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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 2011

Prepared by the Paediatric Medicines Section
Human Medicines Special Areas Sector
European Medicines Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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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 (hereinafter 'the Paediatric Regulation') 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 2011 and follows the same structure as the previous reports prepared by the Agency for the European Commission. Previous reports covered the period from the entry into force of the Paediatric Regulation, i.e. 26 January 2007 to 31 December 2009 and from 1 January 2010 to 31 December 2010. Both reports were published by the European Commission, on 2 June 2010 and 3 May 2011 respectively: http://ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm, and links 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 obligations in this Regulation. The current report lists only the initiatives which have not been previously reported in previous reports.

1.2. Data collection

On 23 November 2011, the Agency sent a letter to all Member States requiring their contributions by 13 January 2012 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).

The Agency contacted the National Patent Offices of each Member State requiring by 13 January 2012 the list of medicinal products that had obtained in 2011 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 6 December 2011).

The Agency received contribution from National Competent Authorities of 23 out of 27 Member States, and from 21 out of 27 National Patent Offices. The quality of the responses is variable, which may be due to the different availability of tracking systems of the information at national level (Annex 2).

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

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

1.3. Overview of the implementation of the Paediatric Regulation

Five years have elapsed since the entry into force of the Paediatric Regulation. The European Commission will provide a report to the European Parliament on the 5-year experience in 2013 (Article 50(2) of the Paediatric legislation). This report will be made publicly available.

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. 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. 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.

For the paediatric requests, members of the PDCO are now routinely involved in the Scientific Advice procedures. This is part of the effective collaboration established under the Executive Director's responsibility (Article 3(3) of the Paediatric Regulation and 64(2.d) of Regulation (EC) No 726/2004).

The number of paediatric-only requests remains stable, with a total of 27 procedures in 2011 as compared to 32 in 2010. The breakdown is displayed in Table 1.

Table 1. Number of requests for paediatric-only 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	2010	2011	Total Protocol Assistance requests	2010	2011
Number of **paediatric only scientific advice**	19	21	Number of **paediatric only protocol assistance**	6	3
Number of **paediatric only follow-up scientific advice**	4	2	Number of **paediatric only follow-up protocol assistance**	3	1

The figures correspond to procedures with a start date in 2011.

A high number of "mixed" scientific advice requests and protocol assistance (for orphan medicines) requests, i.e. covering both adult and paediatric development, have also been submitted. In all cases, at least a member of the PDCO is involved in the procedure. Compared to 2009 and 2010 when 35 and 48 procedures were submitted respectively, the figure increased to 57 in 2011. Figures are in Table 2.

As mixed scientific advices attract a fee for the adult part, and as protocol assistance is funded by the EU's special contribution for orphan-designated medicinal products, they are not considered part of the incentives provided by the Paediatric Regulation. Therefore a 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. questions on both adult and paediatric development)

	2010	2011
Number of advices (Scientific Advice and Protocol Assistance)*	400	433
Mixed (adult and paediatric development questions) advices and follow-up advices *	48	57

Source: EMA databases. * Year of advice letter.

2.1.2. Advice from the National Competent Authorities

Some National Competent Authorities also provide scientific advice to help companies in their paediatric development. In 2011, amongst the 21 Members States reporting the information, 5 gave paediatric only scientific advices and 8 gave mixed scientific advice (Figures are displayed in Table 3).

Table 3. Number of national scientific advice provided by Member States in 2011

	Member States	Number of paediatric only scientific advice	Number of mixed advice
1	Austria	0	0
2	Belgium	0	5
3	Cyprus	0	0
4	Czech Republic	0	0
5	Denmark	0	2
6	Estonia	0	0
7	Finland	0	0
8	France	1	2
9	Germany	0	32
10	Hungary	0	0
11	Ireland	0	0
12	Italy	3	1
13	Lithuania	0	0
14	Malta	0	0
15	Portugal	0	0
16	Romania	0	0
17	Slovenia	0	0
18	Spain	1	3
19	Sweden	3	8
20	The Netherlands	0	0
21	United Kingdom	3	12

As compared to 2010, the number of Member States who gave paediatric only or mixed Scientific Advices has doubled with 4 MSs giving paediatric only scientific advices in 2011 versus 2 in 2010, and 8 MSs giving mixed scientific advice in 2011 versus 4 in 2010.

As reported, the total number of paediatric only or mixed Scientific Advices given at National level has also increased significantly, with a total of 73 in 2011 versus 49 in 2010.

2.2. Paediatric Investigation Plans – Waiver

Applications

From January 2011 to December 2011, the PDCO received 187 validated applications for a "new" PIP or waiver, of which 58 (31%) were requests for a "full" waiver (for all specified conditions, in all subsets of the paediatric population). When comparing to the 326 validated applications from 2010, it seems that there has been a significant decrease. However, it should be noted that there was a one-off submission of 115 PIP applications for allergen products in 2010 due to substantial changes in German law for immunotherapy medicinal products. Subtracting these 115 exceptional applications from the 326 received, then 211 valid applications were received in 2010 compared to 189 valid applications in 2011. This may indicate stabilisation of the new applications submitted to the Agency.

The numbers of requests for full waiver were identical, 58 in 2010 and 2011 .

Of the 187 validated applications:

- 153 (82%) referred to medicinal products not yet authorised in the EU at the time of the entry into force of the Regulation.
- 33 (17.5%) referred to products already authorised in the EEA, and covered by a supplementary protection certificate (SPC) or a patent that qualifies for an SPC, with a view to submitting a variation/extension for a new indication, pharmaceutical form or route of administration.
- 1 application (0.5%) 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).

However, some applications for off-patent medicinal products submitted with a view to obtaining a PUMA may also correspond to a first authorisation (i.e. an application under article 7), when the applicant is not the marketing authorisation holder. These are included in the group of products 'not yet authorised'.

Similarly to 2010, the highest proportion of PIP or waiver applications was for medicinal products not yet authorised in the EU.

Opinions

The PDCO adopted in 2011 155 opinions:

- 45 positive opinions on product-specific waivers (29% of all 155 opinions).
- 107 positive opinions on a PIP (69%). These opinions may also contain deferral(s) of all or some measures, and/or waiver(s) of the obligation to perform clinical trial in certain age groups of children.
- 3 negative opinions (2%)., on 2 PIPs and 1 full waiver

The overall success rate is very high with 81% of positive outcomes. Of note, negative outcomes are published negative decisions and "late" withdrawals (less than 4 weeks before adoption of the opinion, or between Opinion and Decision) because the latter are likely to be due to lack of agreement on the content, rather than administrative reasons (few withdrawals and more likely to be happening in the early phases).

The proportions of opinions adopted in 2011 on product-specific waiver and PIPs are similar to 2010.

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. Access to the database of decisions has been improved, and the decisions can now be searched using various criteria, including by condition/disease.

It is planned to increase transparency and publish the full description of the measures (key elements) contained in the opinions in 2012.

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.

The latest EMA decision on class waiver, dated 19 December 2011, can be found on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/12/WC500119981.pdf

Modifications of agreed PIPs

In 2011, the PDCO has adopted 153 positive opinions on modifications of an agreed PIP and 2 negative ones.

As expected the number of modification is higher than in 2010 by almost 50% (103 positive opinions adopted in 2010). As the number of PIPs is increasing over time, the number of modifications is increasing too.

2.3. Compliance statement included in a marketing authorisation

Compliance check is done either as part of validation of applications for marketing authorisation, or variation/extensions, or, on request from the applicant to the PDCO, prior to the submission of such applications.

Once a PIP is completed and all the measures, including timelines, set out in the Agency's Decision have been carried out according to the Decision, a compliance statement can be issued. This document can be provided by marketing authorisation holders to the National Patent Offices. Based on the survey of Member States, no Member State reported having checked compliance of completed PIPs. This may be because the National Competent Authorities had agreed to delegate to the EMA PDCO the check of compliance, or because Marketing Authorisation Holders have chosen to obtain a PDCO Opinion.

In 2011, the PDCO adopted 8 positive opinions on compliance with an agreed PIP. There was no negative opinion on compliance. This number is comparable to 2010 (9 positive opinions).

The Agency has also received 49 applications for interim compliance check for a partially completed PIP, which resulted in the adoption of 45 letters (42 positive, 3 negative). The number of applications for interim compliance check is higher than in 2010 (38 applications).

2.3.1. Compliance statement for centrally-authorised medicinal products

In 2011, 6 companies submitted the results of all studies performed in compliance with an agreed PIP submitted in accordance with Article 8 of the Paediatric Regulation (i.e. for a regulatory submission for either a new indication, a new route of administration and/or a new pharmaceutical form). The assessment resulted in a compliance statement included in the marketing authorisation issued by the European Commission, as the Competent Authority for centrally approved medicines (Table 4). Further

information can be found in the European Public Assessment Reports of these medicinal products, which are available on the Agency website.

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

Companies	Products: invented name	international non-proprietary name (INN)
Sanofi BMS	Plavix and associated names	Clopidogrel
Genzyme	Cholestagel	Colesevelam
Viropharma SPRL	Buccolam	Midazolam
Boehringer	Viramune	Nevirapine
Sanofi Pasteur	Gardasil	HPV vaccine
N.V. Organon, Merck Serono Europe	Ioa, Zoely	Nomegestrol / estradiol

There is a significant increase as compared to 2010, when only 2 compliance statements were included for centralised marketing authorisations. This is a welcome improvement as more companies are able to get the reward for the completion of the PIP.

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 obtained the inclusion of a compliance statement in the marketing authorisation is presented in Table 5. The full list, as received from Member States, is in Annex 3.

Table 5. List of companies and products with a compliance statement (authorised through national/decentralised/mutual recognition procedure, including those subject to Article 29 of the Paediatric Regulation)

Companies	international non-proprietary name (INN)	Products: invented name
Baxter	Alanine, arginine, aspartic acid, calcium, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium, methionine, olive oil, ornithine, phenylalanine, potassium, proline, serine, sodium, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	Numeta and associated names
Arimidex	Anastrazole	AstraZeneca AB
Pfizer	Atorvastatin	Sortis and associated names
Sanofi Pasteur	DTP Polio HiB vaccine	Pediacel

Companies	international non-proprietary name (INN)	Products: invented name
Astra Zeneca AB	Esomeprazole sodium / esomeprazole magnesium	Nexium and associated names
Pfizer	Latanoprost	Xalatan and associated names
Merck Sharp and Dohme	Losartan	Cosaar and associated names
MSD	Montelukast	Singulair
Merck Sharpe and Dohme	Rizatriptan	Maxalt and associated names
Novartis	Valsartan	Diovan and associated names

Ten medicinal products have benefited from the reward. It should be noted that atorvastatin and valsartan were already mentioned in the 2010 report; the reason is that these products are authorised nationally and some Member States have already included the compliance statement in their National MA in 2010, while other MSs did it in 2011. Taking this into account, it is considered that the compliance statement was included for 8 “new” medicinal products in 2011. This is a significant and welcome increase compared to 2010, where there were 3.

2.4. Extension of the Supplementary Protection Certificate / Market Exclusivity

In order to be eligible for the 6-month extension of the Supplementary Protection Certificate (SPC), several conditions need to be met (including that the SPC extension application is made on time according to the provisions of Regulation (EC) No 469/2009):

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

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

iii) the Summary of Product Characteristics (SmPC) includes 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 National Patent Offices. Therefore, the companies have to file for an SPC extension with the National Patent Office of each Member State where the active substance of the medicinal product is protected by a patent which qualifies for an SPC, or an SPC. Annex 4 compiles the information received from Patent Offices on companies and products which were granted the 6-month extension of the Supplementary Protection Certificate in 2011.

About the same number of products benefited from the 6-month extension of the SPC in 2011 (9 products) and in 2010 (8 products). However this result has to be interpreted with caution as 6 products are still listed in the 2011, from among the 8 products listed in 2010. These 6 products

benefited in 2011 of extension of SPC in additional MSs, compared to 2010. Three “new” products are listed in 2011.

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.

In 2011, the first application for a PUMA was submitted to the EMA and authorised through the centralised procedure. The marketing authorisation was granted on 5 September 2011 to Buccolam (midazolam, oromucosal use) and will benefit from the 10-year data and marketing protection. Refer to http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002267/human_med_001479.jsp&mid=WC0b01ac058001d124 on the EMA website.

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, including those which failed to lead to an indication, should 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.

In 2011, 30 centrally authorised medicinal products (26 for new MA and 4 through variation/extension) included such a mention (Table 6). The number of centrally authorised medicinal products with waiver or deferrals added in the SmPC in 2011 is comparable to 2010.

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	Marketing Authorisation (MA) / Variation (V)	Date of EU CD
Fluenz	influenza vaccine (live attenuated, nasal)	MedImmune, LLC	X		MA	27/01/2011
Esbriet	pirfenidone	InterMune Europe Ltd	X		MA	28/02/2011
Xiapex	collagenase clostridium histolyticum	Pfizer Limited	X		MA	28/02/2011
Pumarix	pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	GlaxoSmithKline Biologicals s.a.		X	MA	04/03/2011
Teysuno	tegafur / gimeracil /	Taiho Pharma Europe, Limited	X		MA	14/03/2011

Invented name	International non-proprietary name	Marketing authorisation holder	Full waiver	Deferral	Marketing Authorisation (MA) / Variation (V)	Date of EU CD
	oteracil					
Gilenya	fingolimod	Novartis Europharm Limited		X	MA	17/03/2011
Halaven	eribulin	Eisai Europe Ltd	X		MA	17/03/2011
Jevtana	cabazitaxel	Sanofi-aventis	X		MA	17/03/2011
Viread	Tenofovir disoproxil fumarate	Gilead Sciences International Ltd.		x	V	24/03/2011
Trobalt	retigabine		X	X	MA	28/03/2011
Eliquis	apixaban	Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House		X	MA	18/05/2011
Yellox	bromfenac	Croma Pharma GmbH	X		MA	18/05/2011
Cinryze	c1 inhibitor, human	ViroPharma SPRL		X	MA	15/06/2011
Nulojix	belatacept	Bristol-Myers Squibb Pharma EEIG		X	MA	17/06/2011
Benlysta	belimumab	Glaxo Group Limited		X	MA	13/07/2011
Yervoy	ipilimumab	Bristol-Myers Squibb Pharma EEIG	X		MA	13/07/2011
Victrelis	boceprevir	Merck Sharp & Dohme Ltd		X	MA	18/07/2011
Fampyra	fampridine	Biogen Idec Limited	X		MA	20/07/2011
Trajenta	linagliptin	Boehringer Ingelheim International GmbH		X	MA	24/08/2011
Vibativ	telavancin	Astellas Pharma Europe B.V.		X	MA	02/09/2011
Zytiga	abiraterone	Janssen-Cilag International NV	X		MA	05/09/2011
Incivo	telaprevir	Janssen Cilag International NV		X	MA	19/09/2011
Vectibix	Panitumumab	Amgen Europe B.V.	x		V	10/11/2011
Vyndaqel	tafamidis	Pfizer Specialty UK Limited	X		MA	16/11/2011
Edurant	rilpivirine	Janssen-Cilag International NV		X	MA	28/11/2011
Eviplera	emtricitabine / rilpivirine / tenofovir disoproxil	Gilead Sciences International Limited		X	MA	28/11/2011
Dificlir	fidaxomicin	FGK Representative Service GmbH		X	MA	05/12/2011
Ipreziv	azilsartan	Takeda Global Research		X	MA	07/12/2011

Invented name	International non-proprietary name	Marketing authorisation holder	Full waiver	Deferral	Marketing Authorisation (MA) / Variation (V)	Date of EU CD
	medoxomil	and Development Centre (Europe) Ltd				
Mabthera	Rituximab	Roche Registration Ltd.	X		V	14/12/2011
Nevanac	Nepafenac	Alcon Laboratories (UK) Ltd.	X		V	22/12/2011

For medicinal products authorised through national/decentralised/mutual recognition procedure, no information on those that have been granted a marketing authorisation or varied and that include such a statement in their SmPC was received.

2.6. Price/reimbursement benefits

The Agency has not received new information on price or reimbursement benefits for paediatric medicines in the Member States. Hungary reported that 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

Funding of studies into off-patent medicinal products has been made available since 2007 (Article 40). The funding was provided through the EU Framework Programmes for Research and Technological Development; it covers the development of off-patent medicinal products with a view to the submission of a PUMA.

In agreement with DG Research, the PDCO maintains a priority list of off-patent products for which studies are needed.

The funding of off-patent paediatric medicinal products was not part of the 6th Call of the 7th Framework Programme of the European Union in 2011. The EMA did not publish a revised priority list for studies into off-patent paediatric medicinal products for 2011. Funding will be provided in 2012.

2.7.2. European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

A European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population has been established, and is coordinated by the Agency.

Membership of the network is based on self-assessment. Networks were classified according to 3 categories:

- category 1: networks fulfilling all minimum criteria for membership of Enpr-EMA;
- category 2: networks potentially fulfilling all minimum criteria but in need of clarifying some issues before becoming a member of Enpr-EMA;
- category 3: networks currently not yet fulfilling minimum criteria.

Enpr-EMA published a list of applicants for membership in January 2011 (http://bit.ly/IvoGI5). To date, 34 networks have submitted their self-assessment reports to the EMA (http://bit.ly/IJcz9E).

Eighteen networks are recognised as category 1; 2 are recognised as category 2; and 14 are recognised as category 3.

Table 7: Enpr-EMA networks

Type of network	Category 1	Category 2	Category 3
National	NIHR-MCRN, FinPedMed, MCRN-NL, MICYRN, Scotmcn, CICPed		IPCRN, NCCHD, BLF, RIPPS, Futurenest CR, BPDN
Oncology (solid / haematologic malignancies)	Newcastle-CLLG, ITCC, IBFMSG, EPOC	CLG of EORTC	
Diabetes / Endocrinology / metabolic disorders / Gynaecology			AMIKI
Gastroenterology / Hepatology			ESPGHAN
Allergology / Immunology/ Rheumatology	PRINTO		JSWG of PRES
Stem Cell and Organ Transplantation / Haematology (non malignant) / Haemostaseology	EBMT		IPTA
Respiratory diseases / Cystic Fibrosis	ECFS-CTN		
Cardiovascular diseases / Nephrology			
Psychiatry / Neurology	EUNETHYDIS		
Infectious diseases / Vaccinology	PENTA, UKPVG		PENTI
Special Activities / Age groups			
Intensive Care / Pain / Anaesthesiology / Surgery		Network of Excellence for research in paediatric clinical care-NL	
Neonatology	GNN		EuroNeoNet, Neo-circulation, INN
European Paediatric Pharmacists			
Special Activities (pharmacovigilance, long-term follow up, community paediatricians)	FIMP-MCRN		
Expertise in Clinical Trial Methodology			TEDDY*, PRIOMEDCHILD*, ECRIN*, GRIP*

* Unable to provide filled self-assessment report

Enpr-EMA does not cover all paediatric therapeutic areas. Therefore, one of the most important activities of the Enpr-EMA is to stimulate and foster new European networks such as in paediatric cardiology, gastroenterology, and diabetes, and helping create a larger network for example in neonatology. The activities are performed in collaboration with the relevant learned societies, and existing networks serve as models and mentors.

In March 2011, a workshop held at EMA, provided the opportunity for Enpr-EMA to meet all stakeholders including academia, regulators and pharmaceutical companies.

Enpr-EMA has a Co-ordination group of 20 members (including 2 PDCO members, a Chair (Dr Peter Helms), and a co-chair from EMA (Dr Irmgard Eichler) and collaborates with the PDCO, which acts as the network's 'scientific committee' as defined in the strategy of the network.

- The main activities in 2011: Publication of self-assessment reports and list of network members of Enpr-EMA; - composition of coordinating group (CG) and call for expression of interest to chair CG.
- Discussion meeting with EnCEPP.
- Third network workshop (first day only networks: election of chair of coordinating group and discuss priority tasks of CG; second day: first meeting between networks and industry and patient organisations).
- Two meetings of coordinating group at EMA, including with a representative of Patients and Consumers Working Party (PCWP) as co-opted member).
- Adoption of Policy on transparency and handling of research Interests.
- Adoption of Mandate of Coordinating group (CG).
- Adoption of Enpr-EMA Mission statement.
- Workshop with emerging networks in cardiology, endocrinology and gastroenterology.

2.7.3. Inventory of paediatric needs

In 2011 the PDCO continued working on the inventory of paediatric needs (article 43). It is planned to publish the first inventory in 2012 in the cardiovascular area.

2.7.4. National initiatives

For this year report, the National Competent Authorities were asked to mention new information or changes to what was reported in the previous report. The following was provided:

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).

France:

Paediatric is a priority axis in the national PHRC programme, funding for trials in public hospitals (Programme Hospitalier de Recherche Clinique or hospital clinical-research plan).

Germany

As of 2011, results of the first KiGGS study (2003-2006), a first health survey of the German paediatric population can be found in English:
http://www.kiggs.de/experten/erste_ergebnisse/English_Articles/index.4ml

The project is still on-going and data collection will continue until June 2012.

Hungary

As above, medicinal products included in the National Immunisation programme are provided free of charge by the Hungarian government.

Italy

The Programme on Independent research on drugs funded by the Italian Medicines Agency, AIFA, described in the previous report is in place and the objectives are the same as previously described. The 2009 Programme preliminary results are available. A selection of projects is on-going.

Malta

Research on medicinal products, including those for paediatric use, can be funded under the National Research and Innovation Programme 2012. It funds research on projects in Health & Biotechnology. However there is no specific incentive in place for paediatric medicines.

2.8. Authorisation of paediatric clinical trials

The authorisation of clinical trials in the European Union is under the responsibility of the Member States, according to Directive 2001/20/EC. However, making public the information on paediatric trials entered into the EU Database on Clinical Trials (EudraCT) is under the EMA's responsibility.

The Agency (including its Scientific Committees) has 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.

Availability of protocol-related information from EudraCT for registered trials, including all trials with the paediatric population, has been achieved since March 2011 in EU CTR (https://clinicaltrialsregister.eu). This achievement greatly improves transparency and allows stakeholders to be informed on trials and enrolment. Transparency will aid preventing unnecessary trials and finding trials of interest, and will allow the checking of figures and analysis of trends. The initiative is on-going and should result in the online publication of trial results (phase I to IV in the case of paediatric trials) in the next few years.

Data extracted from EudraCT for 2011 are reported in Table 8.

Table 8 Paediatric clinical trials authorised in 2011 (or, protocol upload into EudraCT in 2011).

Paediatric trials (n.)	360
of which, paediatric trials that are part of an agreed PIP (n.)*	*70 (19%)*
Total number of trials (adults and / or children)	3,622
Proportion of paediatric trials among all trials	**!H2 Is Not In Table**

Source: EudraCT Data Warehouse using pre-defined query on 3 April 2012 and counting the first authorised trial only, in case of more than one Member State. As National Competent Authorities of Member States upload data into EudraCT irrespective of the study population, the year of authorisation is a better indicator of the initiation than the year of upload.
* This information requires sponsors using a Clinical Trial Application form that was only available from November 2009, for use with version 8 of EudraCT.

The initiative is on-going and should result in the online publication of trial results (phase I to IV in the case of paediatric trials) in the next few years

Amongst the Member States who answered the question on incentives for paediatric clinical trials, Slovenia mentioned 2 clinical trials that received a fee waiver/reduction in 2011:

- sponsor: Martin Luther Universitaet Halle-Wittenberg, Magdeburger Strasse 27, 06108 Halle, Germany; INN: procarbazine, dacarbazine.
- sponsor: Pfizer Inc., 235 East 42nd Street, New York, NY 10017, USA; Medicinal product: Enbrel (INN: etanercept).

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.

With respect to fees, 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. There are no other fee reductions for centralised procedure for medicinal products for use in children, or for extension of the marketing authorisation to add a new paediatric indication, pharmaceutical form and/or route of administration for paediatric use. .

In 2011, the first application for a PUMA was submitted to the EMA and benefited from fee reductions. The marketing authorisation was granted on 5 September 2011 to Buccolam (see section 2.5 of this report).

Another application for a PUMA for Fluad Paediatric was submitted on 13 December 2010. During the scientific assessment by the Committee for Medicinal Products for Human Use (CHMP), the applicant decided to withdraw the application as it was unable to address the questions of the Committee within the required timeline. See the EMA press release published in February 2012 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002299/wapp/Initial_authorisation/human_wapp_000129.jsp&mid=WC0b01ac058001d128&source=homeMedSearch&category=human).

2.10. Article 45/46 of the Paediatric Regulation

2.10.1. Article 45 submissions

In accordance with Article 45 of the Paediatric Regulation, paediatric 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.

- In October 2011, the complete list of paediatric studies submitted under Article 45 was made publicly accessible in a searchable database on the EMA website (for centralised and non-centralised products), with results-related information as soon as submitted for assessment.
- For centrally authorised medicinal products, by 2011 the CHMP had completed the assessment of all submitted data, covering 55 active substances in 61 medicinal products. Since January 2008, the SmPCs of 12 medicinal products had been changed subsequent to the assessment; none of these changes were made in 2011.
- For products authorised through national/decentralised/mutual recognition procedures, 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 on-going work-sharing exercise between Member States and the assessment is being performed in waves. In 2011, 4 additional waves have been agreed to be included in the work-sharing, corresponding to 55 substances (10th to 13th waves). The

assessment of the data has been finalised for 34 active substances. The list of substances and the resulting recommended amendments of the SmPCs with a public assessment report are presented in Annex 61. Further information can be found on the CMD(h) website (http://www.hma.eu/99.html).

2.10.2. Article 46 submissions

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 of the trial.

When regulatory action is necessary (i.e. in case of amendments to SmPC, labelling and/or PL identified by the MAH) MAHs are advised to submit straightaway a variation containing the Article 46 paediatric study(ies) (here included).

- For centrally authorised products, approximately 24 procedures of evaluation of studies submitted through this Article have been finalised in 2011. Out of these 24 procedures, the CHMP recommended a change in the product information in 6 cases (corresponding to 5 medicinal products). The list of products and the resulting amendments of the SmPCs is presented in Annex 7. As compared to 2010, the number of procedures is lower in 2011, but the proportion of changes in product information is higher, with 15% of the procedures leading to a change in the Product Information in 2010 and 25% in 2011, which is very encouraging.
- For nationally authorised medicinal products, and those authorised through mutual recognition or decentralised procedures, a total of 45 studies were submitted in 2011. The assessment has been finalised for 20 procedures. A public assessment report has been published for 17 of these studies, recommending for 4 of them to amend the SmPCs. As compared to 2010, the proportion of changes in product information further to assessment has decreased in 2011 with 24% of the evaluation leading to changes versus 46% in 2010. The list of products and resulting amendments of the SmPCs are presented in Annex 72. Further information can be found on the CMDh webpage.

2.11. Article 33 (register of placing on the market)

The Regulation requires monitoring of products that have been placed on the market following the authorisation of a paediatric indication (in compliance with a completed PIP). The Agency is developing the register and the tool through a modification of the paediatric database (PedRA), which should be in place before September 2012. The database includes procedural and scientific information on all procedures and therefore covers both centrally and nationally-approved medicinal products. This information will be made public before the end of 2012 on the Agency's website.

2.12. Article 35 (transfer of data after discontinuation of marketing)

The Agency has not received any information about either a marketing authorisation holder transferring the MA or providing access, or an applicant requiring access to data at centralised or national level, but the first medicinal products have been authorised recently for the paediatric population following the completion of a PIP.

[1] correct as at 31 January 2012
[2] figures of 31 January 2012

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

3.1. Submission of PIP and waiver applications to the PDCO

Article 16 of the Paediatric Regulation requires pharmaceutical companies to submit applications for a PIP and/or a waiver no later, except when duly justified, than upon completion of the human pharmacokinetic (PK) studies in adults; it is considered that this corresponds approximately to the end of phase 1.

Late submissions for PIPs or waivers may delay the submission or the validation of the applications for the marketing authorisation in adults if the applicant does not have an Agency decision at the time of submission.

An indicator on the late submission of PIP/waiver applications was reported for the first time in the 2010 Annual report, and included the names of applicants that submitted applications with a delay greater than 6 months. In some cases, the delay was such that the PIP was submitted when the paediatric studies were completed. This put the PDCO in a difficult situation as the evaluation may conclude that insufficient studies or trials have been performed, or the PDCO is unable to request further data for ethical reasons to avoid exposing children to repetitive trials.

Indicators for 2011 are reported in Table 9 below:

Table 9 Time lag between completion of PK studies and submission of applications for PIPs and waivers in 2011.

Delayed applications (submissions 6 months or more later than deadline)	2010	2011
Number of delayed PIP applications	65 (74%)	44 (59%)
Reference: number of all PIP applications	*88*	*74*
Time lag in months, median (range)	22	35 (9-159)
Number of delayed applications for full waiver	26 (59%)	13 (42%)
Reference: number of all applications for full waiver	*44*	*31*
Time lag in months for delayed full waiver applications, median (range)	18	35 (9-137)

Source: EMA Paediatric database.

In 2011, more than half of the PIP applications were submitted late. The timing has improved as compared to 2010, where 74% of the PIPs applications were late. However The length of delay is greater with a median of 35 months as compared to 22 months in 2010.

From the 44 PIPs submitted late (more than 6 months):

- 4 included a valid justification (9% PIPs),
- 28 included a justification that was not considered acceptable (64%),
- 12 did not have any justification (27%).

There is a lack of appropriate justification provided by applicants when submitting a PIP more than 6 months after the completion of the human pharmacokinetic (PK) studies in adults. For 91% of the late PIPs, delays were either not justified in an acceptable way, or no information was provided. Applicants should submit PIPs on time or properly justify the delay in submitting.

With regards to submissions of application for full waivers, there is an improvement with 42% of the applications submitted late in 2011 as compared to 59% in 2010. However the length of the delay has almost doubled in 2011 (median 35 months) compared to 2010 (median 18 months).

The EMA / PDCO have regularly addressed the issue of timing of submissions in meetings with the pharmaceutical industry and this issue is still a concern. The reasons often given for late submissions are that preparing Paediatric plans for a number of products for which development will be discontinued would be a waste of resources and that there would be still many unknowns at this stage, leading to uncertainties and potential multiple modifications of agreed PIPs. On the other hand, the benefits of early dialogue include a better integration of paediatric needs already in adult development for formulations and pharmaceutical forms, toxicology (reproduction toxicity), animal models and juvenile animal data, modelling and simulation for PK and pharmacodynamic studies. This also avoids delays at the time of submission of the application for adults, if the PIP or waiver has not been agreed on time. The earlier submission of plans (end of phase 2) to the FDA according to the new 2012 Act (FDA Innovation and Safety act) may provide a further reason for companies to come earlier.

3.2. Validation of applications 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 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).
- A decision of the Agency on a PIP including the granting of a deferral.
- A decision of the Agency granting a product-specific waiver.
- A decision of the Agency granting a class waiver.

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.

There were no reports of applications falling under Article 7 or 8 that were validated without having complied with these requirements at the Agency or at national level.

3.3. 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 out in the Regulation.

3.4. Mention of Decisions on waivers or deferrals in product information

From the answers of Member States, all products authorised/varied through Mutual Recognition Procedure in 2011 included the mention of a Decision on waivers or deferrals in the product information where applicable.

Similarly, all centrally-authorised products falling under the requirements of Article 7 or 8 with a marketing authorisation granted in 2011 had this statement included in the product information.

3.5. Annual reports on deferrals

The Agency has published guidance and a form for the electronic submission of the annual reports (Article 34(4) of the Paediatric). The EMA has received 56 annual reports on deferral in 2011 as compared to 31 in 2010. This increase was expected as the total number of agreed PIPs is increasing over time and many PIPs have agreed deferrals; however, there are a number of MAH who have not submitted these reports.

There were 36 annual reports on deferral, out of the 56 submitted, which showed that the paediatric development was continuing according to the plans.

3.6. International exchange of information in view of global development

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 facilitating global development of medicinal products. The Japanese authorities (MHLW and PMDA) joined the Paediatric Cluster teleconferences in November 2009 and Health Canada joined in September 2010, following the establishment of the respective confidentiality agreements.

A report dated June 2011 on all interactions of the EMA and the US FDA from September 2009 to September 2010 is available on the EMA website (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/06/WC500107900.pdf).

4. CONCLUSION

This 3rd 2011 report corresponds to the 5th year since the entry into force of the Paediatric Regulation.

As already seen in 2010, the reflection on, and planning of the development of a medicinal product in children is now part of the global development of medicinal products previously focused on adults only. More paediatric information is included in the product information and new paediatric indications granted, through different regulatory procedures. Statements on deferrals and waivers have been routinely added.

Two projects have significantly moved forward this year:

- Enpr-EMA provides the forum for a discussion between networks and pharmaceutical companies engaged in paediatric medicine development. The workshop was the opportunity to discuss with all stakeholders including academia, regulators and pharmaceutical companies on the collaboration. A major issue was identified with the need for financial support of network infrastructures.
- Transparency of clinical trials data was increased. Data relating to protocols of trials included in EudraCT including all trials with the paediatric population are publicly available since March 2011 through EU-CTR. This achievement allows all stakeholders to be informed on trials objectives and enrolment.

Transparency was also increased with the publication in October 2011 on the EMA website of the first paediatric studies submitted under Article 45 for Centrally Authorised Products (http://art45-paediatric-studies.ema.europa.eu/clinicaltrials).

In 2011, the first application for a PUMA was submitted to the EMA, and subsequently authorised through the centralised procedure.

The major deviations from the obligations set by the Regulation are represented by delays in submitting applications for PIPs or Waivers to the Agency, with a median of 35 months. This lag time has almost doubled compared to 2010. This represents a missed opportunity for early dialogue, although this possibility and the binding character of scientific advice was repeatedly requested by pharmaceutical industry in the past. Additionally, delays in submitting PIPs were justified in only 9% of the cases. Another deviation is the lack of follow up of PIP implementation as MAHs fail to submit PIP annual reports to the Agency.

The update of the Commission Regulation on financial penalties (Commission Regulation (EU) No 488/2012, which is applicable as of 2 July 2012 may serve if future as an additional deterrent.

Although there is evidence that new paediatric indications and new paediatric information are included in product information for medicines used in children, pharmaceutical companies seem to be meeting their obligations, both in terms of submissions of PIP or waiver applications, and in terms of performance of clinical trials in children, for the sole purpose of validation of applications for marketing authorisations. This is also confirmed by PIP modifications showing major delays in trials, and plans not progressing in a substantial proportion of annual reports (for those submitted).

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 2011 to 31 December 2011.
- 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 2011
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 ☐

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 2011

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 2011

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 2011 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 2011 (please highlight if some of the information is confidential).

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 2011.

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 2011.

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.

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.

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 2011.

Infringement

Are there cases in 2011 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	
Bulgaria		X
Cyprus	X	
Czech Republic	X	X
Denmark	X	X
Estonia	X	X
Finland	X	X
France	X	
Germany	X	X
Greece		
Hungary	X	X
Ireland	X	X
Italy	X	X
Latvia	X	
Lithuania	X	X
Luxembourg		X
Malta	X	X
The Netherlands	X	X
Poland	X	X
Portugal	X	X
Romania	X	X
Slovakia		X
Slovenia	X	X
Spain	X	
Sweden	X	X
United Kingdom	X	X
Iceland		
Norway		

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
Baxter Healthcare GmbH	Numeta G 13 % / 16 % / 19 % E Emulsion zur Infusion	alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, , methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil	DC SE/H/0918/001-003/DC 1-30164, 1-30165, 1-30166	National implementation: 17.03.2011	http://pharmaweb.ages.at/index.jsf

Belgium

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Cyprus

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Czech Republic

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter Czech spol.s.r.o	Numeta G 13%E		SE/H/918/001	National implementation: 25.06.2010	
Baxter Czech spol.s.r.o	Numeta G 16%E		SE/H/918/002	National implementation: 25.06.2010	
Baxter Czech spol.s.r.o	Numeta G 19%E		SE/H/918/003	National implementation: 25.06.2010	

Denmark

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter A/S	Numeta G13E	Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine,	45931	Authorised through DC procedure (SE/H/0918/01-03/DC) 09.02.2011	

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
		taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil			
Baxter A/S	Numeta G13E	Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil	45932	Authorised through DC procedure (SE/H/0918/01-03/DC) 09.02.2011	

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter A/S	Numeta G13E	Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil	45933	Authorised through DC procedure (SE/H/0918/01-03/DC) 09.02.2011	

Estonia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Finland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter Oy	Numeta G13 E infuusioneste emulsio	amino acids electrolytes, glucose and lipids	28119 SE/H/918/01/DC	24.3.2011	
Baxter Oy	Numeta G16 E infuusioneste emulsio	amino acids electrolytes, glucose and lipids	28120 SE/H/918/02/DC	24.3.2011	
Baxter Oy	Numeta G19 E infuusioneste emulsio	amino acids electrolytes, glucose and lipids	28121 SE/H/918/03/DC	24.3.2011	

France

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Sanofi Pasteur	Pediacel	Purified diphtheria Toxoid, purified tetanus,5 component acellular pertussis Inactivated poliomyelitis vaccine (Vero) – Type 1 (Mahoney), Type 2 (MEF-1) and Type 3 (Saukett) Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus	N - 64968141	05-Apr-11	

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
		protein (PRP-T)			
Baxter	Numeta h	Alanine, Arginine, Aspartic acid, Cysteine/Cystine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine monohydrate, Methionine, Ornithine hydrochloride, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine Sodium chloride, Potassium acetate, Magnesium acetate, tetrahydrate, Calcium chloride, Sodium glycerophosphat e Glucose Olive oil, refined, Soya-bean oil, refined Paediatric Triple Chamber Bag	DC - 69278991648758196890328 3	18/05/2011	http://afssaps-prd.afssaps.fr/php/ecodex/extrait.php?specid=68903283 http://afssaps-prd.afssaps.fr/php/ecodex/extrait.php?specid=69278991 http://afssaps-prd.afssaps.fr/php/ecodex/extrait.php?specid=64875819

Germany

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Astra Zeneca	Axanum 81 mg/20 mg Hartkapseln	Acetylsalicylic acid and esomeprazole	DE/H/2749/001/DC 81047.00.00	28.09.11	
Allmirall Hermal GmbH	Actikerall 5 mg/g + 100 mg/g Lösung zur Anwendung auf der Haut	Fluorouracil and Salicylic acid	DE/H/2645/001/DC 80136.00.00	21.06.11	
Zars (UK) Ltd	Pliaglis 70 mg/g + 70 mg/g, Creme	Lidocain und Tetracain	DE/H/3287/001/DC	Pending	
MEDA Pharm GmbH & Co. KG	Dymesta / Synaze / Azeflu / Xatalin Nasenspray	Azelastinhydrochlorid und Fluticasonpropionat	DE/H/3355-3358/001/DC	Pending	
Shire Pharmaceutical Contracts Ltd.	Venvanse 30 mg / 50 mg / 70 mg Hartkapseln	Lis-Dexamfetamindimesilate	UK/H/3326/001-003/DC	Pending	
Biotest	Fovepta	Biotest Pharma GmbH		Pending	

Hungary

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Ireland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Provepharm SAS	Provelblue	Methylthioninium Chloride	EU/1/11/682/001	28-Jun-11	www.imb.ie
InterMune Europe Ltd	Esbriet	Pirfenidone	EU/1/11/667/001-003	11-May-11	www.imb.ie
Nycomed GmbH	Daliresp	Roflumilast	EU/1/11/668/001-003	11-May-11	www.imb.ie
Nycomed GmbH	Libertek	Roflumilast	EU/1/11/666/001-003	11-May-11	www.imb.ie

Italy

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Pfizer Italia S.r.l.	Xalatan	latanoprost	033219015/033219027	15-Jan-11	

Latvia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Lithuania

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Malta

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

The Netherlands

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Poland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Portugal

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter Médicom-Farmacêutica, Lda (PT)	Numeta G13%E, Numeta G16%E e Numeta G19%E	Aminoacids + Glucose + Lipids	SE/H/918/01-03/DC	04/07/2011	

Romania

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Slovenia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
None.					

Spain

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
MERCK SHARP AND DOHME DE ESPAÑA, S.A.	SINGULAIR 4 mg GRANULADO	Montelukast Sodico	65429	Authorised through RM procedure FI/H/104/004/003/II/052 National implementation date 22/12/2011	http://www.aemps.gob.es/cima/especialidad.do?metodo=verPresentaciones&codigo=65429
MERCK SHARP AND DOHME DE ESPAÑA, S.A.	SINGULAIR 4 MG COMPRIMIDOS MASTICABLES	Montelukast Sodico	63673	Authorised through RM procedure FI/H/104/004/003/II/052 National implementation date 22/12/2011	http://www.aemps.gob.es/cima/especialidad.do?metodo=verPresentaciones&codigo=63673
MERCK SHARP AND DOHME DE ESPAÑA, S.A.	MAXALT 10 MG COMPRIMIDOS	Rizatriptan Benzoato	62289	Authorised through RM procedure NL/H/0144/001-004/II/0043 National implementation date 21/12/2011	http://www.aemps.gob.es/cima/especialidad.do?metodo=verPresentaciones&codigo=62289

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
MERCK SHARP AND DOHME DE ESPAÑA, S.A.	MAXALT MAX 10 mg LIOFILIZADO ORAL	Rizatriptan Benzoato	62291	Authorised through RM procedure NL/H/0144/001-004/II/0043 National implementation date 21/12/2011	http://www.aemps.gob.es/cima/especialidad.do?metodo=verPresentaciones&codigo=62291

Sweden

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Baxter Medical AB, Sweden	Numeta G13E, Numeta G6E, Numeta G19E, Emulsion for infusion	olive oil, refined, cysteine, glutamic acid, histidine, ornithine hydrochloride, phenylalanine, taurine, aspartic acid, potassium acetate (E261), threonine, glycine, magnesium acetate tetrahydrate, isoleucine, tyrosine, arginine, leucine, serine, valine, glucose monohydrate,	433020 433030 433040	08-Apr-11	

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
		soya-bean oil, refined, calcium chloride dihydrate, lysine monohydrate, proline, sodium glycerophosphate, hydrated, alanine, methionine, tryptophan			

United Kingdom

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of marketing authorisation	Link to official webpage if available
Prothrics PLC	Digifab	Digoxin immune Fab	PL21744/0001	Jul-11	

3.2 Marketing authorisation extended/varied for already authorised medicinal products in 2011

Austria

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme GmbH	Maxalt 5 mg / 10 mg – Tabletten Maxalt Rapitab 5 mg / 10 mg Lyotabletten	Rizatriptan	MRP NL/H/0144/001-004 1-22636, 1-22637, 1-22638, 1-22639	National implementation: 07.12.2011	http://pharmaweb.ages.at/index.

Belgium

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Cyprus

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme B.V., Netherlands	Maxalt tabs 5mg	Rizatriptan benzoate	21091(MRP)	National implementation: 06.12.2011	
Merck Sharp & Dohme B.V., Netherlands	Maxalt tabs 10mg	Rizatriptan benzoate	21092(MRP)	National implementation: 06.12.2011	
Merck Sharp & Dohme B.V., Netherlands	Maxalt oral lyophilisate tabs 5mg	Rizatriptan benzoate	21093(MRP)	National implementation: 06.12.2011	
Merck Sharp & Dohme B.V., Netherlands	Maxalt oral lyophilisate tabs 10mg	Rizatriptan benzoate	21094(MRP)	National implementation: 06.12.2011	

Czech Republic

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
MSD	Singulair 4MG granule	Montelukastum	FI/H/104/004	National implementation: 05.05.2011	
MSD	Maxalt 5 mg tablety	Rizatriptanum	NL/H/144/001	National implementation: 21.12.2011	
MSD	Maxalt 10 mg tablety	Rizatriptanum	NL/H/144/002	National implementation: 21.12.2011	
MSD	Maxalt 5 mg peror. lyof	Rizatriptanum	NL/H/144/003	National implementation: 21.12.2011	
MSD	Maxalt 10 mg peror. lyof	Rizatriptanum	NL/H/144/004	National implementation: 21.12.2011	

Denmark

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme B.V.	Singulair	Montelukast	31761 44116	FI/H/0104/03-04/II/52 6 January 2011	
Merck Sharp & Dohme B.V.	Maxalt	Rizatriptan	30079 30080	NL/H/0144/01-04/II/043 29 November 2011	
Merck Sharp & Dohme B.V.	Maxalt Smelt		30081 30082	NL/H/0144/01-04/II/043 29 November 2011	

Estonia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Finland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Pfizer Oy	Xalatan 50 mikrog/ml silmatipat, liuos	Latanoprostum	12694	04-Jan-11	Implementation of the commission decision following an Article 29 application under regulation (EC) No 1901/2006 Commission Decision ((2010)7267 UK/H/179/01/IB/73 Compliance statement
MSD	Maxalt 5 mg tabletti	Rizatriptani benzoas	13603	16-Dec-11	NL/H/144/01/11/43 Compliance statement
MSD	Maxalt 10 mg tabletti	Rizatriptani benzoas	13604	16-Dec-11	NL/H/144/02/11/43 Compliance statement
MSD	Maxalt Rapitab 5 mg tabletti kylmakuivattu	Rizatriptani benzoas	13590	16-Dec-11	NL/H/144/03/11/43 Compliance statement
MSD	Maxalt Rapitab 10 mg tabletti kylmakuivattu	Rizatriptani benzoas	13591	16-Dec-11	NL/H/144/04/11/43 Compliance statement

France

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Sanofi Aventis	Primperan 2.6 mg/mL infants children solution	Metoclopramide chlorhydrate	14/10/2010 declaration to stop marketing N - 6 753 653 9 Withholding of MAA (“suspension AMM” decision): effective on		

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
			09/02/2011 (article 31)		

Germany

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

Hungary

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Ireland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
AstraZeneca UK Limited	Nexium		PA0970/027/004		www.imb.ie
Boehringer Ingelheim Limited	Catapres Tablets 300 micrograms.		PA0007/014/002		www.imb.ie
Clonmel Healthcare Ltd	Amiodarone		PA0126/186/001		www.imb.ie
Clonmel Healthcare Ltd	Risontel Once a Week		PA0126/197/001		www.imb.ie
Sanofi-Aventis Ireland Limited	Cerubidin		PA0540/096/001		www.imb.ie
McDermott Laboratories Ltd t/a Gerard Laboratories	Zesger 5 mg Tablets.		PA0577/041/001		www.imb.ie
McDermott Laboratories Ltd t/a Gerard Laboratories	Zistap		PA0577/058/001		www.imb.ie

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
McDermott Laboratories Ltd t/a Gerard Laboratories	Risedronate Mylan Once a Week		PA0577/127/001		www.imb.ie
McDermott Laboratories Ltd t/a Gerard Laboratories	Risedronate Mylan Once a Week		PA0577/127/001		www.imb.ie
Rowex Ltd	Lispril		PA0711/047/002		www.imb.ie
Rowex Ltd	Mirap		PA0711/062/001		www.imb.ie
Rowex Ltd	Mirap DisTab		PA0711/094/001		www.imb.ie
B. Braun Melsungen AG	Ondansetron B.Braun		PA0736/027/001		www.imb.ie
Janssen-Cilag Ltd	SPORANOX		PA0748/009/001		www.imb.ie
Teva Pharma B.V.	Mirtazapin Teva		PA0749/017/001		www.imb.ie
Teva Pharma B.V.	Mirtazapin Teva		PA0749/017/001		www.imb.ie
Pfizer Healthcare Ireland	Zarontin Syrup, 250mg/5ml		PA0822/017/002		www.imb.ie
Pfizer Healthcare Ireland	Topiramate Pfizer		PA0822/051/001		www.imb.ie
AstraZeneca UK Limited	Diprivan 1% w/v Emulsion for Injection or Infusion		PA0970/005/004		www.imb.ie
Arrow Generics Limited	Topirama		PA1130/009/001		www.imb.ie
Arrow Generics Limited	Topirama Capsules		PA1130/009/007		www.imb.ie
Arrow Generics Limited	Famlov		PA1130/013/001		www.imb.ie
PIERRE FABRE Ltd	NAVELBINE		PA1287/001/001		www.imb.ie
Aurobindo Pharma Limited	Mirtazapine Aurobindo 15 mg Orodispersible Tablets		PA1311/012/001		www.imb.ie
Pharmathen S.A.	Bonapenya		PA1368/008/001		www.imb.ie
Actavis Group	Lestace		PA1380/007/001		www.imb.ie

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
PTC ehf					
Actavis Group PTC ehf	Paroxetine		PA1380/009/001		www.imb.ie
Actavis Group PTC ehf	Valsartan Actavis 40 mg film-coated tablets		PA1380/022/001		www.imb.ie
Zaklad Farmaceutyczny Adamed Pharma S.A.	Risedronate Sodium Adamed Pharma Once a Week		PA1525/004/001		www.imb.ie

Italy

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Latvia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Lithuania

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme UAB, Lithuania	Maxalt	Rizatriptan	LT/1/11/2615/001-020	15/11/2011	

Malta

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme	Maxalt Tablets 5 mg	Rizatriptan	MA058/01901	01/01/2012	
Merck Sharp & Dohme	Maxalt Tablets10 mg	Rizatriptan	MA058/01902	01/01/2012	
Merck Sharp & Dohme	Maxalt oral lyophilisate 5 mg	Rizatriptan	MA058/01903	01/01/2012	
Merck Sharp & Dohme	Maxalt oral lyophilisate 10 mg	Rizatriptan	MA058/01904	01/01/2012	

The Netherlands

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Poland

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warszawa	Maxalt	Rizatriptanum	18564	16/05/2011	
MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warszawa	Maxalt	Rizatriptanum	18565	16/05/2011	
MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warszawa	Maxalt RPD	Rizatriptanum	18566	16/05/2011	
MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warszawa	MaxaltT RPD	Rizatriptanum	18567	16/05/2011	

Portugal

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme, Lda.	Singulair	Montelukast	FI/H/104/03/II/52	24-Jun-11	
Merck Sharp & Dohme, Lda.	Singulair	Montelukast	FI/H/104/04/II/52	24-Jun-11	
Heptafarma - Companhia Farmacêutica, Sociedade Unipessoal, Lda.	Singulergy	Montelukast	FI/H/214/01/II/19	26-Jun-11	
Merck Sharp & Dohme, Lda. PR	Maxalt	Rizatriptan	NL/H/144/01/II/043	16-Dec-11	
Merck Sharp & Dohme, Lda. PR	Maxalt	Rizatriptan	NL/H/144/02/II/043	16-Dec-11	
Merck Sharp & Dohme, Lda. PR		Rizatriptan	NL/H/144/03/II/043	16-Dec-11	
Merck Sharp & Dohme, Lda. PR	Maxalt RPD	Rizatriptan	NL/H/144/04/II/043	16-Dec-11	

Romania

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
AstraZeneca AB, Sweden	Nexium 10 mg, gastro-rezistent	Esomeprazole magnesium (as trihydrate)	3268/2011/01	22-Aug-11	http://www.anm.ro/anm/anm_list.asp
Pfizer Europe MA EEIG	Xalatan 0,005%	Latanoprost	5417/2005/01-02	11-Jan-11	http://www.anm.ro/anm/anm_list.asp

Slovenia

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme d.o.o., MERCK SHARP & DOHME B.V., Waarderweg, Haarlem, The Netherlands	Maxalt 5 mg oral lyophilisates	rizatriptan	5363-I-2270/11	12-Dec-11	www.zdravila.net
Merck Sharp & Dohme d.o.o., MERCK SHARP & DOHME B.V., Waarderweg, Haarlem, The Netherlands	Maxalt 10 oral lyophilisates	rizatriptan	5363-I-2270/11	12-Dec-11	www.zdravila.net
Merck Sharp & Dohme d.o.o., MERCK SHARP & DOHME B.V., Waarderweg, Haarlem, The Netherlands	Maxalt 5 mg tablets	rizatriptan	5363-I-2268/11	12-Dec-11	www.zdravila.net
Merck Sharp & Dohme d.o.o., MERCK SHARP & DOHME B.V., Waarderweg, Haarlem, The Netherlands	Maxalt 10 mg tablets	rizatriptan	5363-I-2269/11	12-Dec-11	www.zdravila.net

Spain

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
None.					

Sweden

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Merck Sharp & Dohme, The Netherlands	Maxalt 5 mg and 10 mg, Tablet	Rizatriptan	14444, 14445	29-Nov-11	
Merck Sharp & Dohme, The Netherlands	Maxalt Rabitab, 5 mg and 10 mg, Oral lyophilisates	Rizatriptan	14446, 14447	29-Nov-11	

United Kingdom

Marketing authorisation holder	Invented name	INN	Marketing authorisation number	Date of variation/ line extension	Link to official webpage if available
Astra Zeneca	Nexium	Esomeprazole IV solution	Systemic treatment of GORD 1-18 years of age	Jul-11	

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 2011

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2011 in	SPC extension pending in	No application for SPC extension in[1]	Product with no SPC or patent which qualifies for an SPC in[2]
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	Austria Estonia Finland Slovenia Sweden United Kingdom	Bulgaria Lithuania Luxembourg Romania		Romania (no SPC) Slovak Republic
AstraZeneca AB	Arimidex and associated names	Anastrazole		Romania		Bulgaria Greece Hungary Portugal Slovak Republic Slovenia *(no SPC)*
Merck Sharp and Dohme	Cancidas	Caspofungin	Finland	Czech Republic Hungary Poland Romania Slovak Republic		Luxembourg
Sanofi BMS	Plavix and associated names	Clopidogrel	Finland Germany Portugal Sweden	Ireland Italy The Netherlands United Kingdom	Hungary Italy (SPC granted)	
Pfizer	Xalatan and associated	Latanoprost	Austria (year not reported, possibly 2011)		Greece Portugal	Bulgaria *(SPC refused)*

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2011 in	SPC extension pending in	No application for SPC extension in[1]	Product with no SPC or patent which qualifies for an SPC in[2]
	names		Denmark Finland Germany Ireland Italy Luxembourg Portugal Sweden The Netherlands United Kingdom		Spain	Germany Greece Hungary Romania *(no SPC)* Slovak Republic Slovenia *(no SPC)*
Merck Sharp & Dohme	Singulair	Montelukast	Ireland Slovenia Sweden The Netherlands	Germany Italy Luxembourg The Netherlands	Denmark Finland Greece Ireland Portugal Romania	
Boehringer	Viramune	Nevirapine	Portugal Sweden	Italy Luxembourg		
Novartis Pharma AG	Diovan and associated names	Valsartan	Germany United Kingdom			Bulgaria Greece Romania (no SPC) Slovak Republic
Novartis	Zometa and associated names	Zoledronic acid	Austria (year not reported possibly 2011) Finland	Hungary Romania	France Finland Greece Ireland	Bulgaria Slovak Republic

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2011 in	SPC extension pending in	No application for SPC extension in[1]	Product with no SPC or patent which qualifies for an SPC in[2]
					Romania	

[1,2] Some national patent offices have ticked both columns 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 no application 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 in 2011

Funded off patent medicines projects and agreed PIPs

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of ethosuximide for the treatment of absence and of myoclonic epilepsies in children	NA
2	NEO-CIRC	2011	To provide safety and efficacy data for dobutamine, to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
3	TAIN	2011	To develop a neonatal formulation of hydrocortisone for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA

NA = Not available

Investigator-driven clinical trials of off-patent antibiotics

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	AIDA	2011	Assessment of clinical efficacy by a pharmacokinetic / pharmacodynamic approach to optimise effectiveness and reduce resistance for off-patent antibiotics	NA

NA = Not available

Annex 6

List of medicinal products assessed in 2011 further to submission of data through Article 45 and resulting amendment of the SmPC

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.

International Non-proprietary name	Outcome of assessment	Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)[3]	Years
Alendronic acid	Paediatric information clarified	Sections 4.2 & 5.1	2009-2011
Amikacin	Paediatric information clarified	Sections 4.1, 4.2, 4.4, 4.5, 4.6 & 5.2	2010-2011
Amiodarone	Paediatric information clarified	Sections 4.2, 4.3, 4.4, 5.1 & 5.2	2011
Amlodipine	New indication	Sections 4.2, 5.1 & 5.2	2010-2011
Amoxicillin	Paediatric information clarified	Sections 4.2, 4.4 and 5.2	2010-2012
Baclofen	New indication	Sections 4.1, 4.2 & 4.4	2011
Bisacodyl	New indication	Section 4.2	2010-2011
Calcitonin (salmon synthetic)	No change	Section 4.2	2009-2011
Chondroitin sulfate	Paediatric information clarified	Section 4.2	2011
Clarithromycin	Paediatric information clarified	Sections 4.1 & 4.2	2011
Clobazam	Paediatric information clarified	Section 4.2	2011
Clonidine		Sections 4.2 & 5.1	2011
Diclofenac	Paediatric information clarified	Sections 4.2, 4.3 & 4.8	2011
Ethosuximide	Paediatric information clarified	Syrup formulation Sections 4.2 & 5.1 Capsule formulation Sections 4.2 & 5.1	2011
Famciclovir	Paediatric information clarified	See outcome of Art.30 Procedure in April 2010	2011
Felodipine	New study data	Sections 5.1 & 5.2	2010-2011
Fentanyl	Paediatric information clarified	Fentanyl patches Sections 4.1 & 4.2	2009-2011

[3] 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

		Fentanyl Injection Sections 4.2, 4.3 & 4.4 Fentanyl Lozenge Sections 4.1, 4.2, 5.1, 5.2 & 5.3	
Flumazenil	New indication	Sections 4.1, 4.2 & 5.2	2011
Gentamicin	New safety information	Intravenous and intramuscular use Sections 4.1, 4.2, 4.4, 5.2 Topical otic Section 4.4 Topical use other than otic None Intrathecal use None	2010-2011
Itraconazole	Paediatric information clarified	Sections 4.2, 4.8, 5.1 & 5.2	2011
Levothyroxine	Paediatric information clarified	Section 4.2	2009-2011
Lisinopril	New indication	Sections 4.2, 4.8, 5.1 & 5.2	2009-2011
Mepivacaine	Paediatric information clarified	Section 4.2 & 4.3	2010-2011
Mesalazine	Paediatric information clarified	Section 4.2	2010-2011
Metoclopramide	New safety information	i.v. Form Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9 Oral & Rectal Forms Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9	2008, 2011, 2012
Metronidazole, Metronidazole / Spiramycin	Paediatric information clarified	Sections 4.1, 4.2 & 4.8	2010-2011
Milrinone	New indication	Sections 4.1, 4.2 4.4, 4.8, 5.1, 5.2 & 5.3	2011
Mirtazapine	New study data	Sections 4.2, 4.8 & 5.1	2010-2011
Oxybutynin	Paediatric information clarified	Section 4.1 & 4.4	2010-2011
Paclitaxel	Paediatric information clarified	Section 4.2	2010-2011
Propofol	Paediatric information clarified	Sections 4.4 & 5.2	2010-2011
Propranolol	New indication	Sections 4.2 & 4.8	2011
Quinapril	New study data	Sections 5.1 & 5.2	2011-2012
Remifentanil	Paediatric information clarified	Sections 4.1, 4.2, 4.4 & 5.1	2010-2011
Risedronic acid[4]	New study data	Sections 4.2 & 5.1	2010-2011
Timolol	Paediatric information	Sections 4.2, 4.4, 5.1 & 5.2	2011

[4] Covers also the sequential treatment with risedronic acid, calcium and colecalciferol

	clarified		
Topiramate	New study data	Sections 4.4, 4.8 & 5.1	2010-2011
Tranexamic acid	New study data	Section 4.2, 4.3, 4.4, 4.8, 5.1 & 5.2	2010-2011
Triptorelin	Paediatric information clarified	Sections 4.2, 4.4 and 4.8	2010-2011

Annex 7

List of medicinal products assessed in 2011 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	Recommended change in SmPC[5]
Virus, live attenuated, measles, virus, live attenuated, mumps, virus, live attenuated, rubella, virus, live attenuated, varicella	Proquad	Sanofi Pasteur MSD, SNC	Section 4.8
Adalimumab	Humira	Abbott Laboratories Ltd.	Sections 1, 4.1, 4.2, 5.1, 5.2, 6.3, 6.5
Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.2, 4.4, 4.6, 4.8 5.1, 5.2 and 5.3
Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.4, 5.1
Rufinamide	Inovelon	Eisai Ltd.	Section 4.8
Adefovir dipivoxil	Hepsera	Gilead Sciences International Ltd.	Sections 4.2 and 5.1

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 2011)[6]			
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)[7]**
Alfuzosin	Film-coated tablet, prolonged-release tablet	New study data	Section 4.2, 5.1
Esomeprazole	gastro-resistant granules for oral	New study data	Sections 4.2 and 5.1

[5] Section 4.2 Posology and method of administration
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties
5.3 Preclinical safety data
[6] Correct as at 31 January 2011
[7] 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

Medicinal products authorised through national/mutual recognition/decentralised procedure (End of Procedure in 2011)[6]			
	suspension/ sachet		
Famciclovir	Film-coated tablets	Paediatric information clarified (in conjunction with Article 45)	Sections 4.2, 5.1 and 5.2
Lansoprazole	Capsule, oro-dispersible tablet	Paediatric information clarified	Sections 4.2
Ropinirole	Film-coated tablets	New study data	Sections 5.2

Annex 8

These lists only include 2011 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 on-going are not listed.

List of companies with delayed (>6 months) submission of applications for a PIP

Company	Substance	Delay in months
BioAlliance Pharma	Aciclovir	69
Clinuvel (UK) Limited	Afamelanotide	13
Novartis Europharm Ltd	Alisporivir	26
Ablynx NV	ALX-0081, anti-von Willebrand Factor Nanobody	20
Celgene Europe Limited	Apremilast	58
Gilead Sciences International Ltd	Aztreonam	35
Exelixis, Inc.	Cabozantinib (S)-malate	35
LFB Biotechnologies	Chimeric monoclonal anti-Shiga toxin (Stx) antibodies cαStx1 and cαStx2	56
Mitsubishi Pharma Europe Ltd	Colestilan	32
Otsuka Frankfurt Research Institute GmbH	Delamanid	19
Daiichi Sankyo Development Limited	Edoxaban tosylate	10
Clavis Pharma ASA	elacytarabine	15
Genzyme Europe B.V.	Eliglustat (tartrate)	65
Gilead Sciences International Limited	Elvitegravir	41
ORFAGEN	Ethanol (96 per cent)	12
Bayer Schering Pharma AG	florbetaben	22
Aegerion Pharmaceuticals	Lomitapide	159
Alexza UK Limited	Loxapine	18
Voisin Consulting SARL	lumacaftor	18
Takeda Global Research & Development Centre (Europe) Ltd.	lurasidone hydrochloride	70
Glaxo Group Limited	migalastat hydrochloride	31
GlaxoSmithKline Trading Service Limited	N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]- 6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-D]pyrimidin-1(2H)-yl]phenyl]acetamide, dimethylsulfoxide solvate	21
GlaxoSmithKline Trading Service Limited	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt	11

Company	Substance	Delay in months
ARIAD Pharma, Ltd.	ponatinib	13
Teva GmbH	recombinant human granulocyte colony stimulating factor coupled with recombinant human albumin fusion protein	17
Novartis Europharm Ltd	Recombinant salmon calcitonin	137
Novartis Europharm Ltd.	Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl- 1-butylcarbamoyl)propionate -(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'- ylmethyl}amino)butyrate] hemipentahydrate	12
Norgine Ltd	ulimorelin hydrochloride monohydrate	42
BAXTER Innovations GmbH	Vonicog alfa (recombinant human von Willebrand Factor)	11

List of companies with delayed (>6 months) submission of applications for a full waiver

Company Name	Substance	Delay in months
Intendis GmbH	Deoxycholic acid	33
Merck Sharp & Dohme (Europe), Inc.	atorvastatin calcium / ezetimibe	50
Auris Medical Limited	Esketamine hydrochloride (Esketamine)	41
Novo Nordisk A/S	Liraglutide / Insulin degludec	19
Celgene Europe Limited	CC-930 (4-[[9-[(3S)-tetrahydro-3-furanyl]-8-[(2,4,6-trifluorophenyl)amino]-9H-purin-2-yl]amino]-trans-cyclohexanol)	17
Teva Pharmaceuticals Europe B.V.	Progesterone	13
Avanir Pharmaceuticals, Incorporated	Quinidine sulfate / Dextromethorphan hydrobromide	23
Bristol-Myers Squibb / AstraZeneca EEIG	metformin hydrochloride / dapagliflozin	9
Novartis Europharm Ltd	Recombinant salmon calcitonin	137
Eurand Pharmaceuticals Limited	Pancreas Powder	40
Takeda Global Research and Development Centre (Europe) Ltd	Metformin hydrochloride / Alogliptin benzoate (as alogliptin)	11
IBSA Farmaceutici Italia Srl	Progesterone	35
Janssen-Cilag International	Metformin / Canagliflozin (1s)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate	33

Corrections in Annex 8

On page 69, the delay of 55 months for Aztreonam (Gilead Sciences International Ltd) should instead read 35 months.

On page 71, the delay of 3 months for Metformin / Canagliflozin [(1s)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate] (Janssen-Cilag) should instead read 33 months.

On page 69 and 70, the list of PIPs has been amended by deletion of 12 medicines corresponding to waivers erroneously included. The correct list of waivers is on page 71.