16 January 2013
EMA/PDCO/24099/2013
Paediatric Committee (PDCO)

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

09-11 January 2013

Opinions on paediatric investigation plans

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

- Hydrocortisone, from Diurnal Limited, for the treatment of adrenocortical insufficiency;
- Eribulin, from Eisai Europe Ltd, for the treatment of soft tissue sarcoma;
- Enzastaurin (hydrochloride), from Eli Lilly & Company Limited, for the treatment of diffuse large B-cell lymphoma, treatment of Burkitt lymphoma and treatment of Burkitt-like lymphoma;
- Talimogene laherparepvec, from Amgen Europe B.V., for the treatment of solid malignant non-CNS tumours;
- Bivalirudin, from The Medicines Company UK Limited, for the prevention of thrombosis and treatment of atherosclerosis;
- Volasertib, from Boehringer Ingelheim International GmbH, for the treatment of acute myeloid leukaemia;
- Obinutuzumab, from Roche Registration Limited, for the treatment of mature B-cell lymphoma and acute lymphoblastic leukaemia;
- Proteinase, metallo- (synthetic nociceptin receptor-binding) 1290102-81-6 (AGN214868), from Allergan Pharmaceuticals Ireland, for the treatment of postherpetic neuralgia and treatment of overactive bladder;
- [N-{4-Chloro-2-[(1-oxido-4-pyridinyl)carbonyl]phenyl}-4-(1,1-dimethylethyl) benzenesulfonamide, sodium salt, from Glaxo Group Limited, for the treatment of Crohn's Disease;
- Darunavir / cobicistat, from Janssen-Cilag International NV, for the treatment of HIV-1 infection;
- Tiotropium bromide (monohydrate), from Boehringer Ingelheim International GmBH, for the treatment of asthma;

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- Azithromycin, from Only for children pharmaceuticals, for the prevention of bronchopulmonary dysplasia;
- 2,6-Bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt, from Starpharma Pty Ltd, for the treatment of bacterial vaginosis.

The PDCO adopted an opinion on the **refusal** of a PIP, including waiver and deferral, for Tolvaptan, from Otsuka Pharmaceutical Europe Ltd., for the treatment of hyponatraemia, treatment of autosomal dominant polycystic kidney disease (ADPKD) and treatment of autosomal recessive polycystic kidney disease (ARPKD).

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:

- Perindopril / indapamide / amlodipine, from Pharma-Regist Kft., for the treatment of hypertension;
- Valsartan / indapamide, from Gedeon Richter Plc., for the treatment of essential hypertension, treatment of acute myocardial infarction and treatment of heart failure;
- Amlodipine / losartan, from Krka, d.d., Novo mesto, for the treatment of essential hypertension;
- Amlodipine (besylate) / atorvastatin (calcium), from HCS bvba, for the treatment of concomitant hypertension and dyslipidaemia, treatment of concomitant angina and dyslipidaemia and prevention of cardiovascular events in hypertensive patients and diabetes mellitus type 2 patients with multiple risk factors for cardiovascular disease;
- Strontium (succinate), from Les Laboratoires Servier, for the treatment of osteoporosis;
- Strontium succinate / Vitamin D3, from Les Laboratoires Servier, for the treatment of osteoporosis;
- Aztreonam, from Gilead Sciences International Ltd, for the treatment of gram-negative endobronchial infection in bronchiectasis patients;
- Frovatriptan (succinate monohydrate) / dexketoprofen (trometamol), from Menarini Ricerche S.p.A. for the treatment of migraine.

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:

- Lixisenatide, from Sanofi-Aventis R&D, for the treatment of type 2 diabetes mellitus;
- Tenofovir (disoproxil fumarate), from Gilead Sciences International Limited, for the treatment of human immunodeficiency virus (HIV) disease resulting in other conditions and treatment of chronic viral hepatitis B;
- Boceprevir, from Merck Sharp & Dohme Ltd, for the treatment of chronic hepatitis C;
- Cilengitide, from Merck KGaA, for the treatment of high-grade glioma;
- Poly(oxy-1,2-ethanediyl),alpha-hydro-omega-methoxy-133 ester with granulocyte colony-stimulating factor [methionyl,133-[O-[2-(acetylamino]-6-O-[N-[N-carboxyglycyl)amino]-alpha neuraminosyl]-2-deoxy-alpha-D-galactopyranosyl]-L-threonine]] (human), from Teva Pharma B.V., for the treatment of chemotherapy-induced neutropenia and prevention of chemotherapy-induced febrile neutropenia;
- Fluticasone furoate / triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, from Glaxo Group Limited, for the treatment of asthma;
- Dimethyl fumarate, from Biogen Idec Ltd., for the treatment of multiple sclerosis;
- Rituximab, from Roche Registration Ltd, for the treatment of diffuse large B-cell lymphoma and treatment of autoimmune arthritis;
- C1 inhibitor, from ViroPharma SPRL, for the treatment of C1 inhibitor deficiency;
- Conestat alfa, from Pharming Group N.V., for the treatment of hereditary angioedema;
- Solifenacin (succinate), from Astellas Pharma Europe B.V., for the treatment of idiopathic overactive bladder and treatment of neurogenic detrusor overactivity.

Opinion on compliance check

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

- Ezetimibe, from Merck Sharp & Dohme Limited, for the treatment of hypercholesterolaemia and treatment of sitosterolaemia;
- Antigen of pre-pandemic strain A/Vietnam/1203/2004 propagated in Vero cells, from Baxter Innovations GmbH, for the prevention of influenza infection caused by an influenza strain contained in the vaccine or related to a strain contained in the vaccine;

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 four applications were withdrawn during the late stages of the evaluation (30 days or less before opinion).

Committee interactions

The PDCO adopted an opinion on a List of Question issued by the CHMP to the PDCO on an ongoing assessment of Privigen in the field of immunology.

New meeting dates adopted

The PDCO adopted the meeting dates for 2015 during the January meeting. These dates are important for applicants in planning the submission of applications for PIPs, requests for waivers, requests for modification of an agreed PIP, and requests for compliance checks. The dates are published on the EMA website.

Cooperation with the National Center for Child Health and Development, Japan

At the January meeting, the PDCO welcomed a representative of the Japanese National Center for Child Health and Development, who attended within the framework of the international collaboration activities. The objective of this cooperation in the field of paediatric medicines is to facilitate the framework for global paediatric development plans, compatible for all agencies involved, with the aim of avoiding exposing children to unnecessary trials.

Other matters

The next meeting of the PDCO will be held on 06-08 February 2013.

– 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

Enquiries only to: paediatrics@ema.europa.eu

Annex of the January 2013 PDCO meeting report

	2011 (January to December)	2012 (January to December)	2013 (January to current month)	Cumulative total (2007 to present)
Total number of validated PIP/waiver applications	187	178	18	1340[1]
Applications submitted for a product not yet authorised *(Article 7[2])*	153	149	17	1016 *(76%)*
Applications submitted for a product already authorised and still under patent, in view of a submission of a variation/extension for a new indication, pharmaceutical form or route of administration *(Article 8[2])*	33	28	1	297 *(22%)*
Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation *(Article 30[2])*	1	1	0	27 *(2%)*
PIPs and full waiver indications covered by these applications	220	218	18	1820

Number of Paediatric Committee (PDCO) opinions	2011	2012	2013	Cumulative total (2007 to present)
Positive on full waiver	45	47	8	276
Positive on PIP, including potential deferral	107	87	13	613
Negative opinions adopted	3	3	1	31
Positive opinions adopted on modification of a PIP	153	165	11	491
Negative opinions adopted on modification of a PIP	2	1	0	7
Positive opinions on compliance with a PIP	9	4	2	37
Negative opinions on compliance check with a PIP	0	0	0	1
Opinions adopted under Art. 14.2	0	0	0	2

[1] Of which 344 have been requests for a full waiver.
[2] Applications submitted in accordance with the referenced article of Regulation (EC) No 1901/2006, as amended.

Areas covered by PIPs/waiver applications	2011 *(Number of areas covered)**	2012 *(Number of areas covered)**	2013 *(Number of areas covered)**
Neurology	11	11	0
Uro-nephrology	4	5	0
Gastroenterology-hepatology	10	8	1
Pneumology-allergology	10	9	1
Infectious diseases	15	19	4
Cardiovascular diseases	21	34	1
Diagnostics	5	3	2
Endocrinology-gynaecology-fertility-metabolism	28	27	2
Neonatology-paediatric intensive care	0	2	2
Immunology-rheumatology-transplantation	13	15	0
Psychiatry	9	0	0
Pain	2	9	0
Haematology-haemostaseology	18	9	1
Otorhinolaryngology	2	1	0
Oncology	19	19	1
Dermatology	10	14	2
Vaccines	12	2	1
Ophthalmology	8	5	0
Anaesthesiology	1	2	0
Nutrition	0	0	0
Other	7	16	2

** One PIP can cover several therapeutic areas*