant tuberculosis;
- Odanacatib, from Merck Sharp & Dohme (Europe), Inc., for the treatment of osteoporosis;
- Dolutegravir / abacavir / lamivudine, from ViiV Healthcare UK Limited, for the treatment of human immunodeficiency virus (HIV-1) infection;
- Tilmanocept, from Navidea Biopharmaceuticals Limited, for the visualisation of lymphatic drainage of solid malignant tumours for diagnostic purposes;
- Obeticholic acid (6 alpha-ethylchenodeoxycholic acid), from Intercept Italia s.r.l., for the treatment of primary biliary cirrhosis and treatment of biliary atresia;
- Vosaroxin, from Sunesis Europe Ltd, for the treatment of acute myeloid leukaemia;
- Grazoprevir, from Merck Sharp & Dohme (Europe), Inc., for the treatment of chronic hepatitis C;
- Elbasvir, from Merck Sharp & Dohme (Europe), Inc., for the treatment of chronic hepatitis C;
- Grazoprevir / elbasvir, from Merck Sharp & Dohme (Europe), Inc., for the treatment of chronic hepatitis C.

The PDCO also adopted a revised opinion on the modification to an agreed PIP for the following product:

- Pneumococcal polysaccharide serotype 6B conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 1 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 18C conjugated to tetanus toxoid / Pneumococcal polysaccharide serotype 5 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 19F conjugated to diphtheria toxoid / Pneumococcal polysaccharide serotype 14 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 9V conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 4 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 23F conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein / Pneumococcal polysaccharide serotype 7F conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein, from GlaxoSmithKline Biologicals S.A., for the prevention of diseases caused by streptococcus pneumoniae and prevention of acute otitis media caused by non-typeable Haemophilus influenzae.

Opinion on compliance check

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

- Bevacizumab, from F.Hoffmann-La Roche Ltd, for the treatment of high-grade glioma;
- Bilastine, from Faes Farma S.A., for the treatment of allergic rhinoconjunctivitis and treatment of urticaria;

- Human normal immunoglobulin, from Baxalta Innovations GmbH, for the treatment of primary immunodeficiency (PID) as model for replacement therapy.

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.

Withdrawals

The PDCO noted that 7 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 to the opinion adopted during the PDCO October 2015 meeting for *Yersinia pestis* recombinant F1V antigen (F1 capsular protein fused to V antigen), from DynPort Vaccine Company LLC, for the prevention of *Yersinia pestis* infections, has been withdrawn before the decision was adopted by the Agency.

Interaction with external experts

The PDCO has regular interactions with academic experts, with a view to bringing state-of-the-art knowledge to the PDCO scientific discussions. Dominik Sturm, an expert with clinical expertise in paediatric oncology, was invited to participate, via teleconference, to the PDCO November 2015 meeting, and contributed to the discussions concerning a medicinal product targeting the treatment of solid malignant tumours (excluding melanoma).

Cooperation with US Food and Drug Administration (FDA)

At the PDCO November meeting, the PDCO welcomed representative(s) of the US Food and Drug Administration (FDA), joining part of the meeting via teleconference.

The objective of the cooperation between the Agency and FDA in the field of paediatric medicines is to facilitate the framework for global paediatric development plans, compatible for both agencies, with the aim of avoiding exposing children to unnecessary trials.

Results of survey project 'Questionnaire to children about taking medicines and participation in clinical trials'

The results of the survey on the views of the paediatric population (from 10 to less than 18 years of age) on taking medicines and participation in clinical trials carried out in European Union Member States, were presented by Sofia Nordenmalm, expert from Karolinska Institute in Sweden, at the PDCO November 2015 meeting. As a following step, the Committee considered the opportunity to publish these results in a scientific paper.

Guidelines

Guideline on Clinical investigation of recombinant and Human plasma-derived factor IX products (replacing EMA/CHMP/BPWP/144552/2009)

The PDCO noted the final guideline. The PDCO was in agreement with the content of the final guideline which included comments and input provided by PDCO members. The guideline provides applicants and regulators with harmonised requirements for applications for marketing authorisation for recombinant or plasma-derived factor IX products.

Guideline on Clinical investigation of recombinant and human plasma-derived factor VIII products (Rev. 1)

The PDCO was in general agreement with the content of the draft guideline providing applicants and regulators with harmonised requirements for applications for marketing authorisation for recombinant or plasma-derived factor VIII products. Additional PDCO comments may be provided in advance of the guideline adoption.

Other matters

The next meeting of the PDCO will be held on 9-11 December 2015.

– 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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