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Human Medicines Development and Evaluation

Report to the European Commission

On companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this Regulation, covering the year 2010

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1. INTRODUCTION

1.1. Scope of the report

Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereinafter 'the Paediatric Regulation') was adopted on 12 December 2006. It was published in the Official Journal of the European Communities on 27 December 2006 and entered into force on 26 January 2007.

Article 50(1) states*: "On the basis of a report from the Agency, and at least on an annual basis, the Commission shall make public a list of the companies and of the products that have benefited from any of the rewards and incentives in this Regulation and the companies that have failed to comply with any of the obligations in this Regulation. The Member States shall provide this information to the Agency."*

This report covers the year 2010 and follows the same structure as the previous report prepared by the Agency for the European Commission which covered the period from the entry into force of the Paediatric Regulation, i.e. 26 January 2007 to 31 December 2009 (report published by the European Commission on 2 June 2010: http://ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm and on the Agency website). This report lists the companies and products that have benefited from any of the rewards and incentives in this Regulation both at the European Union and at national level. The report examines also the situation where companies have failed to comply with any of the obligations in this Regulation. Incentives available at EU level are supported by complementary national initiatives, such as fiscal incentives and funding of national research projects. Pursuant to Article 39(2) of the Paediatric Regulation, the European Commission published an inventory of national measures based on information received from 18 of 27 Member States on 30 July 2008. This report lists only the initiatives which have not been previously reported in this inventory or in the previous report.

1.2. Data collection

On 7 December 2010, the Agency sent a letter to all Member States requiring their contributions by 14 January 2011 for the preparation of this report (letter sent to all Head of Agencies and to the paediatric contact point in the National Competent Authorities, and copied to the respective Permanent Representatives of the Member States of the European Union). The letter contained the list of information to be provided (Annex 1). Reminders were also sent.

The Agency contacted the National Patent Offices of each Member State requiring by 17 January 2011 the list of medicinal products that had obtained in 2010 a 6-month extension of the Supplementary Protection Certificate (SPC) as a reward for the fulfilment of all conditions set in the Regulation. Information of medicinal products for which the extension of the SPC was pending, as well as those which do not have any SPC or patent which qualifies for an SPC was also requested (letter sent on 13 December 2010).

The Agency informed the Coordination Group for Mutual Recognition and Decentralised Procedure – human (CMDh).

In addition the Agency contacted DG Research to obtain information on the projects funded through the 7th framework programme (FP7) in the context of article 40 of the Paediatric Regulation.

Finally the Agency liaised with the EFTA States (European Free Trade Association) to obtain an update. Until December 2010, the Paediatric Regulation was still not part of the European Economic Area (EEA) Agreement and therefore not been implemented in Iceland, Liechtenstein and Norway.

Nonetheless Iceland and Norway have actively contributed to the work of the Paediatric Committee since its establishment. Iceland and Norway requested the submission of paediatric data according to Article 45 and 46 of the Paediatric Regulation and participate in the worksharing for the assessment of these data.

The Agency received contribution from most of the Member States and nearly all National Patent Offices. The response rate has increased compared to that for the preparation of the previous report. With one exception all National Patent Offices answered. Responses were received from 19 out of 27 National Competent Authorities. The quality of the responses is nonetheless variable, which may be due to the availability of a tracking system of the information at national level (Annex 2). This will need to be further addressed as the completeness of the report relies mainly on the contributions received, particularly from the Member States.

At the Agency level, the preparation of this report has also highlighted the need for further improving the way of collecting data both qualitatively and quantitatively.

1.3. Overview of the implementation of the Paediatric Regulation

Four years have elapsed since the entry into force of the Paediatric Regulation whose objectives are:
i) to increase the availability of medicines intended for children,

ii) to make information on those medicines widely available and

iii) to stimulate high quality paediatric research. This Regulation includes a set of obligations and rewards/incentives for industry to compensate the investment in paediatric development.

One of the pillars of the Regulation is the Paediatric Committee (PDCO) that is primarily responsible for reviewing and agreeing applications for paediatric investigation plans (PIPs) including deferrals, and/or waivers. Since its first meeting on 4 July 2007, the PDCO has performed efficiently as shown by the figures presented in the report. This has been possible thanks to the preparation and motivation of Committee members, who are supported for most of them by National Competent Authorities. Strikingly, all Committee members have actively participated in the review process, in full collaboration with the Agency secretariat, namely the Paediatric Medicines section of the Human Medicines Special Areas sector, which supports the Committee in its activities.

The Paediatric Regulation has created new tasks for the Agency and Member States, which had a major impact on the resources of the Agency as well as of the National Competent Authorities.

Most of the tasks have been achieved, and the legal deadlines have been met with success. Again this has been possible thanks to the cooperation of all partners and stakeholders.

Further information on the status of the implementation of the Paediatric Regulation can be found on the Agency website (Medicines for Children http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea).

2. COMPANIES AND PRODUCTS THAT HAVE BENEFITED FROM ANY OF THE REWARDS AND INCENTIVES IN THE REGULATION

2.1. Scientific advice

2.1.1. Advice from the Agency

In accordance with Article 26 of the Regulation, the Agency provides free scientific advice for any request containing questions on the paediatric development. Scientific advice and protocol assistance (the special form of scientific advice available for the development of designated medicines for 'orphan' or rare diseases) may be given to companies on the design and conduct of trials necessary to demonstrate the quality, safety and efficacy of the medicinal product. The advice is provided by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use (CHMP) and is adopted by the CHMP. For the paediatric requests, members of the PDCO are routinely involved in the procedure as experts. This is part of the effective collaboration established under the Executive Director's responsibility (Article 3(3) of the Paediatric Regulation).

Applicants may choose to request scientific advice either before submitting an application for a PIP to help them to prepare such plan, or after the Agency decision on a PIP to discuss, for example, combined adult and paediatric development in light of the PIP requirements. Simultaneous applications for a PIP and request for a scientific advice are discouraged, as the procedures' overlap creates unnecessary duplication of work. Active collaboration between the PDCO and the Scientific Advice Working Party is fully operational, minimising the theoretical risk of divergences which could arise as the two groups may not have the possibility to discuss all details of the applications.

In contrast with PIP decisions, scientific advice/protocol assistance received from the Agency is not binding, either on the Agency/CHMP or the sponsor, with regard to any future marketing-authorisation application for the product concerned.

Since the entry into force of the Paediatric Regulation, the number of paediatric only requests has increased steadily, with a total of 32 procedures in 2010. The breakdown figures are displayed in Table 1.

Table 1. Number of requests for paediatric scientific advice (SA)/protocol assistance (PA) and follow-ups (i.e. all questions relate to the development of the product in children)

Total Scientific Advice requests	**332**	**Total Protocol Assistance requests**	**68**
Number of **paediatric only scientific advice**	19	Number of **paediatric only protocol assistance**	6
Number of **paediatric only follow-up scientific advice**	4	Number of **paediatric only follow-up protocol assistance**	3

The figures correspond to procedures with a start date in 2010.

As information on scientific advice is considered commercially confidential, the list of the companies and products that have benefited from this incentive is not included in this report but can be found as a separate document.

A high number of so-called "mixed" scientific advice/protocol assistance requests, i.e. covering both adult and paediatric development, have also been submitted for which members of the PDCO are

generally involved. Compared to 2009 where 35 procedures were submitted, the figure increased to 48 in 2010. The breakdown figures are displayed in Table 2.

As "mixed" scientific advices are not free of charge for the adult part, and as protocol assistance is funded by the EU's special contribution, they are not considered part of the incentives provided by the Paediatric Regulation. Therefore the corresponding list of companies and products that have submitted such "mixed" requests is not reported.

Table 2. Number of "mixed" requests for scientific advice/protocol assistance and follow-up (i.e. including questions on both adult and paediatric development)

Number of mixed advice request	25
Number of mixed advice follow-up scientific advice	6
Number of mixed protocol assistance	12
Number of mixed follow up protocol assistance	5

The figures correspond to procedures with a start date in 2010.

2.1.2. Advice from the National Competent Authorities

Some National Competent Authorities also provide national scientific advice to help companies in their paediatric development. In 2010, a few Member States have done so, mainly for mixed scientific advice (Table 3). In the United Kingdom, there is a fee waiver offered for paediatric-only advice. The other Member States have not introduced a provision for fee-waiver for paediatric-only scientific advice.

Table 3. Number of national scientific advice provided by Member States in 2010

Member States	Number of paediatric only scientific advice	Number of mixed advice
Belgium	-	7
Germany	-	23
Sweden	2	7
United Kingdom	3	7

2.2. Paediatric Investigation Plans – Waiver

Applications

From January 2010 to December 2010, the PDCO received 326 validated applications of which 58 (18%) were requests for a full waiver for all conditions and all subsets of the paediatric population.

Of the 327 validated applications covering 403 indications:

- 280 applications (73 %) referred to medicinal products not yet authorised in the EU at the time of the entry into force of the Regulation (so called "Article 7 applications").

- 43 applications (24%) referred to products already authorised, still under patent or supplementary protection certificate, in view to submitting a variation/extension for a new indication, pharmaceutical form or route of administration (so called "Article 8 applications").
- 4 applications (3%) referred to an off-patent product developed specifically for children with an age-appropriate formulation (so called "Article 30 applications", with a view to submitting a Paediatric Use Marketing authorisation or PUMA).

In the first year of the implementation of the Regulation, most of the applications were "Article 8 applications". After about a year, the balance changed towards a higher proportion of "Article 7 applications". This change is confirmed in 2010. For "Article 30 applications", the number of applications submitted is still very low.

Of the 326 valid applications for PIP/deferral/waiver from all companies, 18 applications were from Small and Medium-Sized Enterprises (SMEs).

The Agency experienced in 2010 a considerable increase in the number of applications compared to the previous years, due in part to the change in the German Law which now requires that allergens immunotherapy medicinal products (formerly prescribed on a "Named-Patient basis") for the treatment of the most prevalent allergies obtain a marketing authorisation under the enactment of the German Regulation for Therapy Allergens; all applications for allergens marketing authorisation had to be submitted by 1 December 2010 to the German authorities. Consequently, according to Article 7 of the Paediatric Regulation, all these products had to have an Agency decisions. Out of the 326 applications, 115 applications were for allergen medicinal products. To efficiently manage the anticipated workload in a short timeframe, the PDCO agreed on a document, a so-called standard PIP, in November 2009 (revised in February 2010 after an expert meeting), which defined a standard set of measures that applicants could include in their application for a PIP in order to speed up the evaluation procedure.

Since the beginning of 2010, the Agency has offered pre-submission meetings to SMEs and to those companies developing a product intended to treat pain. To date, about 10 pre-submission meetings have taken place (by teleconference), half of them for SMEs; none related to products developed for pain. The other meetings concerned mostly the preparation for re-submission of applications further to a withdrawal. The Agency has now opened pre-submission discussions to all types of applications.

Opinions

The PDCO adopted in 2010:

- 52 positive opinions on product-specific waivers (20% of all opinions), of which 7 were submitted by SMEs.
- 201 positive opinions on a PIP (77%), of which 10 were submitted by SMEs. An opinion on a PIP may also contain a deferral and/or waiver of the obligation to gather clinical trial data in certain age groups of children. Of those 201, 101 opinions were for allergen products.
- 7 negative opinions (3 %).

The overall success rate is very high with 84% of positive outcomes (when including "late" withdrawals and negative opinions in the negative outcomes).

The content of the decisions issued by the Agency following PDCO opinions is published in a summarised form and can be found on the following webpage: http://www.ema.europa.eu/htms/human/paediatrics/decisions.htm. The decisions can be searched using various criteria including condition/disease.

Class Waivers

In accordance with the Paediatric Regulation, the PDCO has adopted a list of conditions that occur only in the adult population and for which all classes of medicinal products intended for treatment, would be exempt from the requirements for a PIP and/or a product-specific waiver. This is contributing to reducing the administrative burden for applicants and for the Agency/Paediatric Committee.

The list has to be updated at least once a year. In 2010, the PDCO has updated the list twice (in April 2010 and December 2010).

The Agency decisions on the PDCO opinions on the class waivers can be found on the following webpage: http://www.ema.europa.eu/htms/human/paediatrics/decisions.htm.

Modifications of agreed PIPs

As anticipated, the number of requests for modification of an agreed PIP has increased dramatically in 2010 with 110 applications for modification received. In the same year, the PDCO has adopted 103 positive opinions on modifications of an agreed PIP and 4 negative ones.

It is expected that the number of modifications will continue to increase significantly over the coming years. Indeed in order to establish an early dialogue between the sponsor and the PDCO, the Paediatric Regulation sets a deadline for the submission of the application for a PIP and/or waiver at an early stage of the development of the medicinal product. As the development of medicinal products is a dynamic process depending on the results of ongoing studies and trials, it is estimated that 3 to 5 modifications will be submitted per agreed PIP.

2.3. Compliance statement included in a marketing authorisation

Once a PIP is completed, there is a need to check compliance when Article 7 or 8 do apply, i.e. to verify that the measures set out in the Agency decision have been carried out accordingly, including its timelines. This is done as part of validation of applications for either a marketing authorisation, or a variation/extensions or prior to the submission of such application on request from the applicant to the PDCO.

As a pilot phase and until now, the National Competent Authorities have requested the PDCO to check the compliance check on their behalf.

The PDCO issues opinions on compliance once the PIP is fully completed. In 2010, 9 applications for compliance check have been received. The PDCO adopted 9 positive opinions on compliance with an agreed PIP. There was no negative opinion on compliance.

The Agency has also received 38 applications for a compliance check for a partially completed PIP.

2.3.1. Compliance statement for centrally-authorised medicinal products

In 2010, 2 companies submitted the results of all studies performed in compliance with an agreed PIP in accordance with Article 8 of the Paediatric Regulation. This resulted in a compliance statement included in the marketing authorisation issued by the European Commission (Table 4). Further information can be found in the European Public Assessment Reports of these medicinal products which are available of the Agency website.

Table 4. List of companies and products with a compliance statement (centrally approved)

Companies	Products: invented name (international non-proprietary name)
Bristol-Myers Squibb Pharma EEIG	Orencia (abatacept) Commission decision issued on 20/01/2010 (EMA/H/C/000701/II/0024)
Novartis Europharm Ltd	Zometa (zoledronic acid) Commission decision issued on 25/01/2010 (EMEA/H/C/336/II/31)

2.3.2. Compliance statement for medicinal products authorised through national/decentralised/mutual recognition procedure, including those subject to Article 29 of the Paediatric Regulation

The list of companies and products which have benefited from the inclusion of a compliance statement in the marketing authorisation is presented in Table 5. So far, this list includes only products which have been subject to an "Article 29" procedure of the Paediatric Regulation. This procedure allows companies to submit an application to the Agency for a new indication (including in children), pharmaceutical form or route of administration for medicines that are already authorised by Member States. Paediatric data supporting such applications have to be generated in accordance with an agreed PIP and are assessed by the CHMP. This results in the adoption of an EU harmonised decision on the use of the medicinal product in the paediatric population. Once the Commission Decision is adopted, the Member States are required to vary the terms of the existing marketing authorisation according to the Decision, within 30 days of its notification. The list, as received by Member States, of medicinal products authorised and/or varied through national/decentralised/mutual recognition procedure which had a compliance statement introduced in the marketing authorisation is displayed in Annex 3.

Table 5. Commission Decision for medicinal products for human use, pursuant to Article 29 of Regulation (EC) No 1901/2006, with a compliance statement

Companies	Products: invented name (international non-proprietary name)
Novartis Pharma AG	Diovan and associated names (valsartan) Commission decision issued on 19/04/2010 (EMEA/H/A-29-PAD/1219 and 1220)
Pfizer Limited	Sortis and associated names (atorvastatin) Commission decision issued on 01/07/2010 (EMEA/H/A-29-PAD-1253-A-29-PAD-1254-A-29-PAD-1255)
Pfizer Limited	Xalatan and associated names (latanoprost) Commission decision issued on 15/10/2010 (EMEA/H/A-29 – PAE/1270)

Further information on these procedures can be found on the Agency website.

2.4. Extension of the Supplementary Protection Certificate/Market Exclusivity

In order to be eligible for a 6-month extension of the Supplementary Protection Certificate (SPC), medicinal products need to meet several conditions (including that the SPC extension application is made in time and complies with the provisions of Regulation (EC) No 469/2009):

i) a compliance statement with the agreed PIP included in the marketing authorisation;

ii) a marketing authorisation for the medicinal product in all Member States;

iii) an Summary of Product Characteristics (SmPC) with results of all the studies conducted in compliance with the agreed PIP. This applies even if the results fail to lead to the authorisation of a paediatric indication.

Extensions of the SPC are granted by the National Patent Offices. Therefore the companies have to file for an SPC extension with the National Patent Offices of each and every Member State where the active substance of the medicinal product is protected by a basic patent or an SPC. Annex 4 compiles the information received from National Patent Offices on those products which, having fulfilled the paediatric requirements, were granted a 6-month extension of the Supplementary Protection Certificate in 2010.

For orphan medicinal products, the reward is a 2-year extension of market exclusivity. So far no orphan medicinal product has benefited from this reward. Orphan medicines represent approximately 20% of the applications for PIPs and waivers.

For Paediatric Use Marketing Authorisation (PUMA), the Paediatric Regulation has defined data and marketing protection periods. So far no PUMA has yet been authorised, so no company has benefited from this reward. The first application for PUMA has been submitted in 2010 through the centralised procedure. The evaluation procedure is currently ongoing and expected to be completed in 2011.

2.5. Marketing authorisation granted or varied with mention of waiver or deferral in the Summary of Product Characteristics

According to Article 28 of the Paediatric Regulation, the results of the studies performed in compliance with the agreed PIP, even those which failed to lead to an indication, should also be reflected in the SmPC. In addition any Agency decision on a waiver or deferral is to be recorded in the Summary of Product Characteristics (SmPC) and if appropriate in the package leaflet of the medicinal product concerned, when the initial marketing authorisation is granted (Article 7) or when the marketing authorisation is varied to include a new indication, including paediatric indication, new pharmaceutical form or new route of administration (Article 8). In 2010, 28 centrally authorised medicinal products (new MA and variation/extension) included such a mention (table 6). The Agency has identified five cases where such mention has been omitted (see section 3.5).
Further information on these medicinal products and product information can be found in the European Public Assessment Reports available on the Agency website.

Table 6. List of centrally authorised products and companies for which a deferral/waiver statement has been included in SmPC

Invented name	International non-proprietary name	Marketing authorisation holder	Full waiver	Deferral	Date of Marketing Authorisation (MA)/ Variation (V)
Daxas	Roflumilast	Nycomed GmbH	x		MA: 05/07/2010
Elonva	Corifollitropin	N. V. Organon		x	MA: 25/01/2010
Silodyx/ Urorec	Silodosin	Recordati Ireland Ltd.	x		MA: 29/01/2010
Revolade	Eltrombopag	GlaxoSmithKline Trading Services Ltd		x	MA: 11/03/2010
Ristaben	Sitagliptin	Merck Sharp & Dohme Ltd		x	MA: 15/03/2010
Menveo	Meningococcal group a, c, w-135 and y conjugate vaccine	Novartis Vaccines and Diagnostics SRL		x	MA: 15/03/2010

Duocover	Clopidogrel/ acetylsalicylic acid	Bristol-Myers Squibb Pharma EEIG	x		MA: 15/03/2010
Duoplavin	Clopidogrel/ acetylsalicylic acid	Sanofi Pharma Bristol-Myers Squibb SNC	x		MA: 15/03/2010
Ristfor	Sitagliptin / metformin hydrochloride	Merck Sharp & Dohme Ltd	x		MA: 15/03/2010
Arzerra	Ofatumumab	Glaxo Group Ltd	x		MA: 19/04/2010
Prolia	Denosumab	Amgen Europe B.V.	x		MA: 26/05/2010
Votrient	Pazopanib	Glaxo Group Ltd	x		MA: 14/06/2010
Ozurdex	Dexamethasone	Allergan Pharmaceuticals Ireland	X		MA: 27/07/2010
Byetta	Exenatide	Eli Lilly Nederland B.		x	V: 06/08/2010
Vpriv	Velaglucerase alfa	Shire Pharmaceuticals Ireland Ltd	x	x	MA: 26/08/2010
Brinavess	Vernakalant hydrochloride	Merck Sharp & Dohme Ltd.	x		MA: 01/09/2010
Sycrest	Asenapine	N.V. Organon		x	MA: 01/09/2010
Raspican	Regadenoson	Gilead Sciences International Ltd.		x	MA: 06/09/2010
Twynsta	Telmisartan / amlodipine	Boehringer Ingelheim International GmbH	x		MA: 07/10/2010
Ruconest	Conestat alfa	Pharming Group N.V.		x	MA: 28/10/2010
Sutent	Sunitinib	Pfizer Ltd	x	x	V: 29/11/2010
Brilique/ Possia	Ticagrelor	Astra-Zeneca AB	x		MA: 03/12/2010
Sprycel	Dasatinib	Bristol Myers Squibb EEIG		x	V: 06/12/2010
Invega	Paliperidone	Janssen-Cilag International NV	x		V: 13/12/2010
Baraclude	Entecavir	BRISTOL-MYERS SQUIBB PHARMA EEIG		x	V: 16/12/2010
Tasigna	Nilotinib	Novartis Europharm Ltd		x	V: 20/12/2010

For medicinal products authorised through national/decentralised/mutual recognition procedure, the information on those that have been granted a marketing authorisation or varied and that include such a statement in their SmPC has only been received from the United Kingdom (table 7).

Table 7. List of products authorised in the United Kingdom and companies for which a deferral/waiver statement has been included in SmPC

(N= national – MRP = Mutual Recognition, RMS)

Marketing authorisation holder	Invented name	INN	Statement on waiver (presence)	Statement on deferral (presence)	Date of marketing authorisation/variation
Novartis Pharmaceuticals UK Limited Frimley Business Park Surrey GU16 7SR - PL 00101/0956	Diovan 3mg/ml oral solution	Valsartan	present	n/a	28/05/2010 (N)
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR - PL 00101/0599	Diovan 40mg Tablets	Valsartan	present	n/a	28/05/2010 (MRP-RMS-SWEDEN)
Novartis Pharmaceuticals UK Limited, Frimley Business Park Surrey GU16 7SR - PL 00101/0600	Diovan 80mg Tablets	Valsartan	present	n/a	28/05/2010 (MRP-RMS-SWEDEN)
Novartis Pharmaceuticals UK Limited, Frimley Business Park Surrey GU16 7SR - PL 00101/0601	Diovan 160mg Tablets	Valsartan	present	n/a	28/05/2010 (MRP-RMS-SWEDEN)
Novartis Pharmaceuticals UK Limited. Frimley Business Park Surrey GU16 7SR - PL 00101/0726	Diovan 320mg Tablets	Valsartan	present	n/a	28/05/2010 (MRP-RMS-SWEDEN)
Pfizer Ireland Pharmaceuticals Pottery Road, Dun Laoghaire Co Dublin, Ireland - PL 16051/0006	Lipitor 5mg Chewable tablets	Atorvastatin (as calcium trihydrate)	present	n/a	03/11/2010 (N)
Pfizer Ireland Pharmaceuticals Pottery Road, Dun Laoghaire Co Dublin, Ireland - PL 16051/0007	Lipitor 10mg Chewable tablets	Atorvastatin (as calcium trihydrate)	present	n/a	03/11/2010 (N)
Pfizer Ireland Pharmaceuticals Pottery Road, Dun Laoghaire Co Dublin, Ireland - PL 16051/0008	Lipitor 20mg Chewable tablets	Atorvastatin (as calcium trihydrate)	present	n/a	03/11/2010 (N)
Pfizer Ireland Pharmaceuticals Pottery Road, Dun Laoghaire Co Dublin, Ireland - PL 16051/0009	Lipitor 40mg Chewable tablets	Atorvastatin (as calcium trihydrate)	present	n/a	03/11/2010 (N)
Pfizer Ireland Pharmaceuticals Pottery Road, Dun Laoghaire Co Dublin, Ireland - PL 16051/0001-3 & 5	Lipitor 10, 20, 40mg & 80mg tablets	Atorvastatin (as calcium trihydrate)	present	n/a	16/11/2010 (N)

2.6. Price/reimbursement benefits

The Agency has not received any new information on potential price or reimbursement benefits for paediatric medicines in the Member States compared to what was reported in the previous report, apart from Hungary where medicinal products included in the National Immunisation Programme are provided free of charge to the children by the Hungarian government.

2.7. Research incentives

2.7.1. EU Framework Programme

Thanks to the Paediatric Regulation (Article 40), funding of studies into off-patent medicinal products (i.e. those not covered by a patent or supplementary protection certificate) has been made available since 2007. This funding was provided through the EU Framework Programmes for Research and Technological Development, and covered the development of off-patent medicinal products with a view to the submission of an application for a PUMA. In order to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population and in agreement with DG Research, the PDCO has adopted then revised a priority list of off-patent products for which studies are required in advance of each call.

The European Commission has launched five calls within the 7th Framework Programme. The 4th call which was launched mid 2009, resulted in 2010 in the selection of 3 projects to be funded for about 16 millions Euros. For this 4th call, the Commission, with the involvement of the Agency, established greater collaboration with the US Food and Drug Administration and National Institute of Health on research in paediatrics, thereby avoiding unnecessary duplication of studies. Further details as provided by DG Research on the projects funded through the 4th call can be found in Annex 5. Further information can be found on the Community Research and Development Information Service (CORDIS) website (http://cordis.europa.eu/).

In July 2010, the Agency published the revised priority list for studies into off-patent paediatric medicinal products for the 5th Call 2011 of the 7th Framework Programme of the European Union.

It is hoped that funding will remain available for studies into off-patent medicines currently used off-label for children.

2.7.2. European Network of Paediatric Research at the European Medicines Agency

The Paediatric Regulation required the setting up of a European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population, to be coordinated by the Agency. Further to the adoption of the implementing strategy for the network by the Agency Management Board on 15 January 2008, the European Paediatric Research Network (Enpr-EMA) has been set up.

The operational centre of Enpr-EMA is a coordinating group which is responsible for implementing the short- and long-term strategy of the network. In May 2010, participants from 38 national research networks and clinical trial centres and the European Medicines Agency agreed on an organisational structure for the network. Also in May 2010, membership of Enpr-EMA was opened to networks that fulfill the requirements laid down as a set of recognition criteria, agreed and published following a public consultation. These recognition criteria establish quality criteria that networks should meet in

order to be able to work together and to perform high quality ethical research with children. Although the network will not fund studies or research per se, its objectives are to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, in order to avoid duplication of studies in children. Pharmaceutical companies will therefore benefit from having such a network as a tool for the development of their medicinal products in children. The network will also contribute to the development of paediatric research in Europe and beyond.

2.7.3. Inventory of paediatric needs

The PDCO adopted in December 2010 a report on the survey of all paediatric uses of medicinal products in Europe, performed in accordance with Article 43 of the Paediatric Regulation. This survey is available on the Agency website.

Based on both the survey results and the existing lists of paediatric needs established by the former Paediatric Working Party (PEG) of the Agency/CHMP, the PDCO is working on establishing an inventory of paediatric needs as per the Regulation. This will help identifying paediatric research priorities.

2.7.4. National initiatives

In the previous report, initiatives taken at national level by some Member States for funding the research and development of medicinal products for paediatric use were listed. For this report the National Competent Authorities were asked to mention any new information or any changes compared to what was reported in the previous report. The following answers were provided.

Belgium

The Belgian Paediatric Society granted funding to establish the list of paediatric clinical research centres and researchers existing in Belgium (as a basis for the Belgian paediatric network).

Finland

Although not specific to paediatrics, funding can be applied from e.g. Tekes – the Finnish Funding Agency for Technology and Innovation (tekes.fi) or SITRA, the Finnish Innovation Fund (sitra.fi).

Italy

The Programme on Independent research on drugs funded by the Italian Medicines Agency AIFA described in the last report is still in place and the contents and finalities are the same as previously described. The 2009 Programme is still ongoing and only preliminary results are available. The projects to be funded have not yet been selected.

In the tables below the list of research areas and specific topics to be funded by AIFA in the 2009 Call For Proposal are reported. Some of these topics are specifically dedicated to paediatric research, whilst some are more general but could include the paediatric population, depending on the clinical topic if applicable to paediatrics.

Area A. Comparisons among drugs and among therapeutic strategies for the treatment of clinical conditions of relevant interest for public health and the NHS

This area specifically refers to phase 3 and 4 randomised controlled study. The studies must involve, normally, only drugs categorised in group A or H and they should examine the risk and benefit profile of single drugs or of pharmacological strategies. The comparison can focus on drug usage and non pharmacological interventions. Of particular relevance are the studies that involve complex patients and/or vulnerable subjects (children, woman, elderly) because of the sample size and the heterogeneity of the received treatment and because of the studies on drugs usage, whether compatible with the project rationale, that are not patented, drugs which patent expires soon and low cost drugs.

Area	Topic	Description
A	1	Comparisons among drugs or among therapeutic strategies in paediatrics: optimization of the use of drugs for the respiratory apparatus, gastro-enteric and cardiovascular. Note: Considering the lack of specific scientific knowledge in children, this research topic refers not only to clinical trials aiming at defining the comparative efficacy of drugs, but also to the evaluation of different dosage forms and drug formulations suitable for paediatric use.
A	2	Comparisons among new antitumorigenic drugs and among standard therapeutic strategies focusing on clarifying the direct value of the new drugs and the correct usage in oncology. Note: the comparison between therapeutic strategy includes the optimisation of drug combination and sequences definition, dosage and rout of administration.
A	3	Comparisons among therapeutic strategies for the treatment of spasticity in neurology. Note: Particularly attention will be given to studies testing the following comparisons: A) between different drugs; B) between different routes of administration; C) between drugs and other therapeutic strategies. Validated and reproducible outcome measures, including scales for the evaluation of the quality of life, should be used in these trials.
A	4	Assessment of the benefit-risk profile of different therapeutic strategies used in intensive care, especially focusing on prevention and treatment of antibiotic resistance, multi-organ failure and sepsis. Note: For antibacterial drugs, the impact on the development of drug resistance should be evaluated.

Area B. Pharmacoepidemiological studies aimed at defining the benefit-risk profile of treatments and the impact of strategies for improving the appropriateness of drug use

This area focuses on studies of commercially available drugs of large and /or increasing usage, categorised in group A or H, that are motivated by the need of expanding the knowledge on the drug risks and evaluating the drug risk and benefit profile. Studies on group C drug category with specific safety study objectives, can be considered of interest. This area is also related to studies that focus on evaluating strategies that impact on improving the appropriateness of drug use. The studies can be designed, according to the characteristic of the study objectives, as experimental randomised or observational studies (descriptive-only studies are not admitted). Studies that involve complex patients and/or vulnerable subjects (i.e. children, woman, elderly) will be considered of a particular relevance also because of the sample size and the heterogeneity of the received treatment. In particular, the studies that focuses on improving the appropriateness of drug use should be designed to allow a comparative intervention evaluation (i.e with agonist controls or "before-after" evaluation) with process markers and, whether possible, clinical and/or subjective endpoints.

Area	Topic	Description
B	1	Strategy to optimise the use of equivalent (generic) drugs in Italy Note: Particularly attention will be given to studies that focus on the following: A) comparison between different generic drugs and the reference drugs via switching, pharmacokinetic, biomarker studies; B) understanding the reasons for a sub-optimal use of generic drugs in Italy; C) intervention to improve the use of generic drugs by the general practitioner and patient.
B	2	Assessment of the appropriateness use of antibiotic, antihistamines, cortisone-like, antidiarrheal in paediatric use. Note: Studies with a prospective design and medium-long term objectives will be considered as of high importance.
B	3	Assessment of the benefit-risk profile of therapeutic strategies adopted in the elderly population with polypathology with the aim of treatment simplification and reduction of drug interactions. Nota: This research topic refers to studies conducted in elderly patients (aged ≥ 65 years) presenting a cardiovascular disease associated with other pathologies such as diabetes, neurological and/or psychiatric diseases, endocrine, respiratory diseases and digestive system diseases. Priority will be given to studies with an experimental design or a prospective cohort design.
B	4	Assessment of the benefit-risk profile of psychoactive drugs used for sedative-hypnotic scope in elderly population and in oligophrenic patients affected by sleep and behavioural disorders. Nota: The clinical studies on antipsychotic, antidepressants, benzodiazepines hypnotic drugs and others aimed to a better understanding of the risk and benefit profile are of reference.

In the previous report, Framework Agreements on Research & Development established by AIFA were described. In 2010, no such Framework Agreements have been established by AIFA.

Malta

Research on medicinal products inclusive for paediatric use can be funded under the National Research and Innovation Programme set up by the Malta Council for Science and Technology. However there is no specific incentive in place for developing paediatric medicines.

United Kingdom

As already reported in the previous report, the UK Government provides support for the NIHR Medicines for Children Research Network (MCRN), which provides infrastructure across all of England to support the development and delivery of paediatric studies although not direct funding.

From its establishment in 2006 to the end of 2010, the MCRN has adopted (supported) a total of 108 industry studies, 37 of which were taken on in 2010 (approx 90% related to PIPs). 122 public (academic/health service) studies have been taken on by the Network, with grants awarded under a number of European, UK and other research programmes (further information can be found on the webpage http://www.mcrn.org.uk/ and MCRN-supported studies: http://public.ukcrn.org.uk/Search/Portfolio.aspx?level1=4).

2.8. Authorisation of paediatric clinical trials

The European Medicines Agency has no responsibility in the authorisation of clinical trials in the European Union. This is under the responsibility of the Member States according to Directive 2001/20/EC. It has to be kept in mind that one of the provisions of the Paediatric Regulation is to make public the information on paediatric trials entered into the EU Database on Clinical Trials (EudraCT). The Agency with the PDCO have been working with the European Commission to produce guidance on the protocol-related information and on the results concerning paediatric clinical trials to be entered as well as the information to be made public. It was originally planned the first roll-out of publicly available protocol-related information would be available in September 2010, to be followed by results-related information. This has been delayed until further notice for technical reasons.

So far the figures from EudraCT have shown a moderate increase in the last years in the number of clinical trials including children conducted in the EEA. It is expected that a further increase will occur over time when more PIPs are implemented. In 2010, 10 % of the clinical trials in the EEA involved children (birth to 18 years). Of those, 56 % were clinical trials enrolling only patients less than 18 years of age.

For those Member States who have answered the question, no fee reduction/fee waiver or priority review has been introduced with respect to paediatric products. In Ireland there is a fee waiver for investigator-sponsored clinical trials but this is not specific to paediatric trials. Similarly in Sweden academic studies can, under certain conditions with no or very limited funding, get a waiver for fee although this is not specific to paediatric trials.

Collaboration between the PDCO and the Clinical Trials Facilitation Group (CTFG) has been initiated to resolve potential issues of divergences between PDCO and national competent authorities regarding trials from the PIP that the competent authorities are authorising. In particular, the CTFG has been given direct access to the paediatric database and the PIP content to facilitate their work.

2.9. Procedures for marketing authorisation

The existing procedures for the granting of a marketing authorisation of medicinal products and for extension of the marketing authorisation to add a new indication, pharmaceutical form and/or route of administration have not been changed by the Paediatric Regulation. The Paediatric Regulation has however introduced a new type of marketing authorisation: the paediatric-use marketing authorisation (PUMA); it may be requested for a medicine which is already authorised or not (in all cases no longer covered by intellectual property rights i.e. patent or supplementary protection certificate), and exclusively developed for use in children in compliance with an agreed PIP. The submission of an

application for a PUMA is automatically eligible to the centralised procedure but it may also be made through the national/decentralised/mutual recognition procedures.

At the Agency level, there are no specific provisions to either prioritise or accelerate the review of medicinal products intended for use in children, including PUMAs. However the CHMP may consider shortening the review time for such products, in accordance with the accelerated assessment procedure.

With respect to fees, the Agency has not introduced any fee reductions for centralised procedure for medicinal products indicated in children or for extension of the marketing authorisation to add a new paediatric indication, pharmaceutical form and/or route of administration relevant for paediatric use. However, the Agency is granting a partial exemption from the payment of the fees laid down in the Fee Regulation for PUMA applications submitted under Article 30 of Paediatric Regulation. In 2010, one company submitted an application for PUMA and benefited from this fee reduction. The evaluation procedure is still ongoing.

The majority of the Member States have no fee reduction for the submission of applications for medicinal products indicated for children, including PUMA and have no priority review of these applications. The United Kingdom has a fee waiver applied in certain cases for products developed specifically for paediatric use, for example for a new paediatric formulation or extension of indications into the paediatric population. Although applications have been received which have been eligible for a fee waiver, none have yet resulted in a marketing authorisation.

2.10. Article 45/46 of the Paediatric Regulation

2.10.1. Article 45

In accordance with Article 45 of the Paediatric Regulation, marketing authorisation holders were required to submit to the competent authorities all paediatric studies completed by the date of entry into force of the Regulation. These studies were to be submitted by 26 January 2008. Upon assessment of the data, the competent authority may update the SmPC and package leaflet and may vary the marketing authorisation.

- For centrally authorised medicinal products, as mentioned in the previous report, data have been submitted for approximately 60 medicinal products. In 2010, the CHMP completed the assessment of the data for the last medicinal products and for 2 of them recommended changes in their Summaries of Product Characteristics (SmPC). In addition in 2010, the SmPC of 2 products have been varied as a consequence of the assessment performed in 2009 of data submitted. The list of products and the resulting amendments of the SmPCs is presented in Annex 6. The Agency will publish in 2011 all assessment reports of studies submitted through Article 45.
- For products authorised through national/decentralised/mutual recognition procedure the extent of information received has been enormous. Information has been received for approximately 1000 active substances, with several documents for each of them (some may relate to the same study). To cope with the workload, there is an ongoing worksharing exercise between Member States and the assessment is being performed in waves.
  In 2010, 4 additional waves have been agreed to be included in the worksharing, corresponding to 59 substances (6 to 9th waves). The assessment of the data has been finalised for 44 active substances (substances coming from different waves). The list of substances and resulting recommended amendments of the SmPCs for the products containing these substances for which a

public assessment report is already published are presented in Annex 6[1]. Further information can be found on the CMDh webpage (http://www.hma.eu/99.html).

2.10.2. Article 46

In accordance with Article 46 of the Paediatric Regulation, a marketing authorisation holder (MAH) has to submit to the Competent Authority any MAH-sponsored studies involving the use in the paediatric population of an authorised medicinal product, whether or not they are part of a PIP, within 6 months of completion.

- For centrally authorised products, 60 procedures of evaluation of studies submitted through this Article have been finalised in 2010. This figure may cover the same study(ies) submitted for multiple applications. Out of these 60 procedures, the CHMP recommended a change in the product information in only 9 cases. In 2 of them, the data have submitted directly through a variation procedure. The Agency will further work with the Committee to ensure that relevant information for the use of medicinal products in the paediatric population is reflected in the product information. The list of products and the resulting amendments of the SmPCs is presented in Annex 7.
- For nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, a total of 56 studies were submitted in 2010. The assessment has been finalised for 19 products. A public assessment report has already been published for 13 of these studies, recommending for 6 of them to amend the SPCs. The list of products and resulting amendments of the SmPCs for those products are presented in Annex 7[2]. Further information can be found on the CMDh webpage.

When regulatory action is necessary (i.e. in case amendments to SmPC, labelling and/or PL are identified by the MAH) MAHs are advised to submit straightaway a variation containing the Article 46 paediatric study(ies). In some cases it was agreed that the assessment of the data could be postponed if the MAHs intended to submit a variation procedure within a short period of time.

It is anticipated that the number of the Article 46 procedures will increase steadily over the next years.

[1] correct as at 31 January 2011
[2] correct as at 31 January 2011

3. FAILURE TO COMPLY WITH THE OBLIGATIONS SET IN THE PAEDIATRIC REGULATION

3.1. Submission of the PIP/waiver application to the PDCO

Article 16 of the Paediatric Regulation requires companies to submit applications for a PIP and/or a waiver for agreement no later than upon completion of the human pharmacokinetic (PK) studies in adults except when duly justified. It is considered that this corresponds approximately to the end of phase 1 for new medicines. This deadline has been included in order to ensure early dialogue between the sponsor and PDCO.

In the first years after the entry into force of the Regulation, companies submitted their application as soon as possible, but the overall development of the product was already beyond that stage for the majority, often reaching confirmatory (phase III) clinical trials in adults. As a consequence, the PDCO had to provide opinions on PIP applications when the 'proposed' paediatric trials and studies were already ongoing or even completed. In some submissions the plan was not considered satisfactory but could not be modified; the PDCO considered that requesting new studies would have led to performing mostly unnecessary studies in children. This was therefore not ethically acceptable despite the lack of proper information resulting from inappropriate, underpowered or insufficient trials. Furthermore, late submissions for PIPs or waivers may delay the submission or the validation of the applications for the marketing authorisation in adults, when the applicant does not have an Agency decision on time.

After 4 years, companies have now the full opportunity to submit a PIP or waiver application in accordance with the timelines indicated by the Paediatric Regulation.
In 2010, the Agency started to monitor the compliance with this provision of the Regulation. At the time of the submission of the PIP/waiver application for a new product, the applicants declare the date of completion of human PK studies in adults in the application form. Out of 132 applications that included such a date, 69% (91/132) were submitted later than this deadline; 74% (65/88) corresponded to late PIP applications and 59% (26/44) to late waiver applications. The median delay in applications was 19 months (22 months for PIPs and 18 months for waivers) with a range of 0-161 months (0 to 161 months for PIPs, and 0 to 92 months for waivers). The list of companies submitting applications in 2010 with a delay longer than 6 months is presented in Annex 8 (only applications for which an EMA decision has been adopted are listed).

Although the data on submission compared to completion of adult PK are not exhaustive and do not consider whether or not an acceptable justification has been provided, there is a signal that most companies, including companies which have submitted a sizeable number of applications may be late in the submissions of PIP/waivers applications in relation to adult development, and some have even completed all paediatric studies. While it is acknowledged that some learning process had to take place and that in some cases there may be a rational justifying a late submission, this situation seems to be prevalent. Therefore based on this signal the Agency will closely monitor the compliance to this requirement to be reported in the next report. In particular the company’s reasons for submitting the application later than upon completion of the human PK studies in adults will be assessed during the PIP/Waiver evaluation procedure.

3.2. Information exchange with the US Food and Drug Administration

Under the confidentiality arrangements with the FDA, the Agency is holding monthly teleconferences to discuss PIP applications and Written Requests or IND information, with a view to global development of medicinal products. The teleconferences were initiated in October 2007, and now include Japanese and Canadian observers. On several occasions, it appeared that companies had been withholding information on safety or ongoing trials to either of the participants. This information will be monitored next year.

3.3. Validation of application for marketing authorisation/extension

As set out in Article 7 of the Paediatric Regulation, applications concerning a medicinal product not authorised in the EEA on 26 July 2008, must include one of the following in order to be considered 'valid':

- The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP).

This means that the application will have to include the PIP decision but also the results in accordance with the agreed PIP.

- A decision of the Agency on a PIP including the granting of a deferral.

This means that the application will have to include the PIP decision including the deferral granted.

- A decision of the Agency granting a product-specific waiver.
- A decision of the Agency granting a class waiver on condition.

The same requirements as set out in Article 8 of the Paediatric Regulation, apply to applications submitted from 26 January 2009, for new indication(s), new pharmaceutical form(s) and/or new route(s) of administration concerning an authorised medicinal product protected either by a supplementary protection certificate or by a patent which qualifies for the granting of such a certificate:

So far it appears that no application falling under Article 7 or 8 has been validated without having complied with these requirements at the Agency or at national level.

3.4. Compliance with the paediatric requirements and rewards

So far there is no indication that a company has benefited from the reward without having complied with the paediatric requirements set in the Regulation.

3.5. Mention of the Decision on waivers or deferrals in the product information

As mentioned in section 2.5, there is a requirement set in Article 28(2) of the Regulation to include in the marketing authorisation granted or varied a statement on the waiver or deferral. The Guideline on the Summary of Product Characteristics revised in September 2009 is applicable since 1 May 2010. The Guideline indicates how to word statements on waivers and deferrals.

Five cases have been identified of centrally-authorised products falling under the requirement of Article 7 or 8 and for which a marketing authorisation was granted or varied in 2010, and for which this statement has been omitted.

- Arepanrix Pandemic Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals S.A. (marketing authorisation now withdrawn)
- Humenza Pandemic influenza vaccine (H1N1, split virion, inactivated, adjuvanted) Sanofi Pasteur S.A
- Mabthera (rituximab) Roche Registration Limited
- Viread (tenofovir disoproxil fumarate) Gilead Sciences International Ltd.
- Aflunov (Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics S.r.l.

The United Kingdom, which is the only Member State reporting information on those products authorised/varied through Mutual Recognition Procedure for which a mention of deferral and/or waiver has been mentioned in the SmPC, reported also 2 cases for which the inclusion of such statement has been omitted.

- Sativex (Delta-9-tetrahydrocannabinol Botanical Drug Substance (THC BDS) [Tetranabinex] and Cannabidiol Botanical Drug Substance (CBD BDS) [Nabidiolex], as extract of *Cannabis sativa)* GW Pharma
- Livazo Pitavastatin Kowa Pharmaceutical Europe Company Ltd

For all these cases identified, it is planned to correct the situation at the next regulatory procedure involving an amendment of the Summary of Product Characteristics.

3.6. Annual reports on deferrals

Article 34.4 of the Paediatric Regulation states that "in the case of a deferral, the marketing authorisation holder shall submit an annual report to the Agency providing an update on progress with paediatric studies in accordance with the decision of the Agency agreeing the paediatric investigation plan and granting a deferral".

The Agency has published guidance and a form for the electronic submission of the reports, and has received 31 annual reports on deferral in 2010.

In 2010 the Agency has identified a few examples which suggest that the companies have not progressed with the paediatric studies in accordance with the agreeing the paediatric investigation plan. From this year, the Agency will therefore closely monitor the fulfilment with such requirement and will analyse the progress with the paediatric studies as agreed in the PIP, especially with respect with the time-limits specified for the initiation and/or the completion of the measures, to report on those companies which do not comply.

4. CONCLUSION

This 2nd report covers the year 2010, which corresponds to the 4th year since the entry into force of the Paediatric Regulation.

Compared to the first years of implementation, the reflection and planning of the development of a medicinal product in children is now part of the development in adults. Applicants and the EMA/Paediatric Committee have established procedures and interactions, More paediatric information is included in the product information, although this could be increased through opportunities like the submission of studies under Article 46.

In terms of number of authorised products for paediatric use, a large number of paediatric developments have been deferred, especially for new products but the number is expected to increase following an increase in paediatric trials. The Regulation is stimulating the conduct of high-quality ethical research, in particular through the European network Enpr-EMA, which is established.

Transparency has been significantly increased with the publication of decisions on PIPs and Waivers, publication of paediatric assessment reports following the ongoing worksharing for studies submitted under article 45, and will continue with increased access to EudraCT and clinical trial data generated by research.

As compensation for the cost and burden of paediatric development obligations, the Regulation includes rewards and incentives. The number of companies which have benefited from an extension of the Supplementary Protection Certificate in some Member States is increasing although this number may still be considered limited. To date, no companies have benefited from 2-year extension of market exclusivity for orphan medicinal products, nor from data and marketing protection periods granted for PUMA.

From this report, the major deviation from the obligations set by the Regulation is represented by delays to submit applications for PIPs or Waivers to the Agency (with a median of 19 months). This is the case for the majority of companies (69%), and represents a missed opportunity for early dialogue, although this opportunity was repeatedly requested by pharmaceutical industry in the past. Delayed submissions are also creating major obstacles (including ethical aspects) for the Paediatric Committee to define the appropriate development plan. Additionally, a few companies have not yet updated the Summary of Product characteristics in order to mention waivers and deferrals.

There is no evidence other infringements found by the Agency or reported by Member States. However not all Member States have provided information on this point. It has to be noted that the Commission Regulation on financial penalties, which could serve as deterrent, has not been revised as indicated in Article 49(3) to make possible financial penalties linked to infringement of the Paediatric Regulation.

In a wider context and on a positive note, the Paediatric Regulation has contributed to initiatives taken outside the EU, for instance the set-up in 2010 of the Paediatric Medicines Regulatory Network coordinated by WHO, to which the Agency contributes actively.

Annex 1

List sent to the Member States regarding information to be provided

Annex (to the letter sent to the Member States)

Guidance to answer

- The information to be provided should cover from 1 January 2010 to 31 December 2010.
- As this is only the 2nd report, please note that we have included the information provided last year for some of the questions.
  - If there have been some changes in 2010 as compared to previous years, please amend.
  - If you hadn't provided any information, please answer the questions for the year 2010 only.
- Please highlight if some of the information is confidential and therefore can be in the report for the European Commission but should be removed before publication.
- Please ensure to answer all the questions, although we acknowledge for some of them, this might not be under your direct responsibilities.

Benefits

I- Scientific advice

1. Please fill below table (the figures reported should correspond to procedures with the start date within the year).

	Year 2010
Number of paediatric only scientific advice (i.e. all questions relate to the development of the product in children)	
Number of mixed advice (i.e. advice including questions related to the paediatric and adult development)	

Please list the sponsors/companies and the product (international non-proprietary name INN/invented name) for paediatric only scientific advice as well mixed advice, highlighting those companies which are small and medium enterprises.

2. Is there a fee waiver for paediatric-only scientific advice in your Agency:

   Yes ☐ No ☐

Response provided for the 1st report (2007-2009):

II- Compliance and Marketing Authorisation

1. Please fill below tables regarding the statement on compliance with the paediatric investigation plan included in a marketing authorisation for products authorised – please specify if authorised through national (N) or decentralised (DC) or mutual recognition procedure (MRP). Please highlight if any of these companies are small and medium enterprises (SMEs).

   1.1. Marketing authorisation for a new medicinal product granted in 2010.

Marketing authorisation holder	**Invented name**	**INN**	**Marketing authorisation number**	**Date of marketing authorisation**	**Link to official webpage if available**

1.2. Marketing Authorisation extended/varied for already authorised medicinal products in 2010.

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available

III- Product information

Please fill the table listing the marketing authorisation granted or extended/varied in 2010 for which the statement on waiver or deferral has been included in the Summary of Product Characteristics (section 5-1). Please specify if authorised through national (N) or decentralised (DC) or mutual recognition procedure (MRP). Please highlight if any of these companies are SMEs.

Marketing authorisation holder	Invented name	INN	Statement on waiver (presence)	Statement on deferral (presence)	Date of marketing authorisation/ variation	Link to official webpage if available

IV- National incentives:

1. Is there any national funding to support research and development for paediatric medicinal product?
   Yes ☐ No ☐

If yes, please list of projects/name of companies or consortium which have received funding in between 1 January to 31 December 2010 (please highlight if some of the information is confidential).

Response provided for the 1st report (2007-2009):

2. For clinical trials, is there any fee waiver/reduction for the procedure for authorising paediatric clinical trial?
   Yes ☐ No ☐

If yes please list the sponsors and name of products (invented name/INN) which received a fee waiver/reduction in 2010.

Response provided for the 1st report (2007-2009):

3. For clinical trials, is there a priority review for authorising paediatric clinical trials?

   Yes ☐ No ☐

If yes please list the sponsors and name of product (invented name/INN) which had a priority review in 2010.

Response provided for the 1st report (2007-2009):

4. For application for marketing authorisation and/or extension of the marketing authorisation is there any fee reduction for the submission of the applications for medicinal products indicated in paediatric, including for Paediatric Use Marketing Authorisation (PUMA)?

Yes ☐ No ☐

If yes please specify the type and amount of fee reduction as well as the list of companies and products (invented name/INN) that have benefited from this fee reduction.

Response provided for the 1st report (2007-2009):

5. Is there any procedure for priority review of the applications for marketing authorisation for products for paediatric use, including PUMA?

   Yes ☐ No ☐

If yes please describe the process and list the companies and products (invented name/INN) that have benefited from this priority review.

Response provided for the 1st report (2007-2009):

6. With respect to price/reimbursement, are there any specific benefits for medicinal products for paediatric use, including for PUMA (e.g. specific conditions in connection with the fixing of prices and reimbursement, including priority review for this process)?

   Yes ☐ No ☐

If yes please specify which ones and list the products (invented name/ INN/marketing authorisation holders) which have benefited from those in 2010.

Response provided for the 1st report (2007-2009):

Infringement

Are there cases in 2010 of:

1. Application for marketing authorisation/extension/variation which have submitted and validated without having fulfilled the requirements listed under Article 7 or 8 of the Paediatric Regulation (i.e. need for EMA decision granting a waiver, EMA decision on a deferral, or results of studies conducted in compliance of a PIP).
   Yes ☐ No ☐
2. Compliance obtained without inclusion on the product information of the paediatric data (please specify products, marketing authorisation holder).
   Yes ☐ No ☐
3. Marketing authorisation granted or varied without any mention of the waiver or deferral in the Summary of Product Characteristics (please specify products, marketing authorisation holder).
   Yes ☐ No ☐

If yes for any of the above please list the name of the product (invented name/INN) and the name of the applicant.

V – Other

Please indicate if there are in your view, any other situations where companies have benefited or infringed the obligations of the Paediatric Regulation:
Yes ☐ No ☐

If yes please list the name of the product (invented name/INN), the name of the applicant and specify the type of benefit or infringement.

Annex 2

List of National Competent Authorities and National Patent Offices which have replied

Member State	National Competent Authorities	National Patent Office
Austria	X	X
Belgium	X	X
Bulgaria		X
Cyprus	X	X
Czech Republic	X	X
Denmark	X	X
Estonia	X	X
Finland	X	X
France		X
Germany	X	X
Greece	X	X
Hungary	X	X
Ireland	X	X
Italy	X	X
Latvia	X	
Lithuania		X
Luxembourg		X
Malta	X	X
The Netherlands	X	X
Poland	X	X
Portugal	X	X
Romania		X
Slovakia		X
Slovenia		X
Spain		X
Sweden	X	X
United Kingdom	X	X

Annex 3

Compliance and Marketing Authorisation

3.1 Compliance and Marketing Authorisation for new medicinal products

Austria

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Novartis Pharma GmbH	Diovan 3 mg/ml Lsg z Einnehmen	Valsartane	1-29223, MRP	19.05.2010	
Novartis Pharma GmbH	Angiosan 3 mg/ml Lsg z Einnehmen	Valsartane	1-29224, MRP	19.05.2010	
Pfizer Corporation Austria GmbH	Sortis 5 mg Kautabletten	Atorvastatine Calcium	1-29554, MRP	11.08.2010	
Pfizer Corporation Austria GmbH	Sortis 10 mg Kautabletten	Atorvastatine Calcium	1-29555, MRP	11.08.2010	
Pfizer Corporation Austria GmbH	Sortis 20 mg Kautabletten	Atorvastatine Calcium	1-29556, MRP	11.08.2010	
Pfizer Corporation Austria GmbH	Sortis 40 mg Kautabletten	Atorvastatine Calcium	1-29557, MRP	11.08.2010	

Belgium

No marketing authorisation through national, decentralised or mutual recognition procedure (Belgium being RMS) for a new medicinal product susceptible to warrant a PIP was granted in 2010 in Belgium.

Bulgaria

No response received.

Cyprus

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Novartis Pharmaceuticals UK Ltd	Diovan oral solution 3mg/ml	Valsartan	20694(MRP)	02/06/2010	/
Pfizer Hellas AE	Xalatan eye drops solution 0,0005%	Latanoprost	20805(MRP)	22/11/2010	/

Czech Republic

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Novartis s.r.o	Diovan 3 mg/ml	Valsartanum	58/550/10-C	30-06-2010	

Denmark

None

Estonia

None.

Finland

None

France

No response received.

Germany

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
	(Clons) Sortis 5, 10, 20, 40 mg Kautabletten		ZNR: 82882.00.00 - 84.00.00 + 82886.00.00		

Greece

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Pfizer Hellas	Lipitor chewable tab 5mg,10mg, 20mg, 40mg	Atorvastatin	60431/7-9-2010 60433/7-9-2010 60434/7-9-2010 60435/7-9-2010	7-9-2010	
WIN MEDICA	Zarator chewable tabs 5mg,10mg, 20mg, 40mg	Atorvastatin	52097/23-9-2010 52098/23-9-2010 63628/23-9-2010 63629/23-9-2010	23-9-2010	
Novartis Hellas	Dalzad oral solution 3mg/ml	Valsartan	29197/1-6-2010	1-6-2010	
Novartis Hellas	Diovan oral solution 3mg/ml	Valsartan	27344/1-6-2010	1-6-2010	

Hungary

Marketing authorisation holder	Invented name	Type of procedure	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Novartis Hungária Kft. Pharma részlege	DIOVAN 3 mg/ml belsőleges oldat	N	Valsartan	OGYI-T-08484/15	2010.05.26	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=36696
C.P. Pharma Kft.	OBRADON 5 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/11	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39929
C.P. Pharma Kft.	OBRADON 10 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/12	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39945
C.P. Pharma Kft.	OBRADON 20 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/13	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39947
C.P. Pharma Kft.	OBRADON 40 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/14	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39949
Pfizer Kft.	SORTIS 5 mg rágótabletta	N	Atorvastatin	OGYI-T-06542/17	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39925
Pfizer Kft.	SORTIS 10 mg rágótabletta	N	Atorvastatin	OGYI-T-06542/18	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39940
Pfizer Kft.	SORTIS 20 mg rágótabletta	N	Atorvastatin	OGYI-T-06542/19	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39942
Pfizer Kft.	SORTIS 40 mg rágótabletta	N	Atorvastatin	OGYI-T-06542/20	2010.08.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=39944

Ireland

Not known

Italy

None

Latvia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Grünental GmbH, DE	Palexia retard 200 mg prolonged-release tablets	Tapentadolum	10-0618 DC	26.11.20010	http://www.zva.gov.lv/index.php?id=377&sa=377&top=112

Grünental GmbH, DE	Palexia 50 mg film-coated tablets	Tapentadolum	10-0612 DC	26.11.20010	http://www.zva.gov.lv/index.php?id=377&sa=377&top=112
Grünental GmbH, DE	Palexia 100 mg film-coated tablets	Tapentadolum	10-0614 DC	26.11.20010	http://www.zva.gov.lv/index.php?id=377&sa=377&top=112
Grünental GmbH, DE	Palexia retard 50 mg prolonged-release tablets	Tapentadolum	10-0615 DC	26.11.20010	http://www.zva.gov.lv/index.php?id=377&sa=377&top=112

Lithuania

No response received.

Luxembourg

No response received.

Malta

None

The Netherlands

Diovan

Lipitor

Poland

None

Portugal

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Farmogene - Produtos Farmacêuticos, Lda.	Texzor	Atorvastatin calcium	10/H/0225/001-004 (Nacional Procedure)	26-08-2010	http://www.infarmed.pt/infomed
Parke-Davis - Produtos Farmacêuticos, Lda.	Atorvastatina Parke-Davis	Atorvastatin calcium	10/H/0226/001-004 (Nacional Procedure)	26-08-2010	http://www.infarmed.pt/infomed
Novartis Farma - Produtos Farmacêuticos, S.A.	Diovan	Valsartan	SE/H/406/07/MR (MRP)	14-07-2010	
Laboratórios Pfizer Lda.	Zarator	Atorvastatin calcium	DE/H/0109/05-08/MR (MRP)	02-08-2010	

Romania

No response received.

Slovakia

No response received.

Slovenia

No response received.

Spain

No response received.

Sweden

None

UK

N/A

3.2 Marketing authorisation extended/varied for already authorised medicinal products in 2010

Austria

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Novartis Pharma GmbH	Diovan 80 mg Filmtabletten	Valsartane	1-24275, MRP	21.05.2010	
Novartis Pharma GmbH	Diovan 160 mg Filmtabletten	Valsartane	1-24276, MRP	21.05.2010	
Novartis Pharma GmbH	Diovan 40 mg Filmtabletten	Valsartane	1-25945, MRP	21.05.2010	
Novartis Pharma GmbH	Diovan 320 mg Filmtabletten	Valsartane	1-26881, MRP	21.05.2010	
Novartis Pharma GmbH	Angiosan 80 mg Filmtabletten	Valsartane	1-24277, MRP	21.05.2010	
Novartis Pharma GmbH	Angiosan 160 mg Filmtabletten	Valsartane	1-24278, MRP	21.05.2010	
Novartis Pharma GmbH	Angiosan 40 mg Filmtabletten	Valsartane	1-25946, MRP	21.05.2010	
Novartis Pharma GmbH	Angiosan 320 mg Filmtabletten	Valsartane	1-26882, MRP	21.05.2010	
Pfizer Corporation Austria GmbH	Sortis 10 mg - Filmtabletten	Atorvastatine Calcium	1-21927, MRP	28.07.2010	
Pfizer Corporation Austria GmbH	Sortis 20 mg - Filmtabletten	Atorvastatine Calcium	1-21928, MRP	28.07.2010	
Pfizer Corporation Austria GmbH	Sortis 40 mg - Filmtabletten	Atorvastatine Calcium	1-21926, MRP	28.07.2010	
Pfizer Corporation Austria GmbH	Sortis 80 mg - Filmtabletten	Atorvastatine Calcium	1-24525, MRP	28.07.2010	
Pfizer Corporation Austria GmbH	Xalatan 0,005 % Augentropfen	Latanoprost	1-22019, MRP	ongoing	
Merck Sharp & Dohme GmbH	Singulair 4 mg Kautab f Kleinkinder	Montelukast Natrium	1-23982, MRP	17.11.2010	
Merck Sharp & Dohme GmbH	Singulair 4 mg Granulat	Montelukast Natrium	1-28170, MRP	17.11.2010	

Belgium

No extension/variation for an already authorised medicinal product through national, decentralised or mutual recognition procedure (Belgium being RMS) susceptible to warrant a PIP were submitted in Belgium in 2010.

Bulgaria

No response received.

Cyprus

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
AstraZeneca UK Ltd	Arimidex tabs 1mg	Anastrozole	17100(N)	02/06/2010	/
Novartis Pharmaceuticals UK Ltd	Diovan fctabs 40mg	Valsartan	19635(MRP)	31/05/2010	/
Novartis Pharmaceuticals UK Ltd	Diovan fctabs 80mg	Valsartan	19384(MRP)	31/05/2010	/
Novartis Pharmaceuticals UK Ltd	Diovan fctabs 160mg	Valsartan	19385(MRP)	31/05/2010	/
Novartis Pharmaceuticals UK Ltd	Diovan fctabs 320mg	Valsartan	20375(MRP)	31/05/2010	/
Pfizer Hellas AE	Lipitor fctabs 10mg	Atorvastatin	19489(N)	28/07/2010	/
Pfizer Hellas AE	Lipitor fctabs 20mg	Atorvastatin	19490(N)	28/07/2010	/
Pfizer Hellas AE	Lipitor fctabs 40mg	Atorvastatin	19491(N)	28/07/2010	/
Merck Sharp& Dohme BV, Netherlands	Singulair chewable tabs 4mg	Montelukast	19291(MRP)	26/10/2010	/
Merck Sharp& Dohme BV, Netherlands	Singulair granules for oral suspension 4mg	Montelukast	19676(MRP)	26/10/2010	/

Czech Republic

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Novartis s.r.o	Diovan 40 mg	Valsartanum	58/176/03-C	7.7.2010	
Novartis s.r.o	Diovan 160 mg	Valsartanum	58/282/01-C	7.7.2010	
Astra Zeneca UK Ltd	Arimidex	Anastrozole	44/1296/97-C	16-12-2009	
Pfizer	Sortis 5mg	Atorvastatinum	31/764/10-C	29-09-2010	
Pfizer	Sortis 10 mg	Atorvastatinum	31/765/10-C	29-09-2010	
Pfizer	Sortis 20mg	Atorvastatinum	31/764/10-C	29-09-2010	
Pfizer	Sortis 40mg	Atorvastatinum	31/767/10-C	29-09-2010	
Pfizer	Xalatan	Latanoprostum	64/164/99-C	18-11-2010	

Denmark

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Novartis Healthcare A/S	Diovan	Valsartan	37642/32751/32752/ 39956	20.04.2010	
Novartis Healthcare A/S	Diovan	Valsartan	46831	20.04.2010	
Pfizer ApS	Xalatan	Latanoprost	18752	15.10.2010	

Estonia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Novartis Finland OY	Diovan	Valsartan	Film coated tablets 40mg, MA number 452504, Film coated tablets 80 mg, MA number 376002, Film coated tablets 160 mg, MA number 375902, Film coated tablets 320 mg, MA number	May 31, 2010 (MRP)	http://193.40.10.165/register/ register.php?keel=eng&inim_vet=inim

			514806, Oral solution 3 mg/ml, MA number 687310		
Pfizer Europe MA EEIG	Sortis	Atorvastatin	Film coated tablets 10 mg, MA number 205698, Film coated tablets 20 mg, MA number 205798, Film coated tablets 40 mg, MA number 205898, Film coated tablets 80 mg, MA number 423003, Chewable tablets 5 mg, MA number 694410 Chewable tablets 10 mg, MA number 694510 Chewable tablets 20 mg, MA number 694610 Chewable tablets 40 mg, MA number 694710	July 29, 2010 (N)	http://193.40.10.165/register/register.php?keel=eng&inim_vet=inim
Pfizer Enterprises SAR	Xalatan	Latanaprost	Eye drops, MA No 284899	November 1, 2010 (MRP)	http://193.40.10.165/register/register.php?keel=eng&inim_vet=inim

Finland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation /line extension	Link to official webpage if available
Novartis Finland	Diovan 3 mg/ml oraaliliuos	Valsartarum	MA no. 27966	21.5.2010	National implementation of line extension and paediatric indication after Commission Decision following Article 29 of the paediatric regulation. Commission Decision (C) (2010) 2580 (N)
Novartis Finland	Diovan 40 mg tabletti, kalvopääll ysteinen	Valsartarum	MA no.20510	19.5.2010	National implementation of paediatric indication after Commission Decision following Article 29 of the paediatric regulation. Commission Decision (C) 2010) 2577 SE/H/406/05/IB/91
Novartis Finland	Diovan 80 mg tabletti, kalvopääll ysteinen	Valsartarum	MA no.16708	19.5.2010	As above. Commission Decision (C) 2010) 2577 SE/H/406/03/IB/91
Novartis Finland	Diovan 160 mg tabletti, kalvopääll ysteinen	Valsartarum	MA no.16709	19.5.2010	As above. Commission Decision (C) 2010) 2577 SE/H/406/04/IB/91
Novartis Finland	Diovan 320 mg tabletti, kalvopääll ysteinen	Valsartarum	MA no.22668	19.5.2010	As above. Commission Decision C(2010) 2577 SE/H/406/06/IB/91
Pfizer Oy	Lipitor 5 mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28932	5.8.2010	National implementation of line extension and paediatric indication after Commission Decision following Article 29 of the paediatric regulation. Commission Decision C(2010) 4677 DE/H/109/05/MR
Pfizer Oy	Lipitor 10mg purutabletti	Atorvastatinum calcicum trihydricum	MA no. 28933	5.8.2010	As above. DE/H/109/06/MR
Pfizer Oy	Lipitor 20mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28934	5.8.2010	As above. DE/H/109/07/MR
Oy	Lipitor	Atorvastatinum	MA no.28935	5.8.2010	As above. DE/H/109/08/MR

	40mg purutabletti	calcicum trihydricum			
Pfizer Oy	Orbeos 5 mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28939	5.8.2010	As above. (N)
Pfizer Oy	Orbeos 10 mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28938	5.8.2010	As above. (N)
Pfizer Oy	Orbeos 20mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28937	5.8.2010	As above. (N)
Pfizer Oy	Orbeos 40 mg purutabletti	Atorvastatinum calcicum trihydricum	MA no.28936	5.8.2010	As above. (N)
Pfizer Oy	Lipitor 10 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.12612	19.8.2010	Implementation of the commission decision following an Article 29 application under regulation (EC) No 1901/2006. Commission Decision C(2010) 4677 DE/H/109/01/IB/102
Pfizer Oy	Lipitor 20 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.12613	19.8.2010	As above. DE/H/109/02/IB/102
Pfizer Oy	Lipitor 40 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.12614	19.8.2010	As above. DE/H/109/03/IB/102
Oy	Lipitor 80 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.16881	19.8.2010	As above. DE/H/109/04/IB/102
Pfizer Oy	Orbeos 10 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.24871	19.8.2010	As above. (N)
Pfizer Oy	Orbeos 20 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.24872	19.8.2010	As above. (N)
Pfizer Oy	Orbeos 40 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.24873	19.8.2010	As above. (N)
Pfizer Oy	Orbeos 80 mg tabletti, kalvopäällysteinen	Atorvastatinum calcicum trihydricum	MA no.24874	19.8.2010	As above. (N)
Merck Sharp	Singulair 4	Montelukastum	MA no.15621	22.10.2010	Update of product information

& Dohme B.V.	mg purutabletti	natricum			with paediatric data. PIP compliance statement. Type II variation. FI/H/214/01/II/19
Merck Sharp & Dohme B.V.	Singulair 4 mg rakeet	Montelukastum natricum	MA no.17099	22.10.2010	As above.
Merck Sharp & Dohme B.V.	Singulair-AR 4 mg purutabletti	Montelukastum natricum	MA no.17968	22.10.2010	As above.

France

No response received.

Germany

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
	Liprimar 10, 20, 40, 80 mg Filmtabletten		ZNR: 39587.00.00-02.00 + 77656.00.00		
	Sortis 10, 20, 40, 80 mg Filmtabletten		ZNR: 39581.00.00-02.00 + 77655.00.00		

Greece

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Pfizer Hellas	Lipitor fc tabs 10mg, 20mg, 40mg, 80mg	Atorvastatin	43277/20-7-2010	20-7-2010	
WIN MEDICA	Zarator fc tabs 10mg, 20mg, 40mg	Atorvastatin	52099/23-9-2010 63633/23-9-2010 63634/23-9-2010	23-9-2010	
Pfizer Hellas	Edovin fc tabs 10mg, 20mg, 40mg	Atorvastatin	76320/12-11-2010 77201/12-11-2010 77202/12-11-2010	12-11-2010	

Hungary

Marketing authorisation holder	Invented name	Type of procedure	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Novartis Hungária Kft. Pharma részlege	DIOVAN 40 mg filmtabletta	MRP, SE/H/406/005	Valsartan	OGYI-T-08484/05-08	2005.03.09	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=22674
Novartis Hungária Kft. Pharma részlege	DIOVAN 800 mg filmtabletta	MRP, SE/H/406/003	Valsartan	OGYI-T-08484/09-12	2002.07.03	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=19002
Novartis Hungária Kft. Pharma részlege	DIOVAN 160 mg filmtabletta	MRP, SE/H/406/004	Valsartan	OGYI-T-08484/01-02, 13-14	2002.07.03	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=19003
Novartis Hungária Kft. Pharma részlege	DIOVAN 320 mg filmtabletta	MRP, SE/H/406/006	Valsartan	OGYI-T-08484/03-04	2006.04.19	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=23961
C.P. Pharma Kft.	OBRADON 10 mg filmtabletta	N	Atorvastatin	OGYI-T-08306/01,04	2002.01.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=19689
C.P. Pharma Kft.	OBRADON 20 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/09-10	2002.01.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=19690
C.P. Pharma Kft.	OBRADON 40 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/05,06	2002.01.18	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=19691
C.P. Pharma Kft.	OBRADON 80 mg rágótabletta	N	Atorvastatin	OGYI-T-08306/08	2004.07.21	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=22679
Pfizer Kft.	SORTIS 10 mg filmtabletta	N	Atorvastatin	OGYI-T-6542/01-03.	1998.01.01	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=13393
Pfizer Kft.	SORTIS 20 mg rágótabletta	N	Atorvastatin	OGYI-T-6542/04-06	1998.01.01	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=13394
Pfizer Kft.	SORTIS 40 mg rágótable	N	Atorvastatin	OGYI-T-6542/07-09	1998.01.01	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_

	tta					details&item=13395
Pfizer Kft.	SORTIS 80 mg rágótabletta	N	Atorvastatin	OGYI-T-6542/10-16	2004.03.14.	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=21860
AstraZeneca Kft.	ARIMIDEX 1 mg filmtabletta	N	Anastrozole	OGYI-T-05682/01	1997.06.30	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=15359
Pfizer Kft.	Xalatan 0,05 mg/ml oldatos szemcsepp	MRP-UK/H/0179/001	Latanoprost	OGYI-T-5637/01-02	1997.01.01.	http://www.ogyi.hu/gyogyszeradatbazis/index.php?action=show_details&item=17538

Ireland

Not known.

Italy

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension
NOVARTIS FARMA S.P.A.	TAREG (MRP)	Valsartan	033178423	20/07/2010
NOVARTIS FARMA S.P.A.	RIXIL (MRP)	Valsartan	034776361	20/07/2010
PFIZER ITALIA S.R.L.	XARATOR(MRP) 4 MA numbers corresponding to 4 pack sizes	Atorvastatin	033005392/ 033005404/033005416/033005428	28/12/2010
PFIZER ITALIA S.R.L.	TORVAST (N) 4 MA numbers corresponding to 4 pack sizes	Atorvastatin	033007396/033007408/033007410/033007422	28/12/2010
BIOINDUSTRIA FARMACEUTICI SRL	LIPITOR (N) 4 MA numbers corresponding to 4 pack sizes	Atorvastatin	033008398/033008400/033008412/033008424	28/12/2010

Latvia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Novartis Finland Oy, FI	Diovan 3mg/ml oral solution	Valsartanum	10-0320 MRP	16.07.2010	http://www.zva.gov.lv/index.php?id=37

					7&sa=377&top=112

Lithuania

No response received.

Luxembourg

No response received.

Malta

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Novartis Pharmaceuticals UK Limited	Diovan 40mg film-coated tablets	Valsartan	MA088/00601	11/6/2010	www.maltamedicineslist.com
Novartis Pharmaceuticals UK Limited	Diovan 80mg film-coated tablets	Valsartan	MA088/00602	11/6/2010	www.maltamedicineslist.com
Novartis Pharmaceuticals UK Limited	Diovan 160mg film-coated tablets	Valsartan	MA088/00603	11/6/2010	www.maltamedicineslist.com
Novartis Pharmaceuticals UK Limited	Diovan 320mg film-coated tablets	Valsartan	MA088/00604	11/6/2010	www.maltamedicineslist.com
Novartis Pharmaceuticals UK Limited	Diovan 3mg/ml oral solution	Valsartan	MA088/00605	04/06/2010	www.maltamedicineslist.com
Pfizer Hellas SA	Xalatan 0.005% eye drops solution	Latanoprost	MA505/02501	12/01/2011	www.maltamedicineslist.com

The Netherlands

Arimidex

Poland

None.

Portugal

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Laboratórios Pfizer Lda.	Zarator	Atorvastatin calcium	DE/H/0109/001-004/IB/102 (MRP)	14-07-2010	
Laboratórios Pfizer	Xalatan	Latanoprost	UK/H/0179/001/IB/0	16-12-2010	

			73 (MRP)		
Laboratório Normal - Produtos Farmacêuticos, Lda.	Tareg	Valsartan	SE/H/0407/001-003/IB/071 (MRP)	01-06-2010	
Novartis Farma - Produtos Farmacêuticos, S.A.	Diovan	Valsartan	SE/H/0406/003-006/IB/091 (MRP)	01-06-2010	
Parke-Davis - Produtos Farmacêuticos, Lda.	Atorvastatina Parke-Davis	Atorvastatin calcium	08/H/0171/001-004 (Nacional Procedure)	26-08-2010	
Farmogene - Produtos Farmacêuticos, Lda.	Texzor	Atorvastatin calcium	07/H/0384/001-004 (Nacional Procedure)	26-08-2010	
AstraZeneca Produtos Farmacêuticos, Lda	Arimidex	Anastrozol	UK/H/0111/001 (MRP)	18-11-2009	

Romania

No response received.

Slovakia

No response received.

Slovenia

No response received.

Spain

No response received.

Sweden

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Novartis Sverige AB	Diovan (MRP)	Valsartan	20464, 17494, 17495, 22840	19 May 2010	
Novartis Sverige AB	Diovan (N) [1)]	Valsartan	43158	19 May 2010	
Pfizer AB, Sverige	Lipitor (MRP)	Atorvastatin	13415, 13416, 13417, 17836	16 July 2010	
Pfizer AB, Sverige	Lipitor (MRP)	Atorvastatin	43475, 43476, 43477	16 July 2010	
Pfizer AB, Sverige	Lipitor (MRP)	Atorvastatin	43473	16 July 2010	
Pfizer AB	Xalatan (N)	Latanoprost	12716	04 November 2010	
Merck Sharp & Dohme	Singulair (MRP)	Montelukast	19833	04 November 2010	
Merck Sharp & Dohme	Singulair (MRP)	Montelukast	16596, 18853	04 November 2010	

United Kingdom

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/line extension	Link to official webpage if available
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR	Diovan 3mg/ml oral solution	Valsartan	PL 00101/0956	Granted 28/05/2010 (N)	
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR	Diovan 40mg Tablets	Valsartan	PL 00101/0599	Granted 28/05/2010 (MRP-RMS SWEDEN)	
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR	Diovan 80mg Tablets	Valsartan	PL 00101/0600	Granted 28/05/2010 (MRP-RMS-SWEDEN)	
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR	Diovan 160mg Tablets	Valsartan	PL 00101/0601	Granted 28/05/2010 (MRP-RMS-SWEDEN)	
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Surrey, GU16 7SR	Diovan 320mg Tablets	Valsartan	PL 00101/0726	Granted 28/05/2010 (MRP-RMS-SWEDEN)	
Pfizer Ireland Pharmaceuticals Pottery Road Dun Laoghaire Co Dublin Ireland	Lipitor 5mg Chewable tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0006	Granted 03/11/2010 (N)	
Pfizer Ireland Pharmaceuticals Pottery Road Dun Laoghaire Co Dublin Ireland	Lipitor 10mg Chewable tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0007	Granted 03/11/2010 (N)	
Pfizer Ireland Pharmaceuticals Pottery Road Dun Laoghaire Co Dublin Ireland	Lipitor 20mg Chewable tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0008	Granted 03/11/2010 (N)	
Pfizer Ireland Pharmaceuticals Pottery Road Dun Laoghaire Co Dublin Ireland	Lipitor 40mg Chewable tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0009	Granted 03/11/2010 (N)	
MSD Hertford Road Hoddesdon, Hertfordshire EN11 9BU	Singulair Paediatric 4mg Chewable Tablets	Montelukast	PL00025/0412	Granted 11/11/2010 (MRP-RMS-FINLAND)	
MSD, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU	Singulair Paediatric 4mg Granules	Montelukast	PL00025/0440	Granted 11/11/2010 (MRP-RMS-FINLAND)	
Pfizer Ireland Pharmaceuticals, Pottery Road, Dun Laoghaire, Co Dublin, Ireland	Lipitor 10mg tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0001	Granted 16/11/2010 (N)	
Pfizer Ireland	Lipitor 20mg	Atorvastatin	PL	Granted 16/11/2010	

Pharmaceuticals, Pottery Road, Dun Laoghaire, Co Dublin, Ireland	tablets	(as calcium trihydrate)	16051/0002	(N)	
Pfizer Ireland Pharmaceuticals, Pottery Road, Dun Laoghaire, Co Dublin, Ireland	Lipitor 40mg tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0003	Granted 16/11/2010 (N)	
Pfizer Ireland Pharmaceuticals, Pottery Road, Dun Laoghaire, Co Dublin, Ireland	Lipitor 80mg tablets	Atorvastatin (as calcium trihydrate)	PL 16051/0005	Granted 16/11/2010 (N)	
Pfizer Limited, Walton Oaks, Dorking Road, Tadworth Surrey KT20 7NS	Xalatan 0.005%w/v Eye Drops	Latanoprost	PL 00057/1057	Granted 16/12/2010 (MRP-RMS-UK)	

Annex 4

List of companies/products which have benefited from 6-months extension of the supplementary protection certificate (SPC) granted by the National Patent Office in 2010

Marketing authorisation holder	Invented name	International non-proprietary name	SPC extension granted on	SPC extension granted on	No application for SPC extension[1]	Product with no SPC or patent which qualifies for an SPC[2]
Merck Sharp and Dohme	Cancidas	Caspofungin	- Austria: 31 May 2010 - Belgium: 21 December 2010 - Greece: 24 November 2010 - Italy: 13 July 2010 - Portugal: 12 March 2010 - Slovenia: 18 May 2010 *(SPC already granted in 2009 in Denmark, France, Germany Ireland The Netherlands , Sweden, United Kingdom)*	- Bulgaria - Czech Republic - Finland - Hungary - Romania - Slovakia - Spain		- Luxembourg
Merck Sharp and Dohme BV	Cozaar and associated names	Losartan	- Austria: 12 February 2010 *(already granted in 2009 in The Netherlands, Germany Denmark, Finland, France, Ireland, Italy, Sweden, UK, Luxembourg)*	- Cyprus	- Greece - Portugal - Romania - Spain	- Bulgaria - Greece - Hungary - Portugal - Slovak Republic - Slovenia *(no SPC)*
AstraZeneca AB	Arimidex and associated names	Anastrazole	- Austria: 8 June 2010 - Belgium: 3 August 2010 - Denmark: 25 May 2010 - Finland: 2 March 2010 - France: 11 June 2010 - Germany: 19 July 2010 - Ireland: 29 June 2010 - Italy: 16 March 2010 - Luxembourg: 27 July 2010 - The Netherlands 1 April 2010 - Sweden: 27 April 2010 - UK: 10 June 2010	- Romania	- Greece - Portugal - Romania *(SPC PENDING)* - Spain	- Bulgaria - Greece - Hungary - Portugal - Slovak Republic - Slovenia *(no SPC)*
Novartis	Diovan and	Valsartan	- Austria: 10 December 2010	- Germany	- Greece	- Bulgaria

Pharma AG	associated names		- Denmark: 1 November 2010 - Finland: 22 October 2010 - France : 10 December 2010 - Ireland: 22 December 2010 - Italy: 05 November 2010 - Luxembourg: 23 December 2010 - The Netherlands: 7 October 2010 - Portugal: 16 December 2010 - Sweden: 30 September 2010	- Spain - UK	- Hungary - Romania - Slovenia	- Greece - Romania (no SPC) - Slovak Republic
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	- Denmark: 21 June 2010 - France : 10 December 2010 - Germany: 16 August 2010 - Ireland: 30 June 2010 - Luxembourg: 23 December 2010 - The Netherlands: 31 August 2010 - Portugal : 2 November 2010	- Austria - Finland - Greece - Spain - UK	- Hungary - Italy *(SPC granted)* - Romania - Slovenia - Sweden	- Romania *(no SPC)* - Slovak Republic
Novartis	Zometa and associated names	Zoledronic acid	- Denmark: 6 April 2010 - France: 11 June 2010 - Germany: 27 May 2010 - Ireland: 28 June 2010 - Italy: 13 July 2010 - Luxembourg: 22 December 2010 - The Netherlands: 3 March 2010 - Portugal: 15 March 2010 - Slovenia: 19 March 2010 - Sweden: 27 April 2010 - UK: 30 June 2010	- Austria - Cyprus - Finland - Greece - Hungary - Romania - Spain		- Bulgaria - Slovak Republic
Pfizer	Sortis and associated names	Atorvastatin		- France - The Netherlands	- Austria - Denmark - Finland - Greece - Ireland	- Bulgaria *(appeal procedure after decision for termination of the procedure for SPC*

					- Italy *(SPC granted)* - Portugal - Romania - Sweden - UK *(SPC granted)*	*granting)* - Germany - Greece - Hungary - Luxembourg - Portugal - Romania *(no SPC)* - Slovak Republic - Slovenia *(no SPC)* - Spain *(SPC denied)*
Pfizer	Xalatan and associated names	Latanoprost		- Denmark - Italy - Spain	- Austria - France - Finland - Greece - Ireland - Luxembourg - Portugal *(SPC granted)* - Romania - Sweden - UK *(SPC granted)*	- Bulgaria *(SPC refused)* - Germany - Greece - Hungary - Romania *(no SPC)* - Slovak Republic - Slovenia *(no SPC)*

[1,2] Some national patent offices have ticked both columns as as SPC could still be applied although in some cases the timelines might not allow for it. In addition unless otherwise stated "no SPC" may indicate that noapplication has been submitted yet but the patent may still qualify for an SPC or that no application was submitted because no SPC was granted.

Annex 5

List of projects on off-patent medicines funded by the European Commission through the EU Framework Programme

Projects funded through 4th call within FP7

1. HIP Trial

Evaluates the efficacy safety, PK, PD, adrenaline and dopamine in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).

2. DEEP

Aims to evaluate PK & PD of deferiprone in in 2-10 years old children in order to produce an approved Paediatric Investigational Plan to be used for regulatory purposes.

3. TINN2

Aims to evaluate PK & PD of azithromycin against urea plasma and in BPD in neonates.

Annex 6

List of medicinal products assessed in 2010 further to submission of data through Article 45 and resulting amendment of the SmPC

Centrally authorised medicinal products

Further information on these medicinal products can be found under the European Public Assessment Report published on the Agency website.

International Non-proprietary name	Invented name	Marketing authorisation holders	CHMP recommendation following assessment of the studies	Recommended change in SmPC[3]
Interferon beta-1a	Avonex	Biogen Idec Ltd.	New study data	Sections 4.2, 4.8 and 5.1
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals S.A.	No change	
Diphtheria, tetanus, acellular pertussis, hepatitis B recombinant (adsorbed), inactivated poliomyelitis and adsorbed conjugated Haemophilus influenzae type b vaccine	Infanrix hexa	GlaxoSmithKline Biologicals S.A.	No change	
Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis B (rdna) (hbv), poliomyelitis (inactivated) (ipv) vaccine (adsorbed)	Infanrix penta	GlaxoSmithKline Biologicals S.A.	No change	
Nitric oxide	INOmax	INO Therapeutics AB	No change	
Lopinavir / ritonavir	Kaletra	Abbott Laboratories Limited	No change	
Insulin detemir	Levemir	Novo Nordisk A/S	No change	
Perflutren	Optison	GE Healthcare AS	New study data	Sections 4.2 and 5.1
Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Wyeth Lederle Vaccines S.A.	No change	
Tacrolimus	Protopic	Astellas Pharma Europe B.V.	No change	
Diphtheria, tetanus, inactivated whole cell	Tritanrix HepB	GlaxoSmithKline Biologicals S.A.	No change	

[3] Section 4.2 Posology and method of administration
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties

pertussis, hepatitis b recombinant, adsorbed vaccine				
Zonisamide	Zonegran	Eisai Ltd.	New study data	Section 5.2

Medicinal products authorised through national / mutual recognition / decentralised procedure

Further information – including the assessment report can be found on the webpage CMDh Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human- http://www.hma.eu/187.html.

Medicinal products authorised through national/mutual recognition/decentralised procedure (End of Procedure in 2010) [4]			
Substances	**Pharmaceutical form(s)**	**Outcome of assessment**	**Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)**[5]
Amoxicillin / Amimox End of Procedure: 13/05/2010 Date of Publication: 05/08/2010	Tablets and powder for oral suspension	Paediatric information clarified	Sections 4.2, 4.4 and 5.2
Amoxicillin / Clavulanic Acid End of Procedure: 14/06/2010 Date of Publication: 05/08/2010	Oral and intravenous formulations	No change	N/A
Baclofen End of Procedure: 10/05/2010 Date of Publication: 26/01/2011	Intrathecal Injection, Infusion Oral solution Tablets	New indication in children/extension of indication to children	Sections 4.1, 4.2 and 4.4
Beclometasone dipropionate End of Procedure: 11/01/2010 Date of Publication: 24/05/2010	Inhaled formulation	No change	N/A

[4] Correct as at 31 January 2011
[5] Section 4.1 Therapeutic indications
Section 4.2 Posology and method of administration
Section 4.3 contraindication
Section 4.4 Special warnings and precaution for use
Section 4.8 Undesirable effects
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties

Betula verrucosa (allergen extract from birch tree Betula Verrucosa or Betula alba End of Procedure: 05/03/2010 Date of Publication: 27/04/2010	Powder and Solution for injection, Intracutaneous test, prick-test or provocation test	Paediatric information clarified	Section 4.2
Canis familiaris / Felis domesticus (specific allergen extract from dog (Canis Familiaris) and cat (Felis domesticus) End of Procedure: 21/05/2010 Date of Publication: 05/08/2010	Suspension for injection Powder and solvent for solution for injection Solution for pricktest	Paediatric information clarified	Section 4.2
Ciclosporin End of Procedure: 16/05/2010 Date of Publication: 01/07/2010	Soft gelatin capsules Oral solution Concentrate for solution for infusion	No change	N/A
Clarithromycin End of Procedure: 26/10/2010 Date of Publication: 24/11/2010	Oral formulations tablets Granules for Oral Suspension ClaroSip® - clarithromycin in a drinking straw Parenteral formulation Powder for Solution for Injection	Paediatric information clarified	Sections 4.1 and 4.2
Dermatophagoides pteronyssinus / Dermatophagoides farinae (allergens extract from house dust mites) End of Procedure: 12/03/2010 Date of Publication: 24/05/2010	Solution for injection, prick-test or provocation test and oral formulation	Paediatric information clarified	Section 4.2
Diclofenac End of Procedure: 27/09/2010 Date of Publication: 24/11/2010	Various formulations systemic and topical	Paediatric information clarified	Sections 4.2, 4.3 and 5.1 depending on the formulation

Famciclovir End of Procedure: 20/07/2010 Date of Publication: 01/10/2010	Film-coated tablets	Paediatric information clarified (*in conjunction with art 46)*	Sections 4.2, 5.1 and 5.2
Filgrastim End of Procedure: 26/04/2010 Date of Publication: 01/07/2010	Parenteral formulation	No change	N/A
Gentamicin sulphate End of Procedure: 06/01/2010 Date of Publication: 23/02/2010 Update: 18/10/2010	Solution for intramuscular, parenteral, or intrathecal administration, ear drops, ophthalmic Solution and ointment, and topical cream and ointment.	Safety information added	Sections 4.1, 4.2, 4.3, 4.4 and 5.2 depending of the formulation
Honey bee venom and vespula venom End of Procedure: 07/12/2010 Date of Publication: 05/01/2011	Suspension for injection Powder and solvent for solution for injection Lyophilisate and solvent for injection	Paediatric information clarified	Sections 4.2 and 4.4
Levofloxacin End of Procedure: 04/10/2010 Date of Publication: 24/11/2010	Oral suspension Film-coated tablets Solution for infusion	No change	N/A
Loratadine End of Procedure: 06/08/2010 Date of Publication: 27/10/2010	Syrup Tablet	No change	N/A
Melphalan End of Procedure: 28/09/2010 Date of Publication: 27/10/2010	Powder and solvent for solution for injection/infusion Film coated tablet	No change	N/A
Mepivacaine End of Procedure: 05/11/2010 Date of Publication: 05/01/2011	Solution for injection	Paediatric information clarified	Sections 4.2 and 4.3
Metronidazole End of Procedure:	Oral and iv formulations.	Paediatric information	Sections 4.1, 4.2 and 4.8

05/10/2010 Date of Publication: 05/01/2011		clarified	
Mianserin End of Procedure: 26/05/2010 Date of publication: 01/07/2010	Tablet	No change	N/A
Mirtazapine End of Procedure: 18/06/2010 Date of Publication: 05/08/2010	Tablets Orodispersible tablets Oral solution	New study data (to reflect lack of efficacy and safety issues)	Sections 4.2, 4.8 and 5.1
Neridronic acid End of Procedure: 19/10/2010 Date of Publication: 27/10/2010	Solution for injection or infusion IV or IM	Paediatric information clarified	Sections 4.1 and 4.2
Oxybutynin hydrochloride End of Procedure: 15/09/2010 Date of Publication: 01/10/2010	Film-coated or prolonged release tablets) Syrup Oral solution	Paediatric information clarified	Sections 4.1 and 4.4
Paclitaxel End of Procedure: 16/04/2010 Date of Publication: 27/04/2010	Concentrate for solution for infusion	Paediatric information clarified	Section 4.2
Phleum pratense (extract grass pollen) End of Procedure: 11/06/2010 Date of Publication: 05/08/2010	Suspension for injection Oral solution Oral lyophilisate	Paediatric information clarified	Section 4.2
Propofol End of Procedure: 21/05/2010 Date of Publication: 06/09/2010	Emulsion for injection / infusion	Paediatric information clarified	Sections 4.1, 4.2, 4.3, 4.4 , 5.1 and 5.2
Remifentanil End of Procedure: 13/09/2010 Date of Publication: 05/01/2011	Injection	Paediatric information clarified	Section 5.1
Rifaximin End of Procedure: 08/01/2010	Film coated tablet: Granules for oral suspension	New study data	Sections 4.1, 4.2 and 5.1

Date of Publication: 26/04/2010			
Risedronate sodium End of Procedure: 14/09/2010 Date of Publication: 01/10/2010	Film-coated tablets	New study data	Sections 4.2 and 5.1
Triptorelin End of Procedure: 17/02/2010 Date of Publication: 01/10/2010	Powder and solvent for suspension for injection	Paediatric information clarified	Sections 4.2, 4.4 and 4.8

Annex 7

List of medicinal products assessed in 2010 further to submission of data through Article 46 and resulting amendment of the SmPC

Centrally authorised medicinal products

Further information on these medicinal products can be found under the European Public Assessment Report published on the Agency website.

International Non-proprietary name	Invented name	Marketing authorisation holders	CHMP recommendation following assessment of the studies	Recommended change in SmPC[6]
Desloratadine	Aerius	Schering-Plough Europe	No change	
Pemetrexed	Alimta	Eli Lilly Nederland B.V.	No change	
Bivalirudin	Angiox	The Medicines Company UK Ltd.	No change	
Duloxetine	Ariclaim	Eli Lilly Nederland B.V.	No change	
Desloratadine	Azomyr	Schering-Plough Europe	No change	
Nonacog alfa	BeneFIX	Wyeth Europa Ltd	No change	
Nonacog alfa	BeneFIX	Wyeth Europa Ltd	No change	
Carglumic acid	Carbaglu	Orphan Europe S.A.R.L.	No change	
Maraviroc	Celsentri	Pfizer Limited	No change	
Duloxetine	Cymbalta	Eli Lilly Nederland B.V.	No change	
Doripenem	Doribax	Janssen-Cilag International NV	No change	
Doripenem	Doribax	Janssen-Cilag International NV	No change	
Etanercept	Enbrel	Wyeth Europa Ltd	No change	
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD, SNC	No change	
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD, SNC	No change	
Mecasermin	Increlex	Ipsen Pharma	No change	
Mecasermin	Increlex	Ipsen Pharma	No change	
Diphtheria, tetanus, acellular pertussis, hepatitis B recombinant (adsorbed), inactivated poliomyelitis and	Infanrix hexa	GlaxoSmithKline Biologicals S.A.	No change	

[6] Section 4.2 Posology and method of administration
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties
5.3 Preclinical safety data

adsorbed conjugated Haemophilus influenzae type b vaccine				
Paliperidone	Invega	Janssen-Cilag International NV	No change	
Saquinavir	Invirase	Roche Registration Ltd.	No change	
Levetiracetam	Keppra	UCB Pharma SA	No change	
Telithromycin	Ketek	Aventis Pharma S.A.	No change	
Insulin detemir	Levemir	Novo Nordisk A/S	No change	
Pregabalin	Lyrica	Pfizer Limited	No change	
Desloratadine	Neoclarityn	Schering-Plough Europe	No change	
Romiplostim	Nplate	Amgen Europe B.V.	No change	
Somatropin	NutropinAq	IPSEN Limited	No change	
Celecoxib	Onsenal	Pfizer Limited	No change	
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Wyeth Lederle Vaccines S.A.	No change	
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Wyeth Lederle Vaccines S.A.	No change	
Aliskiren	Rasilez	Novartis Europharm Ltd.	No change	
Rotavirus serotype G1, serotype G2, serotype G3, serotype G4, serotype P1	RotaTeq	Sanofi Pasteur MSD, SNC	No change	
Rotavirus serotype G1, serotype G2, serotype G3, serotype G4, serotype P2	RotaTeq	Sanofi Pasteur MSD, SNC	No change	
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	Merck Sharp & Dohme Ltd.	No change	
Human papillomavirus vaccine [types 6, 11, 16, 18]	Silgard	Merck Sharp & Dohme Ltd.	No change	

(recombinant, adsorbed)				
Fosamprenavir calcium	Telzir	ViiV Healthcare UK Limited	No change	
Tigecycline	Tygacil	Wyeth Europa Ltd	No change	
Voriconazole	Vfend	Pfizer Limited	No change	
Voriconazole	Vfend	Pfizer Limited	No change	
Duloxetine	Xeristar	Eli Lilly Nederland B.V.	No change	
Duloxetine	Yentreve	Eli Lilly Nederland B.V.	No change	
Miglustat	Zavesca	Actelion Registration Ltd.	No change	
Miglustat	Zavesca	Actelion Registration Ltd.	No change	
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd.	No change	
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd.	No change	
Etravirine	INTELENCE	Janssen-Cilag International NV	No change	
Etanercept	Enbrel	Wyeth Europa Ltd	No change	
Deferasirox	Exjade	Novartis Europharm Limited	No change	
Deferasirox	Exjade	Novartis Europharm Limited	No change	
Dabigatran etexilate mesilate	Pradaxa	Boehringer Ingelheim International GmbH	No change	
Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	No change	
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd.	New study data	Sections 4.2 and 5.1
Palonosetron hydrochloride	Aloxi	Helsinn Birex Pharmaceuticals Ltd.	New study data	Sections 4.2, 5.1 and 5.2
Pramipexole dihydrochloride monohydrate	Mirapexin / Sifrol	Boehringer Ingelheim International GmbH	New study data	Section 5.3
Pramipexole dihydrochloride monohydrate	Mirapexin / Sifrol	Boehringer Ingelheim International GmbH	New study data	Sections 4.2 and 5.1
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Wyeth Lederle Vaccines S.A.	New study data	Section 5.1
Fondaparinux sodium	Arixtra	Glaxo Group Ltd.	New study data	Sections 5.1, 5.2
Virus, live attenuated, measles, virus, live attenuated, mumps, virus,	Proquad	Sanofi Pasteur MSD, SNC	New study data	Product information to be updated

live attenuated, rubella, virus, live attenuated, varicella				
Nitric oxide	INOmax	INO Therapeutics AB	New study data	Sections 4.2, and 5.1
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Wyeth Lederle Vaccines S.A.	New study data	Product information to be updated

Medicinal products authorised through national/mutual recognition/decentralised procedure

Further information – including the assessment report can be found on the webpage CMDh Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human- http://www.hma.eu/187.html

Medicinal products authorised through national/mutual recognition/decentralised procedure (End of Procedure in 2010)[7]

Medicinal products (substances)	Pharmaceutical form(s)	Outcome of assessment	Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)[8]
Adartrel (Ropinirole) End of Procedure: 10/11/2010 Date of Publication: 05/01/2011	Film-coated-tablets	New study data	Section 5.2
Agopton (lansoprazole) End of Procedure: 05/07/2010 Date of Publication: 05/08/2010	Capsule Oro-dispersible tablet	Paediatric information clarified	Section 4.2
Aricept (Donepezil) End of Procedure: 27/11/2010 Date of Publication: 05/01/2011	Film Coated Tablets Oral solution	No change	N/A
Depakin and associated names (sodium valproate)	Modified release granules	No change	N/A

[7] Correct as at 31 January 2011
[8] Section 4.2 Posology and method of administration
Section 4.4 Special warnings and precaution for use
Section 4.5 Interactions
Section 4.8 Undesirable effects
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties

End of Procedure: 09/05/2010 Date of Publication: 27/10/2010			
Elidel (pimecrolimus) DK/W/007/pdWS/001 End of Procedure: 26/01/2010 Date of Publication: 27/04/2010 DK/W/007/pdWS/002 End of Procedure: 24/08/2010 Date of Publication: 24/11/2010	Cream	No change	N/A
Famvir and associated names (famciclovir) End of Procedure: 26/05/2010 Date of Publication: 05/08/2010	Film-coated tablets	Paediatric information clarified (*in conjunction with art 45)*	Sections 4.2, 5.1 and 5.2
Genotropin and associated names (somatropin) End of Procedure: 06/10/2010 Date of Publication: 24/11/2010	Powder and solvent for solution for injection	No change	N/A
Kytril (granisetron) End of Procedure: 06/03/2010 Date of Publication: 01/07/2010	Ampoules Tablets	Safety information added	Sections 4.4, 4.5 and 4.8
Nexium (esomeprazole) End of Procedure: 09/12/2010 Date of Publication: 05/01/2011	gastro-resistant granules for oral suspension/ sachet	New study data	Sections 4.2 and 5.1
Seretide Diskus/ Seretide Eudraler and associated names (Salmeterol xinafoate+Fluticason	Powder for inhalation Pressurised suspension for inhalation	New study data	Sections 4.2 and 5.2

e propionate) End of Procedure: 12/01/2009 Date of Publication: 05/01/2011			
Strattera (atomoxetine) End of Procedure: 07/11/2009 Date of Publication: 27/04/2010	Capsules	No change	N/A
Prograf (tacrolimus) End of Procedure: 13/01/2010 Date of Publication: 01/07/2010	Hard capsules	No change	N/A

Annex 8

List of companies with delayed (>6 months) submission of applications for a PIP and/or waiver

(This list only includes 2010 applications for which a decision on a PIP or waiver has been adopted by the European Medicines Agency; applications that have been withdrawn or whose discussion is ongoing are not listed)

Company	Substance	Delay in months
BioAlliance Pharma	Aciclovir	65
Novartis Europharm Ltd	Sotrastaurin (INN) acetate	33
LFB Biotechnologies	Fibrinogen (human plasma-derived)	53
Gedeon Richter Plc.	amlodipine besilate, atorvastatin L-lysine	16
Avid Radiopharmaceuticals Ireland Limited	(E)-4-(2-(6-(2-(2-(2-[18F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylbenzenamine	8
Theratechnologies Inc	Tesamorelin	19
ORFAGEN	Tazarotene	99
CTI Life Sciences, Ltd.	Pixantrone dimaleate	14
Vanda Pharmaceuticals Limited	Iloperidone	92
LEO Pharma A/S	Ingenol mebutate	12
APT Pharmaceuticals Limited	Ciclosporin	92
Novartis Europharm Ltd	(R)-3(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrilephosphate	19
Novartis Europharm Ltd	Pasireotide	40
Teva Pharma GmbH	Laquinimod sodium	17
Allos Therapeutics Limited	Pralatrexate	8
Almirall S.A.	Linaclotide	32
Genzyme Europe B.V.	Mipomersen sodium	53
Savient Pharmaceuticals, Inc.	Pegloticase	62
Tibotec BVBA	(1R,2S)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol, (1R,2S)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol (2E)-2-butenedioate(1:1) (salt)	22
Sanofi-aventis R&D	Lixisenatide	95
Genzyme Europe B.V.	Ataluren	34
MEDA Pharma GmbH & Co. KG	Clindamycin Phosphate, Tretinoin	89
Allergan Pharmaceuticals Ireland	Dexamethasone	17
Boehringer Ingelheim International GmbH	(2S,3R,4R,5S,6R)-2-(4-Chloro-3-{3-[(S)-(tetrahydrofuran-3-yl)oxy]-benzyl}-phenyl)-6-hydroxymethyltetrahydro-pyran-3,4,5-triol	11
Novartis Europharm Ltd	Sotrastaurin (INN) acetate	58
Teva Pharma B.V.	Levonorgestrel, Ethinylestradiol	71
ZARS Pharma	Lidocaine, Tetracaine	85
Baxter Innovations GmbH	Recombinant human hyaluronidase, Human normal immunoglobulin	22

Merck Sharp & Dohme Ltd.	Vorinostat	52