EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Performance of the Agency's scientific procedures: Survey 2009 for medicinal products for human use[1]

Management Board meeting 18 March 2010

Background note

This is the yearly report to the Management Board on the Performance of the Agency's scientific procedures conveying descriptive statistics on new marketing authorisation applications and extension of indications for medicinal products with existing marketing authorisations that had an outcome in 2009 (a positive or negative opinion or a withdrawal of a marketing authorisation application).

Matters for consideration

The "EMA Scientific Memory" database has been the basis for these analyses. The analysis set encompass applications with an outcome in the CHMP assessment process from 1 January 2009 until 31st December 2009. Duplicate applications, i.e. applications which rely on the same dossiers have been counted only once as far as initial applications are concerned. For initial applications also so called "informed consent" applications have been excluded from the analysis.

The objective of this report is to give insights and be transparent about different aspects of new marketing authorisation applications and extensions of existing indications for already marketed products. In addition, some particular analysis may be included such as for instance the one on "factors associated with success of market authorisation applications (1) recently published in the European Journal of Pharmacology and quoted in this report.

It should be noted that whereas this report refers to marketing authorisation applications with outcomes, the EMA official "Annual Report", refers to the total number of applications submitted or the total number of applications with an outcome during the year. The current report may also count outcomes twice, namely when outcomes for the same MAA occur twice in consecutive years. This may explain why figures may differ between this report and the annual report.

[1] This document presented for information will not be discussed at the meeting unless specifically requested by a member.

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Survey 2009 on the performance of EMA scientific procedures for medicinal products for human use

Executive Summary

The year 2009 saw 140 new marketing authorisation applications reach an outcome in the Committee for Medicinal Products for Human Use (CHMP) scientific evaluation. Excluding duplicate and informed consent applications there were 90 (generic applications included) new applications for marketing authorisation with an outcome in 2009. There was a substantial increase in the number (50) of generic applications in 2009 compared with 2008 (4 applications). Not counting those generic applications, a total of 64 applications (active substances) were evaluated by the CHMP in 2009, which is almost the same number as for 2008 (63 applications). Forty-three of the 64 applications reached a positive CHMP opinion and were recommended for marketing authorization. One application was approved conditionally and 7 applications were approved under exceptional circumstances. None was granted accelerated assessment. As for 2008 a relatively high proportion (33%) of applications had a negative outcome. Particularly orphan medicinal products (36% of such applications were negative) and applications from SMEs (47% of such applications were negative) appeared to have contributed to this. Overall review times for these 64 products ranged from 97 to 666 days (median 392 days) and were longer for applications with negative outcomes, those without previous scientific advice and for those submitted by SMEs. Scientific advice was given to 58% of all applications prior to the marketing authorisation application. The Committee for Advanced Therapies (CAT) commenced its work in 2009 and adopted 3 draft opinions on advanced-therapy medicinal products in preparation of a final CHMP opinion on the respective marketing authorisation applications.

A modification of the existing definition for new active substances was used to construct an estimate of the number of NASs with an outcome during 2009. Thus, biosimilar applications were not to be counted and in the case of multiple products containing the same NAS or multiple indications for the same NAS, only the first one would count. Additionally, the EMA has assessed the NAS status for orphan medicinal products. As a result 48 (75%) of the 64 applications were counted as NASs for 2009. Twenty-nine (67%) of 43 applications with a positive opinion in 2009 were NASs. Notably, 19 (40%) of the 48 new MAAs for NASs reached a negative outcome in the CHMP evaluation compared with 33% of all applications (active substances) as mentioned above.

There have been 49 applications for extensions of indications for centrally authorised products with an outcome in the CHMP scientific evaluation during 2009. Forty-four resulted in a final positive opinion, 3 in a final negative opinion (including 2 during re-examination), and 2 were withdrawn prior to final CHMP opinion. The overall processing time of applications in 2009 (median 291 days) was longer than in 2008 (median 216 days). In terms of assessment, almost all applications had at least one request for supplementary information adopted during assessment, and the proportion of procedures with major objections continued to increase in 2009, compared with 2008. The processing time for procedures with major objections was longer (median time 333 days in 2009) versus those without major objections (median time 182 days in 2009). SAGs were convened during the review of 7 (14%) of extensions of indication procedures in 2009.

Last year's report is available on:

http://www.ema.europa.eu/pdfs/general/manage/MB2009/3075409en.pdf

Explanatory note

The "EMA Scientific Memory database" has been the basis for these analyses. The analysis set encompass applications with an outcome in the CHMP assessment process from 1 January 2009 until 31st December 2009. Duplicate applications, i.e. applications which rely on the same dossiers have been counted only once as far as initial applications are concerned. For initial applications also so called "informed consent" applications have been excluded from the analysis.

The objective of this report is to give insights and be transparent about different aspects of new marketing authorisation applications and extensions of existing indications for already marketed products. In addition, some particular analysis may be included such as for instance the one on "factors associated with success of market authorisation applications (1) recently published in the European Journal of Pharmacology and quoted in this report.

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1. New Applications for Marketing Authorisation 2009

Introduction and scope

There were altogether 140 applications with an outcome (positive, negative, withdrawal) during 2009. Excluding the duplicate and informed consent application there were 90 applications with an outcome. Sixty-four applications remained after exclusion of the generic applications. Some of the characteristics of these applications are further discussed in this report and detailed in the tables in Annex 1.

1.1. Eligibility and legal basis of Marketing Authorization Applications

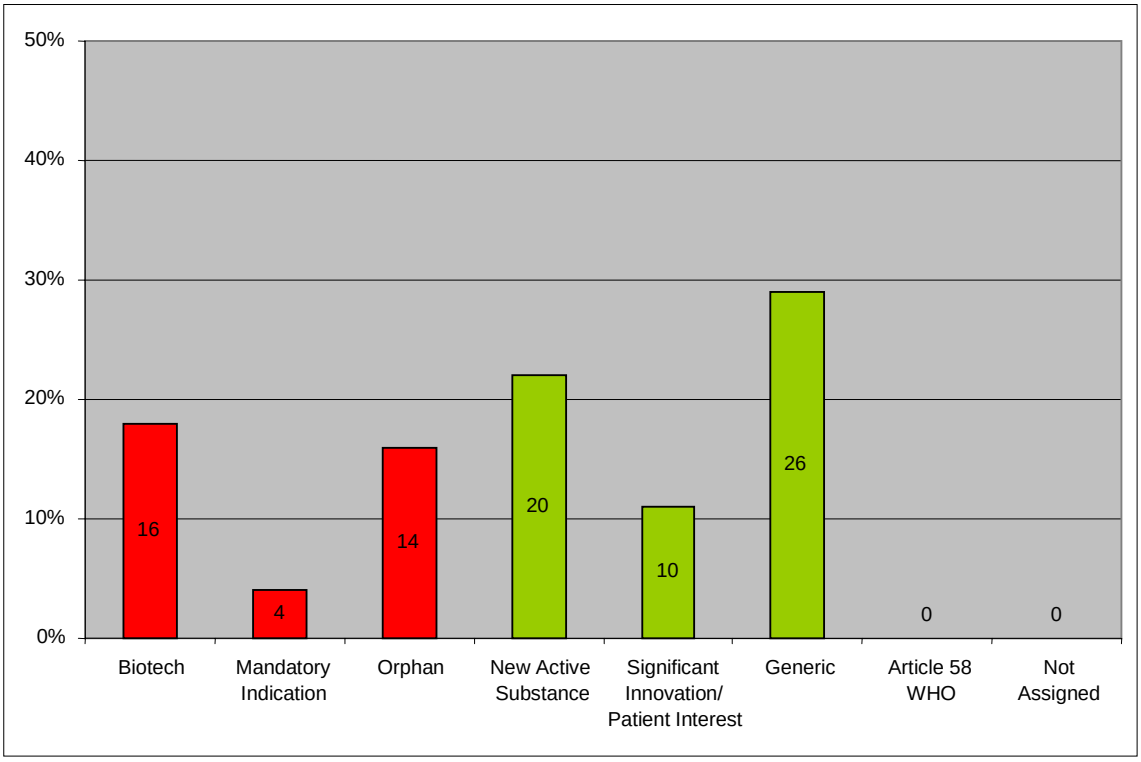
Figure 1 shows the eligibility criteria for the 90 applications with an outcome during 2009.

Products falling into the mandatory scope made up about 38% (34/90) of all applications and products falling into the optional scope made up the remaining 62% (56/90) of all applications with an outcome in 2009. This confirms the decreasing proportion of mandatory applications identified since 2007 (63%) and 2008 (44%). There were only 4 applications under the "mandatory indication" scope this year (Iressa, Victoza, Onglyza, Opaxio), i.e. 2 for diabetes and 2 for cancer. There was also a decrease in the number of orphan medicinal products compared with 2008, i.e. from 19 to 14 applications with an outcome. There was however an increase in the number of biotech products from 7 in 2008 to 16 in 2009. There were no biosimilar applications with an outcome in 2009.

For the applications eligible via the optional scope there was a particular increase in the number of generic applications from 4 in 2008 to 26 in 2009. Generics are further discussed below. "New active substances" remained numerically similar to 2008 whereas applications referring to "Significant innovation/Patient interest" increased from 5 in 2008 to 10 in 2009.

Fifty-nine (66%) of the 90 applications were complete stand alone applications according to article 8(3). Twenty-six (29%) were generic applications according to article 10(1), 1 was a hybrid application (article 10(3)). There were no biosimilar (article (10(4)) applications. There were 2 bibliographical applications (article 10A), and 2 fixed-dose applications (article 10B). The informed consent applications (11) are counted among the duplicate applications and are not included in figure 1.

Figure 1 Eligibility criteria for 90 applications with an outcome during 2009.



*Red bars denote the mandatory scope and green bars the optional scope

Generic Applications

There were altogether 50 generic applications with an outcome during 2009. Not counting the duplicate applications, 26 generic applications entered the Centralised Procedure and had an outcome in 2009. Although, the main focus is with generic copies of Centrally-Authorised Reference Products, the legislation allows other generics to come into the Centralised Procedure (e.g. generic copies of Nationally-Authorised Reference products). Here there is the question of eligibility on the basis of "community interest" and the CHMP, in most cases rejected such applications. So far, it is mainly the bigger generic companies that are behind these applications but smaller companies are increasingly interested in the Centralised Procedure. Standard CHMP policies have been applied to generics, i.e. if there are no major objections, inspections issues or questions on the closed part of the ASMF, then an opinion can be taken at day 120. However, most of the generic applications have had CHMP major objections (mainly on Bioequivalence or GCP issues) and therefore a normal 210-day timetable has been applied

New Active Substance (NAS)

As indicated in figure 1, an application is eligible to enter the Centralised Procedure under different articles corresponding to the mandatory scope (biotechnology-derived products, certain defined clinical indications, orphan medicinal products) and also the optional scope (NAS, article 3(2)). In this case the Agency systematically evaluates whether the application fulfils the definition of NAS. The definition of New Active Substance (Annex to Regulation 726/2004 as interpreted in the Notice to applicants Vol. 2A, chapter 1, Annex 3) is:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;

- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

A modification of the existing definition was used to construct a preliminary estimate of the number of NASs (derived from both the mandatory and optional scopes) with an outcome during 2009. Thus, biosimilar applications (article 10(4)) were not to be counted and in the case of multiple products containing the same NAS or multiple indications for the same NAS, only the first one would count. Additionally, the EMA has assessed the NAS status for orphan medicinal products. It is clear that our interpretation of "newness" and the definition of NAS have little to do with the term "added therapeutic value" that is the result of a different interpretation.

Forty-eight of the 64 applications were counted as NASs for 2009; 29 of the 43 applications with a positive opinion and 19 of the 21 with negative outcomes.

1.2. Adherence to regulatory timelines and review times

There were thus 64 (excluding the 26 generics) applications that reached an outcome during 2009. Tables 1A - E below and tables 1 and 2 in Annex 1 describe active time and clock-stop for these 64 applications.

Tables 1A-E describe the review times from different aspects during 2008 and 2009. Overall review times ranged from 97 to 666 days in 2009 with a median of 392 days. There were no major differences between 2009 and 2008 in any of the comparisons. Whereas the active times remained relatively stable around 200 days in all analyses, clock-stop times vary greatly ranging from 35 days for Ilaris (Zactima was withdrawn before the clock-stop) to 462 days for Emerflu. Clock-stop times were generally longer for applications with negative outcomes (median difference of 84 days, 2009), for those without previous scientific advice (median difference of 90 days, 2009) and for those with SME status (median difference of 88 days, 2009). This difference did not appear for orphan designated products in 2009 but was there in 2008. Requests for extended clock-stops are granted by the CHMP on a case-by-case basis but would typically include the need for inspection and/or additional expert involvement.

Table 1 A - E Active time* and Clock-stop* times for 63 and 64 applications with an outcome 2008 and 2009 (Duplicate and generic applications are excluded)

A. Review times by year, 2008 and 2009

Year	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum	N
2008	63	Overall	365	405	376	435	244	848	63
		ActiveTime	202	193	189	197	117	211	63
		ClockStop	191	212	183	242	49	672	63
2009	64	Overall	392	394	369	419	97	666	64
		ActiveTime	204	195	190	200	97	212	64
		ClockStop	187	199	175	222	0	462	64

B. Review times by outcome and by year

Year	Outcome	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
2008	negative	22	Overall	439	466	413	519	337	848
			ActiveTime	183	185	175	194	117	211
			ClockStop	246	281	230	333	132	672
	positive	41	overall	337	373	340	405	244	757
			ActiveTime	203	197	194	201	161	209
			ClockStop	137	176	143	208	49	552
2009	negative	21	overall	425	419	363	474	97	666
			ActiveTime	196	183	168	197	97	208
			ClockStop	244	236	190	282	0	462
	Positive	43	overall	365	381	355	408	211	556
			ActiveTime	204	201	198	204	172	212
			ClockStop	160	181	154	207	35	361

C. Review times by scientific advice and by year.

Year	SA	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
2008	Given	38	overall	365	413	369	458	244	848
			ActiveTime	202	194	190	198	166	209
			ClockStop	186	219	174	264	49	672
	Not-Given	25	overall	365	393	359	428	267	547
			ActiveTime	201	191	183	200	117	211
			ClockStop	204	202	168	237	69	342
2009	Given	37	overall	358	370	339	400	97	556
			ActiveTime	204	193	186	201	97	212
			ClockStop	160	176	148	205	0	367
	Not-Given	27	overall	456	426	385	468	251	666
			ActiveTime	203	197	190	204	120	210
			ClockStop	250	230	191	268	63	462

D. Review times by SME status and by year

Year	SME status	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
2008	No-SME	51	overall	365	397	365	429	244	848
			ActiveTime	200	192	188	197	117	211
			ClockStop	183	204	172	237	63	672
	SME	12	overall	435	441	358	524	253	757
			ActiveTime	203	194	185	203	173	207
			ClockStop	246	247	163	330	49	552
2009	No-SME	50	overall	365	382	355	409	97	666
			ActiveTime	204	197	192	202	97	212
			ClockStop	171	185	160	211	0	462
	SME	14	overall	454	435	374	497	251	556
			ActiveTime	203	188	170	206	120	210
			ClockStop	259	247	194	301	63	367

E. Review times by Orphan drug status and by year

Year	Orphan status	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
2008	non-orphan	44	overall	365	387	360	413	244	638
			ActiveTime	202	193	187	198	117	211
			ClockStop	190	194	168	221	63	435
	orphan	19	overall	403	448	370	526	253	848
			ActiveTime	200	193	187	200	173	205
			ClockStop	230	254	175	333	49	672
2009	non-orphan	50	overall	407	403	374	433	97	666
			ActiveTime	204	195	189	201	97	212
			ClockStop	216	208	180	236	0	462
	orphan	14	overall	358	359	311	407	211	512
			ActiveTime	203	193	180	207	120	207
			ClockStop	153	166	124	208	35	306

* Denotes the accumulated times, i.e. in relation with the Day 120 List of Questions and Day 180 List of Outstanding Issues but does not include the times during possible re-examinations.

1.3. Early approval

Conditional approval

One orphan medicinal product, Cayston (Aztreonam Lysine), an antibiotic intended for treatment of Cystic fibrosis was approved conditionally in 2009.

Approval under exceptional circumstances (EC)

Considering the informed consent applications (normally counted as duplicate applications in this report) there were a total of 7 applications that were approved under EC. The informed consent applications were 3 influenza H5N1 vaccines. The other 4 EC approvals were Vedrop, Arcalyst, Ilaris and Zenas. There were 3 products approved under exceptional circumstances during 2008.

Products with accelerated assessments

There were no such applications with an outcome during 2009.

1.4. Article 58 opinions

There were no such applications with an outcome during 2009.

1.5. Other characteristics of applications with an outcome in 2009

Annex 1, tables I – IV, display characteristics of all applications (except generics and duplicates) with positive and negative outcomes (negative opinion or withdrawn by the Applicant during the procedure) in 2009. They are described by names, therapeutic areas, review times, orphan status, SME status and if a scientific advisory group (SAG) was convened and if CHMP scientific advice given.

1.5.1. All applications – positive and negative outcomes

After exclusion of duplicate and generic applications there were a total of 64 applications as described in Annex 1.

There were 43/64 (67%) applications with a positive outcome in 2009 and 21 (33%) with a negative outcome. This negative outcome rate is similar to 2008 and thus somewhat higher than in previous years which used to be around 25%. For example from 2008 to 2009, the negative outcome rate was 43/127 (34%) versus 25/105 (24%) in the years 2006 to 2007. However, there have previously been very high negative outcome rates during individual years (e.g. >40% in 1998) and no clear trends have been identified (see also "Survey 2006 on the performance of EMA scientific procedures for medicinal products for human use,"

http://www.ema.europa.eu/pdfs/general/direct/48948206en.pdf.

For the NASs (48 outcomes in 2009, see section 1.1 above), a negative outcome rate of 40% (19/48) was noted which is clearly higher than the overall negative outcome rate (33%, as noted above).

In a recent publication from the Agency (1), the success of MAAs and the impact of various factors were studied in a total of 188 MAAs with an outcome between 1 January 2004 and 31 December 2007. Table 2 summarises the main analysis of factors associated with final outcome of the MAA.

The authors concluded that "the strong association between company size and outcome suggests that resources and experience in drug development and obtaining regulatory approval are critical factors for a successful MAA. In addition, obtaining and complying with SA appears to be a predictor of outcome. Companies, particularly smaller ones and those developing orphan drugs, are recommended to engage in a dialogue with European regulators via the SA procedure. Obtaining SA early in development and at major transition points and compliance with the advice given by the CHMP is recommended".

Table 2 Summary of simple and stepwise logistic regression results of the analysis of factors associated with final outcome.

		Simple Logistic Regression		**Stepwise Logistic Regression**	
	Positive/Total (%) (n=137/N=188)	**Odds-Ratio* [95%-CI]**	**p-value**	**Odds-Ratio [95%-CI]**	**p-value**
CHMP Outcome Year		**0.909 [0.681; 1.215]**	**0.521**		**No candidate (NC)**
2004	29/36 (81%)				
2005	23/36 (64%)				
2006	39/50 (78%)				
2007	46/66 (70%)				
Product Type			**0.2992**		**NC**
Biologic	40/61 (66%)	0.577 [0.239; 1.396]			
NCE	64/84 (76%)	0.970 [0.407; 2.309]			
Known substance	33/43 (77%)	1			
OD Status			**0.0067**		**Candidate**
Non-Orphans	108/138 (78%)	1			
Orphans	29/50 (58%)	0.384 [0.192; 0.766]			
Therapeutic Area			**0.32**		**NC**
Infectious Disorders	30/39 (77%)	1.473 [0.587; 3.696]			
Oncology	22/35 (63%)	0.748 [0.312; 1.790]			
Endocrine and Metabolic	22/29 (76%)	1.389 [0.507; 3.803]			

Disorders					
Neurologic and Psychiatric Disorders	20/23 (87%)	2.946 [0.780; 11.117]			
Others	43/62 (69%)	1			
Company Size†		**2.964 [1.927; 4.560]**	**<.0001**	**2.852 [1.811; 4.490]**	**<.0001**
Small Pharma (1)	26/54 (48%)				
Medium Pharma (2)	37/51 (73%)				
Large Pharma (3)	74/83 (89%)				
SA-given			**0.92**		**NC**
No	87/119 (73%)	1			
Yes	50/69 (72%)	0.968 [0.497; 1.883]			
Compliance [a]			**<0.0001**		**NC**
Non-Compliant to SA	6/20 (30%)	0.166 [0.059; 0.465]			
Compliant to SA	38/39 (97%)	14.709 [1.946; 111.158]			
No-SA (n=119) or SA without a assessment of compliance (n=10)	93/129 (72%)	1			
Compliance (conservative analysis)[b]			**0.0015**		**0.0088**
Non-compliant to SA	12/26 (46%)	0.315 [0.132; 0.753]		0.267 [0.101; 0.703]	
Compliant to SA	38/43 (88%)	2.795 [1.011; 7.724]		1.658 [0.561; 4.902]	
No-SA	87/119 (73%)	1		1	

* For categorical explanatory variables the reference group for the calculation of the odds ratio is indicated by OR=1. An odds ratio OR>1 means that a positive outcome is more likely in this group compared to the reference group. Otherwise an OR<1 means that a positive outcome is less likely compared to the reference group. Outcome year and company size (small=1, medium=2, large=3) were used as continuous explanatory variables.

†Companies were categorised according to size into small (small pharma, code 1), medium-sized (medium pharma, code 2) and large pharmaceutical (large pharma, code 3). Company size categories were based on ranking by total revenues, as reported in Scrip's Pharmaceutical Company League Tables 2006. The large pharma category was defined as companies ranked 1–20; medium pharma were ranked 21–150; and small pharma comprised all companies that were not included in the League Tables. This definition is different from the current EU definition of small andmedium-sized enterprises (SMEs).

[a] All MAAs where compliance could not be assessed either since no SA was given (n=119) or no SA was received related to at least one of the three variables assessed for compliance (n=10) were pooled in one group.

[b] Conservative analysis: n=10 MAAs received SA not related to one or more of the three variables assessed for compliance (primary endpoint, comparator, statistical methods) were treated in this worst case analysis as non-compliant in case of a positive outcome (n=6) and as compliant in case of a negative outcome (n=4); Note in the stepwise logistic regression only the conservative one was used as a candidate.

1.5.2. Orphan medicinal products

Annex 1, tables 1 to 4 describe the orphan designated products with an outcome

Nine years after the implementation of the 'Orphan' legislation, more than 690 products have been designated and 58 have received marketing authorisations in Europe. The orphan designations granted to date cover a wide variety of diseases for which there are either no authorised treatments or only limited treatment options with a need for improvement. Furthermore, with 690 products for orphan conditions designated in Europe, and several ongoing MA applications, more orphan medicinal products are expected to be authorised in the following years. A comprehensive review of the Agency's experience has recently been accepted for publication (2).

There were 14 orphan designated products with an outcome in 2009. Table 3 indicates that orphan medicinal products make up 20-30% of all medicinal products with an outcome over the last 3 years (generics excluded). Nine of the 14 applications during 2009 had a positive outcome, i.e. 5 (36%) had a negative outcome.

This negative outcome rate has been consistently higher for orphan drugs than for non-orphans over the years. For example the negative outcome rate during 2007 to 2009 was 19/46 (41%) for orphans versus 52/169 (31%) for non-orphans (generics excluded). However, orphan drug status does not stand out as an independent factor in a step-wise logistic regression analysis as further discussed above in section 1.5.1

It was noted that 4 of the 14 orphan designated products were submitted by SMEs in 2009. Two of these had a positive and 2 had a negative outcome.

Table 3

Number applications with an outcome	**2007**	**2008**	**2009**
Orphans/All applications	13/55(23)	19/64 (30)	14/64 (22)

1.5.3. Marketing Authorisation applications from Small and Medium Sized Companies (SMEs)

Annex 1 displays some characteristics of the 14 (7 positives and 7 negatives) applications (excludes genrics) with an outcome in 2009. In addition, one SME received a positive opinion for a generic product. In order to convey a more integrated summary of the Agency's experience with MAAs from SMEs the following information was recently published by the Agency's SME office. The full report is available on n http://www.ema.europa.eu/pdfs/SME/79322309en.pdf.

In the 4-year period since December 2005, forty-five SME companies have submitted MAAs, 37 for human medicinal products and 8 for veterinary medicinal products.

For human medicinal products, 14 have received positive outcomes and 20 have resulted in negative outcomes (4 negative opinions and 16 withdrawals). Three applications are currently ongoing.

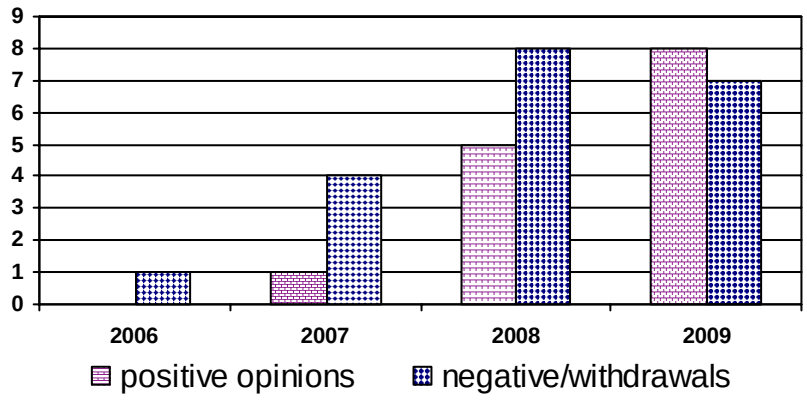
The 14 positive outcomes (listed below) include 6 orphan medicinal products, 1 advanced therapy medicinal product and one generic. One has been evaluated to an accelerated timetable and 3 have been recommended for authorisation under exceptional circumstances.

- Soliris for paroxysmal nocturnal haemoglobinuria
- Firazyr for hereditary angioedema

- Evicel for improvement of haemostasis in surgery
- Ceplene for acute myeloid leukaemia
- Mepact for osteosarcoma
- Ixiaro for immunisation against Japanese encephalitis
- Qutenza for peripheral neuropathic pain
- Ellaone for emergency contraception
- Vedrop for vitamin E deficiency due to malabsorption
- Grepid for prevention of atherothrombotic events
- ChondroCelect for repair of symptomatic cartilage defects
- Resolor for chronic constipation
- Zenas for Lambert-Eaton Myasthenic Syndrome (LEMS)
- Tepadina for conditioning treatment prior to haematopoietic progenitor cell transplantation

Although, the success rate for SMEs over this 4 year period (41%) is much lower than the average for all applicant companies (71%) for the same period, it is encouraging to see the evolution of outcomes by year (figure 2). The relative proportion of positives vs. negatives has increased each year, with the positive outcomes (53%) exceeding the negative (47%) for the first time in 2009.

Figure 2 SME applicants - MAA outcome by year for human medicines (2006-2009)

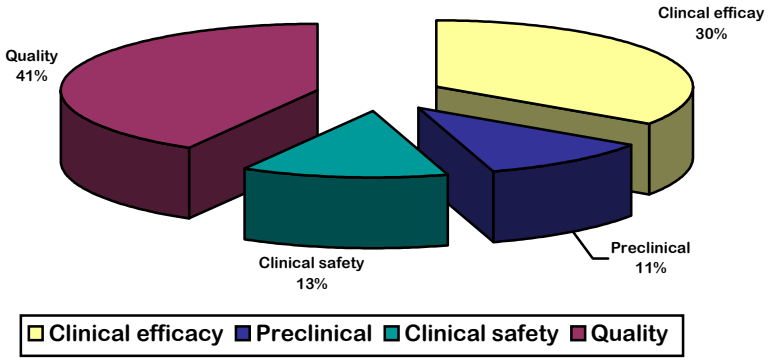


The following observations can be made on the 34 applications from SMEs for medicinal products for human use that have received an outcome to date:

- Overall 41% (14/34) had previously sought scientific advice. Although this proportion applied equally to those companies with positive and negative outcomes, all but two of the companies with negative outcomes failed to take the advice into account in their development.
- The average active time for the centralised evaluations remains similar to that reported previously: 222 days, with an average response (so-called "clock-stop") time for SME companies of around 7 months.

- With regard to the clinical documentation submitted, the SME Office reviewed the phase & design of "pivotal" clinical studies in MAAs with outcomes to September 2009. For those with positive outcomes, 83% contained at least one phase III randomised controlled trial considered as pivotal (50% having only one, 33% having 2 or more). For those applications with negative outcomes, a higher proportion was based on non-controlled trials. Furthermore, those companies with negative outcomes were found to be filing earlier in development and only 6% had two or more pivotal phase III studies.
- On average 9 major objections per application were raised by CHMP at day 120 of the procedure. Although, the main reason for negative outcomes is the need for additional clinical data to support the applications, the quality (module 3) documentation continues to be a problem area for a lot of SMEs, with 41% of major objections being raised in this area alone (figure 3).

Figure 3 Major objections in Day 120 List of Questions for SMEs (34 MAAs)



1.5.4. Scientific Advisory Groups (SAGs) and Expert Groups

The CHMP availed itself of SAGs or ad hoc expert groups for the evaluation of 10 initial applications and for 7 applications that had a re-examination, Annex 1, tables 1 and 2. It was noted that a SAG or expert group was convened for 13/48 NAS applications.

1.5.5. Oral explanations

An oral explanation in front of the CHMP gives the Applicant an opportunity to clarify the Company view on still unresolved issues. Such oral explanations typically take place toward the end of the procedure and during the re-examination phase. There were 42% (27/64) oral explanations this year; 13 of these applications eventually reached a positive opinion and 14 reached a negative outcome. Seven of the 27 were in conjunction with all the 7 re-examination procedures.

1.5.6. The Committee for Advanced Therapies (CAT)

In 2009, the CAT was established in accordance with Regulation (EC) No 1394/2007 on advanced-therapy medicinal products (ATMPs). It is a multidisciplinary committee, gathering together some of the best available experts in Europe to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field. The Committee deals with ATMPs for human use that are based on gene therapy, somatic cell therapy or tissue engineering. The main responsibility of the CAT is to prepare a draft opinion on each ATMP application submitted to the European Medicines Agency, before the CHMP adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the medicine concerned.

See further http://www.ema.europa.eu/htms/general/contacts/CAT/CAT.html

This first year, the Agency received marketing authorisation applications for three ATMPs. For one of these medicines, ChondroCelect, a 'tissue engineered product', which is a type of medicine containing cells or tissues that have been manipulated so that they can be used to repair, regenerate or replace tissue, the CAT adopted a positive draft opinion to the CHMP; for another medicine, Cerepro which is a medicine containing a gene (a Herpes simplex virus thymidine kinase gene) carried by an adenovirus, the CAT adopted a negative draft opinion. The third medicine, Contusugene, which is another 'gene therapy product'. was withdrawn by the applicant prior to the adoption of a final opinion by the CHMP. All these applications were from SMEs.

1.5.7. Scientific Advice/Protocol assistance (SA/PA)

Annex 1, tables 1 and 2 indicate the products for which SA were given.

Over the years an increasing proportion of MAAs has been preceded by CHMP SA. In 2007, 47% of applications were preceded by scientific advice and 56% in 2008.

This year 37 (58%) of the 64 applications (generics excluded) received SA/PA before MAA; 25 of the 43 positives and 12 of the 21 negatives. The numbers include PA for 8 of the 14 orphan medicinal products.

Twenty-one (72%) of 29 NAS applications with a positive outcome had previous SA. Eleven (58%) of the 19 NAS applications with a negative outcome were preceded by CHMP SA.

The impact of SA on the success of the MAA has been addressed above in section 1.5.1

2. Extension of Indications

Introduction and scope

This section consist of a detailed analyses of extensions of indications applications reaching a CHMP opinion, or withdrawn prior to it, in 2009.

In 2009, the CHMP completed the assessment of 67 applications for extensions of indications for centrally authorised products (CAPs). Sixty-four were submitted as extension of indications. One was submitted to update section 4.2 and 5.1 (Pandemrix) and 2 were submitted to update SPC sections 4.1 (therapeutic indication), 4.2 (posology) and 5.1 (pharmacodynamic propertiess) to remove information on patented indications (Ribavirin Teva and Ribavirin Pharma Teva BV). The variations submitted to remove the patented applications were not taken into account in the various analyses. Sixteen of these were duplicate applications and the remaining 49 applications were thus taken into account in the various analyses. Some of the characteristics of these applications are further discussed in this report and detailed in tables (1-3) in Annex II.

For information on other Post-authorisation procedures conducted in 2009 (Other Type II variations, Type I variations, Renewals, Annual-reassessments, follow-up measures/specific obligations and PSURs), please refer to the EMEA Annual Report 2009.

2.1. Review times

The overall, active and clock-stop times for 2009 are presented in table 4, together with review times from 2008. These correspond to the time required to reach the first CHMP opinion. Re-examination

procedures and withdrawals prior to CHMP opinion are excluded from this analysis, leaving 45 applications for this analysis.

In 2009, the review time was longer than in 2008, resulting in a moderate increase of the median overall processing time compared to 2008 (291 days vs. 216). The review time varies from 9 to 543 days depending on the number and complexity of requests for supplementary information. Of note the minimum review time is 9 days in 2009 (vs. 60 days in 2008). This is due to the accelerated review of two Tamiflu variations in relation to the current H1N1 influenza pandemic.

Table 4 Overview of overall, active and clock-stop times for 2008 and 2009

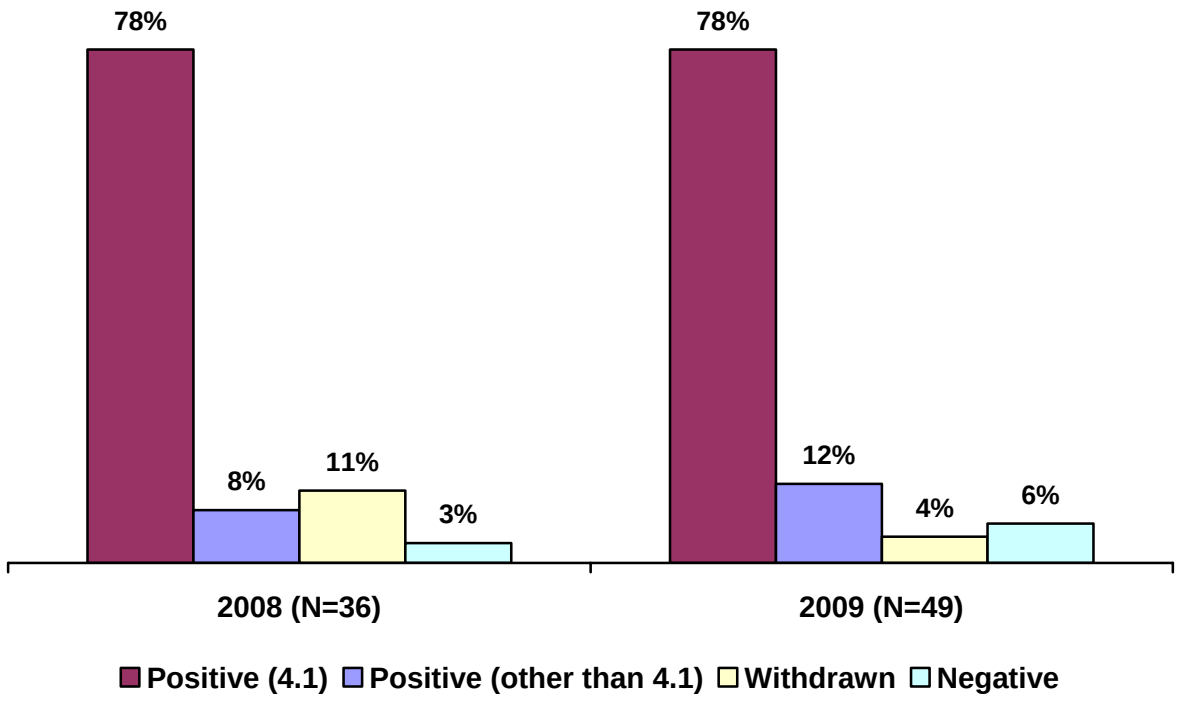
	2008 (n=32)	2009 (n=45)
Overall processing time		
Median (95% CI)	216 (179,256)	291 (209: 333)
Mean (95% CI)	217 (183,250)	273 (238;309)
Min-Max	60-433	9-543
Clock-stop time		
Median (95% CI)	64 (35,84)	92 (59;130) *
Mean (95% CI)	75 (52,91)	101 (79;1230) *
Min-Max	5-195	6-273*
Active Time		
Median (95% CI)	152 (148,178)	187 (154; 205)
Mean (95% CI)	153 (138,170)	179 (162; 197)
Min-Max	60-244	9-284

* This results includes only clock-stop times>0

2.2. Outcome

An overview of the outcome of extensions of indications finalised in 2009 is presented in figure 4 along with a comparison with 2008 data.

Figure 4 Outcome of Extensions of Indications in 2008 and 2009



2.3. CHMP opinions for extensions of indications

Positive opinions

Forty-four, (90%) out of 49 applications reached a positive opinion. For a small subset (12%), the positive opinion related to updates of the product information other than section 4.1 of the SPC ("therapeutic indications").

The CHMP adopted these positive opinions recommending new indications or broadening of patient populations for approved indications, providing additional treatment options for patients. These new indications are primarily related to medicinal products approved for the treatment of various forms of cancer (e.g. non small cell lung cancer, gastrointestinal, ovarian, leukaemia, lymphoma), cardiovascular conditions (e.g. pulmonary arterial hypertension, atherothrombotic cardiovascular disease), metabolic conditions (e.g. diabetes mellitus) and skin conditions (e.g. atopic dermatitis). Several medicines have received an approval to extend their use to paediatric patients for the following conditions: juvenile idiopathic arthritis, hepatitis C and treatment of influenza during a pandemic influenza outbreak.

Annex 2 (table 2) describes the changes made to section 4.1 of the SPC for the 38 approved extension of indications.

Detailed information on CHMP positive opinions, with or without update of section 4.1 of the SPC, is available from the EPARs published on the EMEA webpage.

In addition, there were 6 applications that resulted in the inclusion of new clinical data in section 5.1 of the SPC:

- Celsentri (maraviroc) further to the to the results of a comparative study of maraviroc as a first line treatment in treatment-naïve CCR5 infected HIV-1 adult patients in combination with zidovudine/lamivudine as compared to efavirenz in combination with zidovudine/lamivudine).
- Dynastat (parecoxib sodium) with information about the reduction of dose-dependent adverse effects following dose reduction of opioids.
- Gardasil (human papilloma virus vaccine) based on the results of an efficacy, immunology and safety study in mid-adult women, 24 to 45 years of age.
- Pandemrix (H5N1 spilt antigen influenza vaccine) to include treatment in subjects aged 61 years and above based on clinical trial data.
- Thelin (sitaxentan sodium) with data in patients with pulmonary arterial hypertension in WHO functional class II.
- Zometa (zoledronic acid) regarding clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years.

Negative opinion

The CHMP adopted 3 negative opinions recommending the refusal of extension of indication for the treatment of glioblastoma, non-small cell lung cancer and fibromyalgia (Avastin (bevacizumab), Erbitux (cetuximab), Lyrica (pregabalin) respectively).

In addition two applications were withdrawn prior to receiving a final CHMP opinion (Abilify (aripiprazole), Stalevo (levodopa/carbidopa/entacapone)).

Annex 2 (table 3) sets out the published reasons for not approving the 5 applications with a negative outcome (negative opinion or withdrawn) during 2009.

Detailed information on negative opinions and withdrawals is systematically published on the EMEA webpage (Questions and Answers and CHMP Assessment Report).

2.4. Impact of CHMP Major Objections (MO)

The proportion of procedures for which MOs were adopted continued to increase in 2009 (72%), compared with 2008 (58%). As shown in table 5, MOs contributed considerably to extend the review times

Table 5 Mean and median values of the overall processing time, active review time and

clock-stop time, with and without major objections in 2009.

	Major objections (N=33) *		No major objections (N=13) *	
	Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)
Overall time	324 (295;354)	333 (305;361)	184 (122;246)	181 (159:187)
Active time	202 (189;216)	205 (190;216)	140 (105;175)	152 (147;153)
Clock-stop time	122 (100,144)	113 (93;146)	54 (18;90)	35 (28;35)

* These results includes only clock-stop times>0

As expected, the review time of procedures without major objections is significantly lower than the review times of procedures with MOs in 2009. This is particularly true for clock-stop times (median clock stop time 122 days with MOs, 54 days without MOs).

The review times for procedures without MOs were comparable in 2008 and 2009 whereas there was a slight increase in review times for procedures with MOs in 2009 compared with 2008 (data not shown).

2.5. Oral explanation

Ten (20.4%) applications out of 49 were subject to an oral explanation in 2009. This is substantially more than in 2008 (6%). Six of these 10 oral explanations resulted in solving the major concerns raised by the CHMP. The remaining 4 applications with oral explanations resulted in 3 applications with a negative opinion, and one withdrawal of the application prior to opinion.

2.6. Scientific advisory groups (SAGs) and ad-hoc expert meetings

Scientific advisory groups play an important role in the decision making process, by providing the CHMP with the position of experts on specific unresolved issues. For extensions of indications, SAG are typically convened to assess the clinical relevance of data to the population applied for, or adequate sub-populations, in the context of a specific concern of the CHMP relating to safety, study methodology or the magnitude/consistency of efficacy data.

SAGs were convened during the review of 7 (14%) extensions of applications procedures in 2009 including applications in the oncology, clinical neuroscience and cardiovascular therapeutic areas. During the review of 2 of these applications, more then 1 SAG took place.

3 SAGs were convened for procedures for which a negative opinion was eventually adopted by the CHMP. 2 out of these 3 SAGs took place during re-examination phase.

The final procedure outcomes have been consistent with recommendations given by the SAGs.

No ad-hoc expert group was convened in 2009.

2.7. Scientific Advice (SA)

In 2009, SA was given in relation to the sought new indication for 13 of the 49 procedures (26.5%), which is more than in 2008 (8%). These figures are notably smaller than for initial marketing authorizations (>55%). The small sample size (n=49) does not permit to draw definite conclusions on the potential impact of SA on the subsequent outcome of procedures, or on the concerns raised during the assessment. There was no significant association between prior SA and adoption of major objections (table 6), nor between prior SA and final outcome in 2009.

Table 6 Prior Scientific Advice and occurrence of Major Objections for 49 extensions of indications. (Fisher test assessing the impact of prior Scientific Advise on subsequent Major Objection; p=0.17).

	MO: Yes	MO: No	Total
SA+	11	2	13
SA-	22	14	36
Total	33	16	49

References

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2. Butlen-Ducuing, F., Riviere, F., Aarum, S., Llinares-Garcia, J European Medicines Agency Support Mechanisms Fostering Orphan Drug Development. Drug News & Perspectives. Volume 23, Issue 1, January/February 2010.

ANNEX I

Characteristics of initial MAAs with outcomes in 2009.

Tables I.1 to I.4 - Generics and duplicate applications are excluded.

I.1 – The 43 new applications with a positive outcome in 2009. Twenty-nine were NASs (Red bold).

Product Name	INN	Active Time	Accum ClockStop	SAG/Expert Group	Scientific Advice	Orphan	SME
Lunivia	Eszopiclone	205	230	Yes#			
Synflorix	Pneumococcal Polysaccharide conjugate vaccine	209	149		Yes		
Vedrop	Tocofersolan	210	273	Yes≠			Yes
Conbriza	Bazedoxifene	202	309		Yes		
Exalief	Eslicarbazepine acetate	205	125		Yes		
PANTOZOL Control	Pantoprazole	197	70				
Removab	Catumaxomab	203	183	Yes*	Yes		
Cayston	Aztreonam Lysine	204	154	Yes#	Yes	Yes	
Qutenza	Capsaicin	202	337				Yes
Renvela	Sevelamer carbonate	204	154		Yes		
Ellaone	Ulipristal	203	63				Yes
Modigraf	Tacrolimus	205	244		Yes		
Instanyl	Fentanyl citrate	205	279				
Iressa	Gefitinib	210	119	Yes*	Yes		
Nymusa	Caffeine citrate	204	126			Yes	
Victoza	Liraglutide	204	98		Yes		
Afinitor	Everolimus	206	104	Yes*	Yes	Yes	
Mozobil	Plerixafor	207	131	Yes*	Yes	Yes	
Samsca	Tolvaptan	207	250				
Chondro-Celect	Characterised autologous chondrocytes in suspension	195	361		Yes		Yes
Cimzia	Certolizumab pegol	205	160		Yes		
Javlor	Vinflunine ditartrate	196	288	Yes*			
Onglyza	Saxagliptin	205	132		Yes		
Simponi	Golimumab	177	279		Yes		
Arcalyst	Rilonacept	197	168			Yes	
Exforge HCT	Amlodipine besylate / valsartan / Hydrochlorothiazide	206	96		Yes		
Ilaris	Canakinumab	176	35		Yes	Yes	
Ratioepo	Epoetin theta	205	188		Yes		
Resolor	Prucalopride	206	215		Yes		Yes
MULTAQ	Dronedarone hydrochloride	183	245				
Prevenar 13	Pneumococcal saccharide conjugated vaccine adsorbed	204	70		Yes		
Zutectra	Human hepatitis b immunoglobulin	204	105				
Onbrez Breezhaler	Indacaterol male	178	61		Yes		
Scintimun	Besilesomab	203	253	Yes*			
Firdapse	Amifampridine	196	288			Yes	Yes
Elonva	Corifollitropin alfa	205	125		Yes		

Urorec	Silodosin	205	160				
ImmunoGam	Human hepatitis b immunoglobulin	205	279				
Menveo	MenACWY	205	188		Yes		
Prolia	Denosumab	212	111		Yes		
Tepadina	Thiotepa	206	306			Yes	Yes
DuoPlavin	Clopidogrel hydrogen sulphate / acetylsalicylic acid	172	95				
Revolade	Eltrombopag olamine	199	159	Yes†	Yes	Yes	

* SAG during the initial review; † Ad hoc expert group during the initial review;
# SAG during re-examination; ≠ Ad Hoc Expert group during re-examination

I.2 – The 21 new applications with a negative (negative opinion/withdrawals) outcome 2009. Nineteen were NASs (Red bold)

Product Name	INN	Active Time	Accum ClockStop	SAG/Expert Group	Scientific Advice	Orphan	SME
Ixempra	Ixapebilone	203	189	Yes*#			
Biferonex	interferon-beta-1a	205	349	Yes#			
Vorinostat MSD	Vorinostat	202	251	Yes*	Yes	Yes	
Emerflu	H5N1 split antigen influenza vaccine Alum adjuvanted	204	462				
Cylatron	peginterferon alfa-2b	194	337	Yes*	Yes		
Factive	Gemifloxacin	196	260				
Gemesis	Bercaplermin	204	280	Yes≠			
Milnacipran Pierre Fabre Medicament	Milnacipran	175	217	Yes#	Yes		
Contusugene Ladenovec Gendux	Contusugene Ladenovec - adenoviral vector mediated human p53 gene	120	176		Yes		Yes
Bosatria	Mepolizumab/SB 240563	178	129			Yes	
Ramvocid	Oritavancin	177	244		Yes		Yes
Opaxio	Paclitaxel poliglumex	177	367		Yes		Yes
Zunrisa	Casopitant mesylate	174	255		Yes		
Mersarex	Iclaprim mesylate	208	217		Yes		Yes
Nenad	Lisuride	207	333				Yes
Oncophage	Vitespen	207	186		Yes	Yes	
Zactima	Vandetanib	97	0		Yes		
Cerepro	Sitimagene ceradenovec - adenoviral vector-mediated Herpes Simplex Virus-thymidine kinase gene used with subsequent administration of ganciclovir	206	152		Yes	Yes	Yes

Ethyl Eicosapent Soft Gelatin Capsules	Ethyl eicosapent	120	131			Yes	Yes
Recothrom	Thrombin alfa	197	249				
Sliwens	Eplivanserin hemifumarate	185	174		Yes		

* SAG during the initial review; † Ad hoc expert group during the initial review;
# SAG during re-examination of a negative opinion; ≠ Ad Hoc Expert group during re-examination of a negative opinion

I.3 - Information on initial applications with positive outcomes during 2009

The Question and Answer (Q/A) document has been used for this compilation. When a Q/A document were not yet available, the Summary of the Opinion was used.

(Further information available on the EMA web: www.EMA.europa.eu/index/indexh1.htm)

(Generic applications are not included).

Product Name	**Therapeutic area and Benefit - Risk information**
Lunivia	Insomnia **What documentation did the company present to support its application to the CHMP?** The effects of Lunivia were first tested in experimental models before being studied in humans. The company presented the results of eight main studies involving over 4,000 adults to support its application. The studies looked at 'transient' insomnia (in this case, insomnia caused by spending a night in an unfamiliar setting), at primary insomnia (insomnia with no other cause) and at insomnia caused by other conditions (major depression, generalised anxiety disorder, the menopause and rheumatoid arthritis). All of the studies compared Lunivia with placebo (a dummy treatment). The main measures of effectiveness were how long it took for the patients to fall asleep or how long the patients were awake during the night after first falling asleep. The evaluation had finished and the CHMP had given a positive opinion. The company withdrew before the European Commission had issued a decision on this opinion. **What was the recommendation of the CHMP at that time?** The CHMP had given a positive opinion, recommending that a marketing authorisation be granted for Lunivia for the treatment of insomnia. However, the Committee had also concluded that eszopiclone could not be considered to be a new active substance. As a consequence, Lunivia would not have been able to benefit from 10 years of 'market exclusivity'.

Synflorix	Invasive disease and acute otitis media caused by Streptococcus pneumoniae **What benefit has Synflorix shown during the studies?** In the immunogenicity study, Synflorix produced a similar response to the comparator vaccine for the majority of the *S. pneumoniae* polysaccharides they share in common. Synflorix was as effective as the comparator in triggering the production of antibodies against five of the polysaccharides that the two vaccines shared in common (4, 9V, 14, 18C and 19F), but it was less effective than the comparator for two (6B and 23F). For the three additional polysaccharides (1, 5, 7F), Synflorix was effective in triggering the production of antibodies. In the study looking at otitis media, the investigational vaccine containing the same polysaccharides as Synflorix was more effective than the comparator in preventing otitis media. The occurrence of the first episode of acute otitis media was approximately halved among children who were given the vaccine compared with those given the comparator. Based on a comparison of the immune response of Synflorix with the vaccine used in the study, it is expected that Synflorix would provide similar protection against acute otitis media caused by *S. pneumoniae*. The additional studies showed that although Synflorix produced a lower antibody response in infants and older children than the comparator vaccine, it fulfilled pre-defined criteria and was considered acceptable in this group. Both Synflorix and the comparator showed an increase in antibody production following booster vaccinations. **What is the risk associated with Synflorix?** The most common side effects with Synflorix (seen in more than 1 patient in 10) are pain, redness and swelling at the injection site, drowsiness, loss of appetite, fever and irritability. For the full list of all side effects reported with Synflorix, see the Package Leaflet. Synflorix should not be used in children who may be hypersensitive (allergic) to the active substances or any of the other ingredients. Children who have a severe fever should not receive the vaccine until they have recovered, but they can still be given the vaccine if they have a mild infection such as a cold. As for all vaccines, if Synflorix is used in very premature babies, there is a risk of the babies experiencing apnoea (brief pauses in breathing). Their breathing should be monitored for up to three days after vaccination.
Vedrop	Vitamin E deficiency **What benefit has Vedrop shown during the studies?** The studies showed that Vedrop could correct vitamin E levels in patients with chronic cholestasis and that it might improve or prevent neurological symptoms, especially in patients aged below three years. **What is the risk associated with Vedrop?** The most common side effect with Vedrop (seen in between 1 and 10 patients in 100) is diarrhoea. For the full list of all side effects reported with Vedrop, see the Package Leaflet. Vedrop should not be used in people who may be hypersensitive (allergic) to tocofersolan or any of the other ingredients. It must not be used in

	premature babies.
Conbriza	Osteoporosis **What benefit has Conbriza shown during the studies?** In the first study, Conbriza was more effective than placebo at reducing the number of new spine fractures. After three years, 2% of the patients receiving Conbriza (35 out of 1,724) had new fractures compared with 4% of those receiving placebo (59 out of 1,741). The difference was more relevant in the sub-group of women at higher risk of fractures before the study. Conbriza was not shown to be effective at reducing the number of fractures outside the spine. In the other study, Conbriza was also more effective than placebo at maintaining the bone density of the spine. After two years, the average bone density remained almost unchanged in women who received Conbriza, but in women who received placebo it was reduced by over 1%. In both main studies the effects of Conbriza were similar to the effects of raloxifene. **What is the risk associated with Conbriza?** The most common side effects with Conbriza (seen in more than 1 patient in 10) are hot flushes and muscle spasms. For the full list of all side effects reported with Conbriza, see the Package Leaflet. Conbriza should not be used in people who may be hypersensitive (allergic) to bazedoxifene or any of the other ingredients. It must not be used in women who have had problems with venous thromboembolism including deep vein thrombosis (DVT), pulmonary embolism (a blood clot in the lungs) and retinal vein thrombosis (a blood clot at the back of the eye). It must not be used in women with unexplained bleeding from the womb. Conbriza is only for use in women who have been through the menopause, so it must not be used in women who could become pregnant.
Exalief	Epilepsy **What benefit has Exalief shown during the studies?** Looking at the results of the three studies taken together, Exalief 800 mg and 1200 mg were more effective than placebo at reducing the number of seizures, when used as add-ons to other anti-epileptic medicines. At the start of the study, patients had around 13 seizures per month. Over the 12 weeks of treatment, this fell to 9.8 and 9 seizures per month in patients taking Exalief 800 mg and Exalief 1200 mg respectively, compared with 11.7 per month in those taking placebo. **What is the risk associated with Exalief?** Almost a half of the patients treated with Exalief experience side effects. The most common side effects with Exalief (seen in more than 1 patient in 10) are dizziness and somnolence (sleepiness). For the full list of all side effects reported with Exalief, see the Package Leaflet. Exalief should not be used in people who may be hypersensitive (allergic) to eslicarbazepine acetate, any of the other ingredients or other carboxamide derivatives (medicines with a similar structure to eslicarbazepine acetate, such as carbamazepine or oxcarbazepine). It must not be used in people with

	second or third degree atrioventricular block (a problem with electrical transmission in the heart).
PANTOZOL Control	Reflux symptom **What benefit has Pantozol Control shown during the studies?** Pantoprazole was more effective than placebo and ranitidine at improving the symptoms of acid reflux. In the first study, 74% of the patients taking pantoprazole (80 out of 108) and 43% of those taking placebo (48 out of 111) had no heartburn after two weeks. Pantoprazole was also more effective than placebo at reducing symptoms of acid regurgitation. In the second study, 70% of the patients taking pantoprazole (121 out of 172) and 59% of those talking ranitidine (102 out of 172) had no heartburn after two weeks of treatment. **What is the risk associated with Pantozol Control?** The most common side effects with Pantoprazole Control (seen in around 1 patient in 100) are diarrhoea and headache. For the full list of all side effects reported with pantoprazole, see the Package Leaflet. Pantozol Control should not be used in people who may be hypersensitive (allergic) to pantoprazole, soya or any of the other ingredients. It must not be used with atazanavir (a medicine used to treat human immunodeficiency virus [HIV] infection).
Removab	Malignant Ascites **What benefit has Removab shown during the studies?** Removab with drainage was more effective at treating malignant acsites than drainage alone. On average, patients who received Removab lived for 46 days without the need for further drainage. This compared with 11 days for patients who were treated with drainage alone. **What is the risk associated with Removab?** Around 90% of patients treated with Removab have side effects. The most common side effects with Removab (seen in more than 1 patient in 10) are lymphopenia (low level of lymphocytes, a type of white blood cell), abdominal (tummy) pain, nausea (feeling sick), vomiting, diarrhoea, pyrexia (fever), fatigue (tiredness), chills and pain. For the full list of all side effects reported with Removab, see the Package Leaflet. Removab should not be used in people who may be hypersensitive (allergic) to catumaxomab, to any of the other ingredients, or to murine (rat or mouse) proteins.
Cayston	Cystic Fibrosis (CF) **What benefit has Cayston shown during the studies?** Cayston was more effective than placebo at suppressing lung infection caused by *P. aeruginosa* bacteria in adults with cystic fibrosis. In one study, patients given Cayston required other additional inhaled or intravenous antibiotics after 92 days compared with 71 days for patients who took placebo. In the second study, the

	respiratory symptoms were rated to have improved in patients who took Cayston compared with patients who took placebo. **What is the risk associated with Cayston?** The most common side effects with Cayston (seen in more than 1 patient in 10) are wheezing, cough, pharyngolaryngeal pain (pain in the throat and voice box), nasal congestion (blocked nose) and fever. For the full list of all side effects reported with Cayston, see the Package Leaflet. Cayston should not be used in people who may be hypersensitive (allergic) to aztreonam or any of the other ingredients.
Qutenza	Peripheral neuropathic pain **What benefit has Qutenza shown during the studies?** Qutenza was more effective at reducing neuropathic pain than the control patches. In the two studies of patients with post-herpetic neuralgia, the reduction in pain scores after eight weeks was 30 and 32% in patients who were given Qutenza, compared with 20 and 24% in patients who received the control patches. In one of the studies of patients with HIV-associated neuropathy, patients who were given Qutenza experienced a 23% reduction in pain scores after 12 weeks compared with an 11% reduction in patients who were given the control. In the second study of patients with HIV-associated neuropathy, although Qutenza reduced pain by 30% it was not shown to be more effective than the control. **What is the risk associated with Qutenza?** The most common side effects with Qutenza (seen in more than 1 patient in 10) are pain and erythema (redness) at the site of application. For the full list of all side effects reported with Qutenza, see the Package Leaflet. Qutenza should not be used in people who may be hypersensitive (allergic) to capsaicin or any of the other ingredients.
Renvela	Chronic kidney disease. **What benefit has Renvela shown during the studies?** Renvela was as effective as Renagel in reducing phosphate in patients with chronic kidney disease who were on dialysis. In two studies the average amount of phosphate in the blood during treatments with Renvela or Renagel was similar. In the small study of patients not on dialysis who took Renvela, the average amount of phosphate in the blood was reduced by about a fifth, from 2.0 mmol/l to 1.6 mmol/l. **What is the risk associated with Renvela?** The most common side effects with Renvela (seen in more than 1 patient in 10) are nausea (feeling sick), vomiting, upper abdominal (tummy) pain and constipation. For the full list of all side effects reported with Renvela, see the Package Leaflet. Renvela should not be used in people who may be hypersensitive (allergic) to sevelamer carbonate or any of the other ingredients. Renvela must not be used in

	people with hypophosphataemia (low blood phosphate levels) or with bowel obstruction (a blockage in the gut).
Ellaone	Pregnancy prevention **What benefit has Ellaone shown during the studies?** Ellaone was effective as an emergency contraceptive. Of the women who completed the main study, 2.1% (26 out of 1,241) became pregnant. This is less than the 5.5% of women who would have been expected to become pregnant if they had not taken any contraceptive. Ellaone therefore prevented about three fifths of the expected pregnancies. The additional study, which included women who took the medicine within two days of unprotected sex or contraceptive failure, also supported the effectiveness of Ellaone. **What is the risk associated with Ellaone?** The most common side effects with Ellaone (seen in more than 1 patient in 10) are abdominal (tummy) pain and menstrual disorder (problems with periods). For the full list of all side effects reported with Ellaone, see the Package Leaflet. Ellaone should not be used in women who may be hypersensitive (allergic) to ulipristal acetate or any of the other ingredients. It must not be used in women who are already pregnant.
Modigraf	Prophylaxis of transplant rejection (liver, kidney and heart) and treatment of allograft rejection. **What benefit has Modigraf shown during the studies?** Modigraf was effective at preventing organ rejection in children who had had a liver transplant. In the first study, 79% of patients given Modigraf (22 out of 28) did not have organ rejection. In the second study, the difference between the total number of rejections for the two medicine combinations was not considered to be relevant. However, the Modigraf combination was more effective than the other combination at preventing organ rejections that could not be treated by corticosteroids. **What is the risk associated with Modigraf?** The most common side effects with Modigraf (seen in more than 1 patient in 10) are diabetes, hyperglycaemia (high blood glucose), hyperkalaemia (high blood potassium), insomnia (difficulty sleeping), headache, tremor (shaking), hypertension (high blood pressure), diarrhoea, nausea (feeling sick), abnormal liver function test (abnormal level of liver enzymes), and kidney problems. For the full list of all side effects reported with Modigraf, see the Package Leaflet. Modigraf should not be used in people who may be hypersensitive (allergic) to tacrolimus or any of the other ingredients or to other macrolides (medicines with a similar structure to tacrolimus).

Instanyl	Cancer pain **What benefit has Instanyl shown during the studies?** Instanyl was more effective than placebo at treating breakthrough pain in cancer patients. In one of the main studies, the change in pain intensity after ten minutes was between 1.8 and 2.7 points on the pain scale for patients who took Instanyl, compared with 1.4 for patients who took placebo. The number of patients who responded to treatment was also higher in the Instanyl group than in the placebo group. In the second main study, the change in pain intensity after ten minutes was between 2.0 and 2.7 points after receiving doses of Instanyl compared with 1.3 after receiving placebo. The number of breakthrough pain episodes that responded to treatment was also higher among patients who received Instanyl than those who received placebo. In the third study, patients who received Instanyl had faster pain relief than patients who received the comparator medicine. **What is the risk associated with Instanyl?** The most common side effects with Instanyl (seen in between 1 and 10 patients in 100) are somnolence (sleepiness), dizziness, headache, vertigo (a spinning sensation), flushing (reddening), hot flushes, throat irritation, nausea (feeling sick), vomiting and hyperhidrosis (excessive sweating). For the full list of all side effects reported with Instanyl, see the Package Leaflet. Instanyl should not be used in people who may be hypersensitive (allergic) to fentanyl or any of the other ingredients. It must not be used in patients who are not already taking opioids for maintenance pain control or patients with severe respiratory depression or severe obstructive lung conditions (diseases that severely impede breathing). It must also not be used in patients who have had facial
Iressa	Non-small cell lung cancer **What benefit has Iressa shown during the studies?** In the first main study, Iressa was more effective at preventing the cancer from worsening than the combination. Among patients with the EGFR mutation, those who took Iressa lived for an average of nine and a half months without the disease getting worse, compared with about six months for those who took the combination therapy. In the second main study, patient survival among all patients who took Iressa was similar to those who took docetaxel. **What is the risk associated with Iressa?** The most common side effects with Iressa (seen in more than 1 patient in 10) are loss of appetite, diarrhoea, vomiting, nausea (feeling sick), stomatitis (inflammation of the lining of the mouth), increased level of alanine aminotransferase (a liver enzyme) in the blood, skin reactions such as pustular rash, and asthenia (weakness). There is also a risk of interstitial lung disease in patients taking Iressa. For the full list of all side effects reported with Iressa, see the Package Leaflet. Iressa should not be used in people who may be hypersensitive (allergic) to gefitinib or any of the other ingredients. It must not be

	used in mothers who are breastfeeding.
Nymusa	Apnoea **What benefit has Nymusa shown during the studies?** Caffeine citrate was more effective than placebo at treating apnoea in premature babies. In six out of ten days caffeine citrate was more effective than placebo in reducing the number of apnoea episodes by at least a half. In addition, more babies who were given caffeine citrate had at least eight days with no apnoea: 22% of babies given caffeine citrate compared with none of babies who were given placebo. In the large published study, 46% of babies given placebo (431 out of 932) died or had neurological disabilities compared with 40% of babies given caffeine citrate (377 out of 937). In the review of five studies, fewer babies treated with caffeine or theophylline had treatment failure compared with placebo. **What is the risk associated with Nymusa?** The most common side effects with caffeine citrate (seen in between 1 and 10 patients in 100) are infusion site phlebitis (inflammation of a vein) and inflammation at the site of infusion. For the full list of all side effects reported with caffeine citrate, see the Package Leaflet. Nymusa should not be used in babies who may be hypersensitive (allergic) to caffeine citrate or any of the other ingredients.
Victoza	Type 2 Diabetes Mellitus **What benefit has Victoza shown during the studies?** Combinations containing Victoza were more effective at controlling blood glucose than combinations without the medicine. Dual therapies containing Victoza and metformin or a sulphonylurea led to reductions in HbA1c of around 1% compared with no reduction without Victoza. Triple therapies containing metformin and either a sulphonylurea or a thiazolidinedione led to a reduction of between 1.3 and 1.5% compared with a reduction equal or less than 0.5% without Victoza. When used alone there was also a greater reduction in HbA1c with Victoza than with glimepiride. However, the study was not sufficient to support the use of Victoza as a monotherapy. **What is the risk associated with Victoza?** The most common side effects with Victoza used in combination with other anti-diabetes medicines (seen in more than 1 patient in 10) are hypoglycaemia (low blood glucose), headache, nausea and diarrhoea. For the full list of all side effects reported with Victoza, see the Package Leaflet. Victoza should not be used in people who may be hypersensitive (allergic) to liraglutide or any of the other ingredients.

Afinitor	Renal cell carcinoma **What benefit has Afinitor shown during the studies?** Afinitor was more effective than placebo at treating patients with advanced renal cell carcinoma. The patients who took Afinitor lived for an average of 4.9 months without the disease getting worse, compared with 1.9 months for the patients who took placebo. **What is the risk associated with Afinitor?** The most common side effects with Afinitor (seen in more than 1 patient in 10) are infections, low levels of lymphocytes and neutrophils (types of white blood cell), haemoglobin (the protein found in red blood cells that carries oxygen around the body) and platelets (components that help the blood to clot), increased levels of glucose (sugar), cholesterol and triglycerides (types of fat) and phosphate, loss of appetite, abnormal taste, pneumonitis (inflammation in the lungs), dyspnoea (difficulty breathing), epistaxis (nosebleeds), cough, stomatitis (inflammation of the lining of the mouth), diarrhoea, mucosal inflammation (inflammation of the moist body surfaces), vomiting, nausea (feeling sick), increased levels of alanine aminotransferase and aspartate aminotransferase (liver enzymes), rash, dry skin, pruritus (itching), increased levels of creatinine (a breakdown product of muscle), fatigue (tiredness), asthenia (weakness) and peripheral oedema (swelling of the arms and legs). For the full list of all side effects reported with Afinitor, see the Package Leaflet. Afinitor should not be used in people who may be hypersensitive (allergic) to everolimus, to other rapamycin derivatives (substances with a similar structure to everolimus) or to any of the other ingredients.
Mozobil	Mobilisation of haematopoietic stemcells to the peripheral blood for collection and subsequent transplantation in patients with lymphoma and multiple myeloma **What benefit has Mozobil shown during the studies?** Mozobil was more effective than placebo at mobilising stems cells from the bone marrow into theblood. Among the patients with lymphoma, 60% of those receiving Mozobil achieved the target number of stems cells within four collection days (89 out of 150), compared with 20% of the patients receiving placebo (29 out of 148). Among the patients with multiple myeloma, 72% of those receiving Mozobil achieved the target number of stem cells (106 out of 148), compared with 34% of the patients receiving placebo (53 out of 154). In both studies, there were more patients who received Mozobil that achieved the target number of stem cells and in whom the stems cells were successfully engrafted. **What is the risk associated with Mozobil?** The most common side effects with Mozobil (seen in more than 1 patient in 10) are diarrhoea, nausea (feeling sick) and reactions at the site of injection. For the full list of all side effects reported with Mozobil, see the Package Leaflet. Mozobil should not be used in people who may be hypersensitive (allergic) to plerixafor or any of the other ingredients.

Samsca	Hyponatraemia **What benefit has Samsca shown during the studies?** Samsca was more effective than placebo at increasing sodium levels in the blood in all diseases, but Samsca was more effective in patients with SIADH than with liver or heart problems. Sodium levels were around 129 mmol/l at the start of the study. In patients with SIADH, the levels had increased by an average of 4.8 mmol/l by day 4 in those who took Samsca, compared with 0.2 mmol/l in those who took placebo. By day 30, sodium had increased by an average of 7.4 mmol/l in patients who took Samsca, compared with 1.5 mmol/l in patients receiving placebo. **What is the risk associated with Samsca?** The most common side effects with Samsca (seen in more than 1 patient in 10) are thirst and nausea (feeling sick). For the full list of all side effects reported with Samsca, see the Package Leaflet. Samsca should not be used in people who may be hypersensitive (allergic) to tolvaptan or any of the other ingredients. It must not be used in patients with anuria (an inability to pass urine), very low blood volume, low blood sodium levels with low blood volume, hypernatremia (abnormally high levels of sodium in the blood) or in patients who cannot perceive thirst. It must also not be used in women who are pregnant or breast-feeding.
ChondroCelect	Repair treatment of symptomatic cartilaginous defects of the femoral condyles of the knee. **What benefit has ChondroCelect shown during the studies?** ChondroCelect was more effective than microfracture at healing the defects in the cartilage. After one year, when scans were performed and samples of cartilage were examined, patients who were treated with ChondroCelect showed better structural repair of their cartilage than patients treated with microfracture. ChondroCelect was also as effective as microfracture at improving symptoms. There was no clear evidence of a difference in the change of KOOS in patients treated with ChondroCelect and those treated with microfracture. **What is the risk associated with ChondroCelect?** The most common side effects with ChondroCelect (seen in more than 1 patient in 10) are arthralgia (joint pain), cartilage hypertrophy (overgrowth), joint crepitation (unusual crackling sounds) and swelling of the joint. For the full list of all side effects reported with ChondroCelect, see the Package Leaflet. ChondroCelect should not be used in people who may be hypersensitive (allergic) to any of the other ingredients or to bovine serum (cow's blood).

Cimzia	Rheumatoid Arthritis **What benefit has Cimzia shown during the studies?** Cimzia with methotrexate was more effective than placebo with methotrexate at treating rheumatoid arthritis.In one main study, 57% of patients receiving Cimzia (141 out of 246) achieved 20% reductions compared with 9% of patients receiving placebo (11 out of 127). In the other main study, the results were similar with 59% of patients who received Cimzia (228 out of 388) achieving 20% reductions compared with 14% of patients receiving placebo (27 out of 198). This study also showed that patients who received Cimzia had a greater reduction in the worsening of joint damage as seen on X-rays. In the additional study of Cimzia used on its own, more patients who received Cimzia achieved 20% reductions compared with those who received placebo. **What is the risk associated with Cimzia?** The most common side effects with Cimzia (between 1 and 10 patients in 100) are bacterial infections including abscesses (cavities containing pus), viral infections (including herpes, papillomavirus, and influenza), eosinophilic disorders (disorders of eosinophils, a type of white blood cell), leucopenia (low white blood cell counts including low levels of neutrophils and lymphocytes), headaches (including migraine), sensory abnormalities (such as numbness, tingling, burning sensation), hypertension (high blood pressure), hepatitis (liver inflammation) including increased levels of liver enzymes, rash, fever, pain, asthenia (weakness), pruritus (itching) and reactions at the injection site.For the full list of all side effects reported with Cimzia, see the Package Leaflet.Cimzia should not be used in people who may be hypersensitive (allergic) to certolizumab pegol or any of the other ingredients. It must not be used in patients with active tuberculosis, other severe infections, or moderate to severe heart failure (an inability of the heart to pump enough blood around the body).
Javlor	Treatment of carcinoma of urothelial tract. **What benefit has Javlor shown during the studies?** Javlor with best supportive care was more effective than best supportive care alone in prolonging the lives of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract. Among all patients in the study, there was no clear evidence of a difference in survival between patients who received Javlor and those who did not. However there was a difference among patients who fulfilled the strict criteria entry requirements for the study. In this group those given Javlor lived for 6.9 months compared with 4.3 months for patients who were not given the Javlor. **What is the risk associated with Javlor?** The most common side effects with Javlor (seen in more than 1 patient in 10) are neutropenia, leucopenia (low white blood cell counts), anaemia (low red blood cell counts), thrombocytopenia (low platelet count), loss of appetite, peripheral sensory neuropathy (damage to the nerves outside the brain and spinal cord that results in

	reduced sensation), constipation, abdominal (tummy) pain, vomiting, nausea (feeling sick), stomatitis (inflammation of the lining of the mouth), diarrhoea, alopecia (hair loss), myalgia (muscle pain), asthenia (weakness), injection site reaction, fever and weight loss. For the full list of all side effects reported with Javlor, see the Package Leaflet. Javlor should not be used in people who may be hypersensitive (allergic) to vinflunine or other vinca alkaloids. It must not be used in patients who have or have had a severe infection within the past two weeks or in patients with a neutrophil count of less than 1,500 per mm3 or a platelet count less than 100,000 per mm3. It must also not be used in breastfeeding mothers.
Onglyza	Type 2 diabetes mellitus **What benefit has Onglyza shown during the studies?** Onglyza was more effective than placebo at controlling blood glucose, when used as an 'add-on' in patients in whom previous treatment had failed. In patients who took Onglyza in addition to metformin, HbA1c levels had fallen by around 0.7% after 24 weeks (from around 8.1% to around 7.4%) compared with an increase of around 0.1% in patients taking placebo. For patients who took Onglyza with a sulphonylurea and a thiazolidinedione, HbA1c levels fell by around 0.6% and 0.9%, respectively, compared with an increase of around 0.1% and a decrease of around 0.3%, respectively, in patients who took placebo. The results of the initial combination study were not considered to be clinically relevant and the company withdrew its application for the use of Onglyza as an initial combination medicine in previously untreated patients. **What is the risk associated with Onglyza?** The most common side effects with Onglyza (seen in between 1 and 10 patients in 100) are upper respiratory tract infection (colds), urinary tract infection (infection of the structures that carry urine), gastroenteritis (inflammation of the stomach and gut), sinusitis (inflammation of the sinuses), headache, vomiting and mild to moderate peripheral oedema (swelling, especially of the ankles and feet) in patients taking Onglyza with a thiazolidinedione. For the full list of all side effects reported with Onglyza, see the Package Leaflet. Onglyza should not be used in people who may be hypersensitive (allergic) to saxagliptin or any of the other ingredients.
Simponi	Arthritis **What benefit has Simponi shown during the studies?** Simponi 50 mg was more effective than placebo in all of the diseases studied. In the first rheumatoid arthritis study, in which patients were also given methotrexate, after 14 weeks, 55 % patients who received Simponi (49 out of 89) achieved 20% reductions compared with 33% (44 out of 133) of patients who received placebo. This study also showed that patients who received Simponi had greater improvements in carrying out tasks. In the second rheumatoid arthritis study, after 14 weeks, 35% of patients who received Simponi alone (54 out of 153) achieved 20% reductions compared with 18% of patients who received placebo (28 out of 155). In the third rheumatoid arthritis study, after 24 weeks, 40% of patients who received Simponi with methotrexate achieved 50% reductions (64 out of 159) compared with 29% of patients who received placebo (47 out of 160) and

	methotrexate. In the study of psoriatic arthritis, after 14 weeks, 51% of patients who received Simponi (74 out of 146) had 20% reductions compared with 9% of patients who were given placebo (10 out of 113). In the study of ankylosing spondylitis, after 14 weeks, 59% of patients who received Simponi (82 out of 138) had 20% reductions compared with 22% of patients who were given placebo (17 out of 78). **What is the risk associated with Simponi?** The most common side effects with Simponi (seen in more than 1 patient in 10) are upper respiratory tract infections such as nasopharyngitis (infection of the nose and throat), pharyngitis (infection of the throat), laryngitis (infection of the voice box) and rhinitis (runny nose). For the full list of all side effects reported with Simponi, see the Package Leaflet. Simponi should not be used in people who may be hypersensitive (allergic) to golimumab or any of the other ingredients. It must not be used in patients with tuberculosis, other severe infections, or moderate or severe heart failure (an inability of the heart to pump enough blood around the body). Due to an increased risk of infection, patients taking Simponi must be monitored closely
Arcalyst	Cryopyrin-Associated Periodic Syndromes (CAPS). **What benefit has Arcalyst shown during the studies?** Arcalyst was more effective than placebo at treating symptoms of CAPS. After the six-week treatment, patients who received Arcalyst had a reduction in symptoms of 2.5 points on the scale compared with 0.3 points in patients who received placebo. In the second part of the study, symptoms increased more in patients switched to placebo (0.9 points) compared with patients who remained on Arcalyst (0.1 points). **What is the risk associated with Arcalyst?** The most common side effects with Arcalyst (seen in more than 1 patient in 10) are reactions at the injection site, upper respiratory tract infections (colds), sinusitis (inflammation of the sinuses) and headache. For the full list of all side effects reported with Arcalyst, see the Package Leaflet. Arcalyst should not be used in people who may be hypersensitive (allergic) to rilonacept or any of the other ingredients. It must not be used in patients with an active, severe infection.Blocking interleukin-1 may interfere with the body's immune response to infection and there have been reports of serious infections in patients taking Arcalyst.
Exforge HCT	Treatment of essential hypertension **What benefit has Exforge shown during the studies?** The combination of amlodipine and valsartan was more effective at reducing blood pressure than placebo or either valsartan or amlodipine taken alone. In the studies comparing the effectiveness of the combination in patients who were already taking either amlodipine or valsartan, the blood pressure in patients taking valsartan alone had fallen by 6.6 mmHg after eight weeks, compared with 9.6 and 11.4 mmHg in the patients adding 5 or 10 mg amlodipine, respectively. Patients taking amlodipine

	alone had a fall of 10.0 mmHg, compared with 11.8 mmHg in the patients adding 160 mg valsartan. **What is the risk associated with Exforge?** The most common side effects with Exforge (seen in between 1 and 10 patients in 100) are headache, nasopharyngitis (inflammation of the nose and throat), influenza (flu), various types of oedema (swelling), fatigue (tiredness), flushing (reddening), asthenia (weakness) and hot flushes. For the full list of all side effects reported with Exforge, see the Package Leaflet. Exforge should not be used in patients who may be hypersensitive (allergic) to amlodipine or other medicines in the 'dihydropyridine derivatives' class, to valsartan, or to any of the other ingredients. It must not be used in women who are more than three months pregnant. Its use during the first three months of pregnancy is not recommended. Exforge must also not be used in patients who have severe liver, kidney or bile problems, or in patients undergoing dialysis (a blood clearance technique).
Ilaris	Cryopyrin-associated periodic syndromes (CAPS). **What benefit has Ilaris shown during the studies?** Ilaris was more effective than placebo at treating patients with CAPS. None of the 15 patients who received Ilaris during the 24-week treatment period had a 'disease flare' compared with 81% of patients who received placebo (13 out of 16). **What is the risk associated with Ilaris?** The most common side effects with Ilaris (seen in more than 1 patient in 10) are nasopharyngitis (inflammation of the nose and throat), vertigo (a spinning sensation) and reactions at the injection site. For the full list of all side effects reported with Ilaris, see the Package Leaflet. Ilaris should not be used in people who may be hypersensitive (allergic) to canakinumab or any of the other ingredients. It must not be used in patients with active or severe infection. Because Ilaris may be associated with serious infection, patients should be monitored carefully for signs and symptoms of infection during and after treatment with the medicine.
Ratioepo	Anaemia. **What are the benefit and risk of Ratioepo?** The benefit with Ratioepo is its correction of anaemia in adult patients with chronic renal failure and in adult cancer patients with non myeloid malignancies receiving chemotherapy. The most common side effects are hypertension, influenza-like illness and headache. The product was withdrawn by the Company after approval.

Resolor	Chronic constipation in women in whom laxatives fail to provide adequate relief. **What benefit has Resolor shown during the studies?** Resolor was more effective than placebo at treating chronic constipation. Over the 12-week period, 24% (151 out of 640) of patients who received Resolor 2 mg completely emptied their bowels at least three times a week, compared with 11% (73 out of 645) of patients who received placebo. The result from patients who received Resolor at the higher dose of 4 mg was similar to those who took the 2 mg dose. **What is the risk associated with Resolor?** The most common side effects with Resolor (seen in more than 1 patient in 10) are headache, nausea (feeling sick), diarrhoea and abdominal (tummy) pain. For the full list of all side effects reported with Resolor, see the Package Leaflet. Resolor should not be used in people who may be hypersensitive (allergic) to prucalopride or any of the other ingredients. It must not be used in patients with kidney problems requiring dialysis (a blood clearance technique). It must also not be used in patients with intestinal perforation or obstruction, severe inflammatory conditions of the intestines such as Crohn's disease, ulcerative colitis (inflammation of the large intestine causing ulceration and bleeding) and toxic megacolon and megarectum (very serious complications of colitis).
MULTAQ	Treatment of rhythm control in patients with atrial fibrillation **What benefit has Multaq shown during the studies?** Multaq was more effective than placebo at preventing atrial fibrillation from reoccurring. In the first three placebo studies, it took an average of 116 days for fibrillation to come back in the patients taking Multaq compared with 53 days in the patients taking placebo. In addition, heart rates reduced by an average of 11.0 beats per minute (bpm) in the patients who took Multaq, compared with a rise of 0.7 bpm in the patients who took placebo. In the fourth study, Multaq was less effective than amiodarone at maintaining normal rhythm: after a year, atrial fibrillation had come back or treatment had been stopped in 75% of the patients taking Multaq, compared with 59% of the patients receiving amiodarone. Atrial fibrillation came back more often in patients receiving Multaq, but more patients receiving amiodarone had to stop treatment because of side effects. The fifth study provided further support for the use of Multaq in maintaining normal rhythm and reducing the heart rate. The study showed a reduction in the number of cardiovascular hospitalisations, particularly those related to atrial fibrillations. **What is the risk associated with Multaq?** The most common side effects with Multaq (seen in more than 1 patient in 10) are increased blood levels of creatinine (a breakdown product of muscle) and a prolonged 'QTc Bazett' (an alteration of the electrical activity of the heart). For the full list of all side effects reported with Multaq, see the Package Leaflet.

	Multaq should not be used in people who may be hypersensitive (allergic) to the active substance or any of the other ingredients. It must not be taken with medicines that can cause torsades de pointes (a type of rapid heart beat). Multaq must not be used in patients with certain heart problems, such as some types of altered electrical activity of the heart, very slow heart beats or when the heart cannot pump enough blood around the body. It must also not be used in patients who have severe problems with their liver or kidneys. For the full list of restrictions, see the Package Leaflet.
Prevenar 13	Vaccination of infants and children aged between two months and five years against diseases caused by Streptococcus pneumoniae **What benefit has Prevenar shown during the studies?** Prevenar was effective in preventing *S. pneumoniae* invasive disease. During the main study, 49 cases of infection due to the serotypes 4, 6B, 9V, 14, 18C, 19F and 23F of *S. pneumoniae* were seen among the infants who received the control vaccine, compared with three cases among the infants vaccinated with Prevenar. The additional studies showed that Prevenar was safe and effective in children up to the age of five years. In infants, the two-dose immunisation schedule led to the development of antibodies against *S. pneumoniae*, but to a lower level than the three-dose schedule. However, the CHMP concluded that this is unlikely to lead to a difference in the rate of protection against infection with *S. pneumoniae* following a booster injection, when Prevenar is used as part of a routine immunisation programme in which most infants are vaccinated. **What is the risk associated with Prevenar?** The most common side effects with Prevenar (seen in more than 1 patient in 10) are vomiting, diarrhoea, loss of appetite, reactions at the site of the injection (redness, hardening, swelling or pain), fever, irritability, drowsiness and restless sleep. For the full list of all side effects reported with Prevenar, see the Package Leaflet. Prevenar should not be used in children who may be hypersensitive (allergic) to the *Streptococcus* vaccine, to any of the other ingredients or to the diphtheria toxoid (a weakened toxin from the bacterium that causes diphtheria). As for all vaccines, if Prevenar is used in very premature babies, there is a risk of the babies experiencing apnoea (brief pauses in breathing). Their breathing should be monitored for up to three days after vaccination.
Zutectra	Hepatitis B immunoglobulin The benefits with Zutectra are its ability to maintain anti-HBs serum levels in line with those required for hepatitis B immunoglobulin preparations (> 100 IU/l). This was demonstrated in a study monitoring trough levels of anti-HBs in 23 stable HBsAg-negative, HBV DNA-negative liver transplant patients. In addition, the pharmacokinetic profile was characterised. The product is for subcutaneous use and allows for self-administration which is considered a convenient and feasible alternative provided appropriate training is given, initial supervision is in place and monitoring of anti HBsAg levels is carried out regularly. The most common side effects are injection site reactions (pain, urticaria, haematoma) as well as

	unspecific hypersensitivity reactions such as headache and upper abdominal pain.
Onbreeze Breezsehaler	Chronic obstructive pulmonary disease (COPD) **What benefit has Onbrez Breezhaler shown during the studies?** Onbrez Breezhaler was more effective than placebo at improving how well the lungs work in patients with COPD. On average, the improvement in FEV1 in patients who received Onbrez Breezhaler was between 150 to 190 ml, while for patients who received placebo the change in FEV1 ranged from a decrease of 10 ml to an increase of 20 ml. Overall, the effects of the 150- and 300-microgram doses of Onbrez Breezhaler were similar, but the results showed that the 300-microgram dose may provide better relief in patients with more severe disease. **What is the risk associated with Onbrez Breezhaler?** The most common side effects with Onbrez Breezhaler (seen in between 1 and 10 patients in 100) are nasopharyngitis (inflammation of the nose and throat), upper respiratory tract infection (colds), sinusitis (inflammation of the sinuses), diabetes mellitus and hyperglycaemia (high blood sugar levels), headache, ischaemic heart disease (disease of the heart caused by failure in the blood supply), cough, pharyngolaryngeal (throat) pain, rhinorrhoea (runny nose), respiratory tract congestion (blocked airways), muscle spasm (cramps) and peripheral oedema (swelling, especially of the ankles and feet). For the full list of all side effects reported with Onbrez Breezhaler, see the Package Leaflet. Onbrez Breezhaler should not be used in people who may be hypersensitive (allergic) to indacaterol, lactose or any of the other ingredients.
Scintimun	Osteomyelitis The benefits with Scintimun are in vivo labelling of granulocytes, which avoids the risks of ex vivo blood cells labelling and re-administration (99mTc white blood cells), the satisfactory agreement rate between the two methods and also the good quality of images achieved (technical performance). The most common side effect is the development of Human Anti-Mouse Antibodies (HAMA). Patients who are HAMA positive may have a greater risk for hypersensitivity reactions and therefore should not be administered Scintimun.
Firdapse	Lambert-Eaton Myasthenic Syndrome (LEMS) **What benefit has Firdapse shown during the studies?** Firdapse was more effective than placebo at treating patients with LEMS. In one study, the NDS was reduced from 40 to 22 points in patients taking Firdapse compared with a drop to 35 points in patients taking placebo. The other study showed a reduction in the QMG score of 2 points in patients taking Firdapse compared with a rise of 0.25 points in patients taking placebo. In the third combined study, patients taking Firdapse had better improvements in CMAP than patients taking placebo. **What is the risk associated with Firdapse?** The most common side effects reported with Firdapse in published literature are paraesthesia (unusual sensations like pins and needles) and gastro-intestinal

	disorders such as epigastralgia (pain around the upper part of the stomach), diarrhoea, nausea (feeling sick) and abdominal pain (stomach ache). For the full list of all side effects reported with Firdapse, see the Package Leaflet. Firdapse should not be used in people who may be hypersensitive (allergic) to amifampridine or any of the other ingredients. It must not be used in patients who have epilepsy (fits) in the past or patients with uncontrolled asthma or congenital QT syndromes (disruption of the heartbeat). It must not be used with sultopride (an antipsychotic medicine), or medicines known to cause QTc prolongation (an alteration of the electrical activity of the heart). It must also not be used with medicines that have a narrow therapeutic window. A medicine with a narrow therapeutic window can easily cause side effects if given at a dose a little higher than the recommended dose.
Elonva	Ovarian stimulation The benefits with Elonva are its ability to initiate and sustain multiple follicular growth for an entire week. A single subcutaneous injection of the recommended dose of Elonva may replace the first seven injections of any daily (recombinant) FSH preparation in a COS treatment cycle. The most common side effects are OHSS, pelvic pain and discomfort, headache, nausea, fatigue and breast complaints (including tenderness).
Urorec	Prostate hyperplasia The benefits with Urorec are its ability to improve lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) including decrease in both storage (irritative) and voiding (obstructive) symptoms of BPH. The most common side effects are transient ejaculatory disorders such as retrograde ejaculation and anejaculation (ejaculatory volume reduced or absent).
ImmunoGam	Hepatitis B immunoglobulin The benefits with ImmunoGam are its ability to maintain protective anti-HBs serum levels in line with those required for hepatitis B immunoglobulin preparations (> 10 IU/l) for immunoprophylaxis after intramuscular administration. The pharmacokinetic profile of ImmunoGam was characterised in two studies in healthy adults comparing ImmunoGam with other HBIG licensed products. Furthermore, the efficacy of ImmunoGam administered concomitantly with HBV vaccine was demonstrated in a clinical study with 178 infants and 23 adults. The most common side effects are injection site reactions (local pain or tenderness) as well as headache, nausea, hypersensitivity, diarrhea, pain and pyrexia.
Menveo	Meningococcal disease The benefits with Menveo are its ability to prevent invasive disease caused by Neisseria meningitidis groups A, C, W135 and Y in adolescents (from the age of 11 years old) and adults. The most common side effects are pain, erythema and induration, headache, myalgia, chills, and malaise.
Prolia	Osteoporosis The benefits with Prolia are its ability to significantly reduce the risk of vertebral, hip and non-vertebral fractures and increase bone mineral density in postmenopausal women at increased risk of fractures. Prolia also significantly

	reduces the risk of vertebral fractures and increases bone mineral density in men with prostate cancer at increased risk of fractures receiving hormone ablation. The most common side effects are urinary tract infection, upper respiratory tract infection, cataract, constipation, rash, sciatica and pain in extremity.
Tepadina	Haematologic disease – Cell transplantation The benefits with Tepadina are its cytotoxic and myeloablative ability which are applied to conditioning treatment prior to haematopoietic stem cell transplantation. The most common side effects are infections, pancytopenia, gastrointestinal disorders, haemorrhagic cystitis and mucosal inflammation.
DuoPlavin	Atherothrombotic events DuoPlavin is a new fixed combination and its active substances are clopidogrel hydrogen sulphate and acetylsalicylic acid. The benefit with DuoPlavin is its simplification of treatment, i.e. patients need to take one instead of two tablets. The most common side effect is bleeding.
Revolade	Idiopathic Trombocytopen purpura (ITP) The benefits with Revolade have been shown in two phase III, placebo-controlled, double-blind studies in adults with ITP. In both studies, efficacy has been shown in terms of a durable platelet response compared to patients receiving placebo. The most common side effects are headache, nausea, alanineaminotransferase increased, aminotransferase increased, diarrhoea, fatigue, paraesthesia, constipation, rash, pruritus, blood bilirubin increased, cataract, arthralgia, myalgia and hyperbilirubinaemia.

I.4 - Information on initial applications with negative outcomes during 2009

The Question and Answer (Q/A) document has been used for this compilation. When a Q/A document were not yet available, the Summary of the Opinion was used.

(Further information available on the EMA web: www.EMA.europa.eu/index/indexh1.htm)

(Generic applications are not included).

Product	**Therapeutic area and main concerns of the Committee**
Ixempra	Breast Cancer **What documentation did the company present to support its application to the CHMP?** The effects of Ixempra were first tested in experimental models before being studied in humans. Ixempra has been studied in three main studies involving women with locally advanced or metastatic breast cancer who had been treated with a number of other anticancer medicines in the past. The first study looked at Ixempra given on its own in 128 women, but did not compare it with any other treatment. The main measure of effectiveness was the number of patients whose cancer responded to treatment. The other two studies compared the effects of capecitabine given on its own with the effects of Ixempra given in

	combination with capecitabine in a total of 1,973 women. The main measures of effectiveness were how long the patients lived without their cancer getting worse and how long they survived. The evaluation had finished and the CHMP had given a negative opinion. The company had initiated an appeal process, but this had not yet finished. **What were the main concerns of the CHMP?** The CHMP was concerned that Ixempra's benefits in terms of increasing the time until the cancer got worse did not outweigh the concerns over the medicine's safety. In particular, the Committee was concerned over the risk of patients developing neuropathy (damage to nerve cells), which was a severe and common side effect in patients taking the medicine. Therefore, at the time of the withdrawal, the CHMP's view was that the benefits of Ixempra in the treatment of breast cancer did not outweigh the identified risks.
Biferonex	Multiple sclerosis **What documentation did the company present to support its application to the CHMP?** The effects of Biferonex were first tested in experimental models before being studied in humans. The company presented the results of one main study, in which Biferonex was compared with placebo (a dummy treatment) in 339 adults with relapsing-remitting multiple sclerosis. Each patient receivedeither Biferonex or placebo for two years. The main measure of effectiveness was the reduction in the number of attacks.The company also used information relating to Avonex, and information from the published literature on other medicines containing interferon beta. The evaluation had finished and the CHMP had given a negative opinion. The company had requested a re-examination of the negative opinion, but this re-examination had not yet finished when the company withdrew. **What were the main concerns of the CHMP?** The Committee noted that there were differences between the active substance in Biferonex and other interferon beta-containing medicines available on the market. It therefore concluded that using the published studies on these interferon beta-containing medicines to support the use of Biferonex was not justified, and that studies on Biferonex itself were required. The CHMP was also of the opinion that the results of the single pivotal study of Biferonex did not show enough evidence that the medicine was effective. Based on the information presented to the Committee, it was not clear whether this was due to the way the study was designed, the way the results were analysed, or to the medicine itself. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Biferonex in the treatment of patients with relapsing-remitting multiple sclerosis did not outweigh its risks.

Vorinostat MSD	Cutaneous T-Cell Lymphoma **What documentation did the company present to support its application to the CHMP?** The effects of Vorinostat MSD were first tested in experimental models before being studied in humans. The company presented the results of one main study in which 74 adults with advanced CTCL were given Vorinostat MSD. All of the patients had progressive, persistent or recurrent disease and had received two other systemic treatments. Vorinostat MSD was not compared with any other treatment. The main measure of effectiveness was based on the change in how much of the skin was affected by the disease and the severity of the skin lesions. The application was at day 206 when the company withdrew. **What were the main concerns of the CHMP?** The Committee was concerned over the way the main study was designed. Because Vorinostat MSD was not compared with any other treatment, its safety and effectiveness could not be adequately assessed. In addition, the study did not look at how long the patients survived. In particular, the CHMP was concerned about the risk of thromboembolic events (problems caused by the formation of clots in the blood vessels) in patients taking Vorinostat MSD. Therefore, at the time of the withdrawal, the Committee's view was that a benefit of Vorinostat MSD had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.
Emerflu	Pandemic Flu **What documentation did the company present to support its application to the CHMP?** The effects of Emerflu were first tested in experimental models before being studied in humans. The main study of Emerflu included 600 healthy adults and compared the ability of two doses of Emerflu, to trigger the production of antibodies ('immunogenicity'). The participants received two injections of Emerflu containing one of two different doses of haemagglutinin. The higher dose vaccine also contained the adjuvant. The injections were given 21 days apart. The main measure of effectiveness was the level of antibodies against the flu virus in the blood at three different times: before vaccination, on the day of the second injection (day 21) and 21 days later (day 42). In addition, 100 further people received Emerflu that contained a different strain of flu virus. Some of the participants in the studies of Emerflu went on to receive a third dose of the vaccine, containing either of the two flu virus strains, with or without the adjuvant. **What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?** The CHMP was concerned over the ability of Emerflu to trigger the production of enough antibodies against the flu virus. According to criteria laid down by

	the CHMP, a mock-up vaccine needs to bring about protective levels of antibodies in at least 70% of people for it to be considered suitable. Because antibody production following Emerflu administration was below this level in the main studies (less than 40% in participants aged below 60 years), the CHMP was concerned that Emerflu was not suitable for use as a mock-up vaccine. Similar results were seen in the people who received Emerflu that contained a different strain of flu virus, and there were contradictory results in the studies looking at the effects of a third dose of Emerflu. Therefore, the Committee was also concerned that the vaccine's immunogenicity was low, regardless of the strain of virus included, and that the vaccine might not be able to adequately prepare the immune system for future infections. At that point in time, the CHMP was of the opinion that the benefits of Emerflu used for prophylaxis of influenza in an officially declared pandemic situation did not outweigh its risks. Hence, the CHMP recommended that Emerflu be refused marketing authorisation.
Cylatron	Stage III melanoma **What documentation did the company present to support its application to the CHMP?** The effects of Cylatron were first tested in experimental models before being studied in humans. Cylatron was studied in one main study involving 1,256 adults with stage III melanoma. Patients were either given Cylatron for up to five years or received no treatment. When the study began, all of the patients had recently had surgery to remove lymph nodes containing melanoma cells. The main measure of effectiveness was the how long the patients survived until the disease came back. The application was at day 194 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP had concerns over side effects of Cylatron, particularly fatigue (tiredness) and depression. It was also concerned that, although the medicine showed some effects in delaying the return of the cancer, it had not been shown to be effective in increasing how long the patients survived.
Factive	Community acquired pneumonia (CAP) of mild to moderate severity and Acute exacerbation of chronic bronchitis (AECB). **What documentation did the company present to support its application to the CHMP?** The effects of Factive were first tested in experimental models before being studied in humans. In four main studies, 1,874 adults with mild to moderate community-acquired pneumonia were treated for at least seven days with Factive or other antibiotics. In another study of patients with community acquired pneumonia, 510 adults were given Factive either as a five- or seven-day treatment. In three other main studies, 1,652 adults with acute

	exacerbation of chronic bronchitis were treated with Factive for five days or with other antibiotics. The main measures of effectiveness for the studies were based on the number of patients who got better after treatment. The application was at day 196 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP was concerned that Factive may be more genotoxic (harmful to the DNA, the genetic material in cells) and that it may therefore cause more damage to the DNA than other fluoroquinolones. The Committee was also concerned there was not enough evidence of effectiveness of Factive in patients with moderate community-acquired pneumonia when given as a five-day treatment. The seven-day treatment was not considered acceptable because of the risk of side effects. The Committee also noted that the information presented did not support the use of Factive for chronic bronchitis because no studies were carried out to investigate whether Factive was better than other treatments for this type of infection and because there were problems with the studies that were performed. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Factive in the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis caused by bacterial infection did not outweigh its risks.
Gemesis	Periodontally related defects **What documentation did the company present to support its application to the CHMP?** The effects of Gemesis were first tested in experimental models before being studied in humans. In one main study involving 180 adults with advanced periodontal disease, Gemesis was compared with the matrix alone. The main measure of effectiveness was the change in 'clinical attachment level' (CAL) after 24 weeks. CAL is a measure of the loss of support to the teeth from surrounding tissue. **What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?** The CHMP was of the opinion that the main study failed to show that Gemesis was effective in treating periodontal defects. The CHMP noted that the company did not at this time have sufficient information on how strongly becaplermin binds to receptors and did not sufficiently demonstrate that Gemesis used in clinical studies was comparable to the product intended to be placed on the market. The CHMP was also concerned about the level of product-related impurities present. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Gemesis for bone and periodontal regeneration in adults did not outweigh its risks. Hence, the CHMP recommended that Gemesis be refused marketing authorisation.
Milnacipran Pierre Fabre Medicament	Fibromyalgia syndrome **What documentation did the company present to support its**

	application to the CHMP? The effects of Milnacipran Pierre Fabre Médicament/Impulsor were first tested in experimental models before being studied in humans. In three main studies, 2,960 adult patients with fibromyalgia were given either Milnacipran Pierre Fabre Médicament/Impulsor or placebo (a dummy treatment) for around four to seven months. The main measure of effectiveness was the change in the patients' symptoms, particularly pain levels and their overall state of health. **What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?** The CHMP was of the opinion that the effect of the medicine was marginal. There was also a lack of data on the long-term effects in a European population. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Milnacipran Pierre Fabre Médicament/Impulsor in the treatment of fibromyalgia did not outweigh its risks. Hence, the CHMP recommended that Milnacipran Pierre Fabre Médicament/Impulsor be refused marketing authorisation.
Contusugene Ladenovec Gendux	Refractory squamous cell carcinoma of the head and neck **What documentation did the company present to support its application to the CHMP?** The effects of Contusugene Ladenovec Gendux were first tested in experimental models before being studied in humans. In one main study involving 123 patients with refractory or recurrent squamous cell carcinoma of the head and neck, Contusugene Ladenovec Gendux was compared with methotrexate (another anti-cancer medicine). The main measure of effectiveness was how long the patients lived. The application was at day 120 of the procedure when the company withdrew. **What were the main concerns of the CHMP?** The Committee was of the opinion that the company had not shown that Contusugene Ladenovec Gendux was beneficial to patients. Also, the company had not supplied enough evidence to demonstrate that the product was safe, that it could be made in a reliable manner, or that it would not be harmful to the environment or to people in close contact with the patient. Finally, the CHMP noted that there was insufficient information on the product's toxicity, its distribution in the body and the role of some genes and impurities found in the product
Bosatria	Hypereosinophilic syndrome **What documentation did the company present to support its application to the CHMP?** The effects of Bosatria were first tested in experimental models before being studied in humans. In one main study involving 85 adults with hypereosinophilic syndrome, Bosatria was compared with placebo (a dummy treatment). All patients lacked the FIP1L1-PDGRF fusion gene and were

	receiving treatment with prednisone (a corticosteroid) that was helping to stabilise their symptoms. During the study the patients received either Bosatria or placebo while the amount of prednisone they received was gradually reduced. The main measure of effectiveness was the number of patients who could have their daily prednisone dose reduced to 10 mg or lower for a period of eight weeks. The application was at day 180 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP was of the opinion that the main study did not provide sufficient evidence to show that Bosatria was effective in reducing the need for corticosteroid treatment. The CHMP was also concerned that the method used by the company to quantify the different forms of the active substance in the medicine was not appropriate. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Bosatria did not outweigh its risks in the treatment of adults with hypereosinophilic syndrome who lack the FIP1L1-PDGRF fusion gene, to reduce or eliminate the need for corticosteroid therapy and to reduce blood eosinophil counts.
Ramvocid	Complicated skin and soft tissue infections **What documentation did the company present to support its application to the CHMP?** The effects of Ramvocid were first tested in experimental models before being studied in humans. The company presented results from one main study involving 1,267 patients with complicated skin and soft tissue infections. Patients were given either Ramvocid for seven days or vancomycin with or without cephalexin (other antibiotic medicines) for between 10 and 14 days. The main measure of effectiveness was the number of patients who were cured after treatment. The application was at day 180 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP was concerned that the company had not provided enough evidence to support the use of Ramvocid to treat complicated skin and soft tissue infections at the dose proposed, particularly in patients with MRSA. The Committee was also concerned over the way the company had measured the levels of impurities in the medicine.
Opaxio	Non-small cell lung cancer **What documentation did the company present to support its application to the CHMP?** The effects of Opaxio were first tested in experimental models before being studied in humans. The company presented results of one main study involving 477 patients with advanced non-small cell lung cancer and a performance status of 2. In this study, Opaxio was compared with gemcitabine or vinorelbine (two other anticancer medicines). The main

	measure of effectiveness was how long the patients lived. The application was at day 180 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP noted that the main study did not show that Opaxio was effective in patients with advanced non-small cell lung cancer who have an ECOG performance status of 2. The company's view that the study showed that Opaxio was as least as good as the comparators was not accepted by the Committee because it was not clear that the comparators themselves were effective in the type of patients involved in the main study. In addition, the studies did not show that Opaxio was more effective than the two comparators. The CHMP also had concerns about the side effects of the medicine, especially neuropathy (damage to the nerves) and unexplained deaths. There were also concerns about impurities in the medicine and about the way paclitaxel is released and distributed in the body when Opaxio is given.
Zunrisa	Nausea and vomiting **What documentation did the company present to support its application to the CHMP?** The effects of Zunrisa were first tested in experimental models before being studied in humans. The company presented data from large studies in cancer patients receiving chemotherapy. The patients were given a combination of Zunrisa with two other medicines (dexamethasone and ondansetron) or the combination without Zunrisa. The main measure of effectiveness was the number of patients who did not vomit or needed to be given rescue medication for vomiting in the first five days following the start of a cycle of chemotherapy. The company also presented data from studies in patients at a high risk of having nausea and vomiting after surgery. The patients received Zunrisa with ondansetron or ondansetron alone. The main measure of effectiveness for the study was the number of patients who did not vomit or needed to be given any rescue medication in the first 24 hours after surgery. The application was at day 180 when the company withdrew. **What were the main concerns of the CHMP?** After looking at the results of the main studies, the CHMP noted that, while the studies showed that Zunrisa was effective in some cancer patients receiving chemotherapy, its use in patients receiving chemotherapy treatments that are moderate triggers of nausea and vomiting was not fully supported by the results. The Committee also asked the company to reconsider the target population for patients having surgery to ensure it adequately reflected the kind of patients who were involved in the studies.
Mersarex	Complicated skin and soft tissue infection **What documentation did the company present to support its application to the CHMP?**

	The effects of Mersarex were first tested in experimental models before being studied in humans. The company presented results from two main studies involving 991 adults with complicated infections of the skin and soft tissues. Around half of the patients were treated with Mersarex, while the others were treated with linezolid (another antibiotic). The study looked at whether Mersarex given for up to 14 days was as good as linezolid. The main measure of effectiveness was the number of patients who were cured. The application was at day 181 when the company withdrew. **What were the main concerns of the CHMP?** The CHMP was of the opinion that the results did not show that Mersarex was as good as the comparator medicine and that there were insufficient data from clinical studies to justify the dosage proposed by the company. There were also concerns that the medicine may cause side effects affecting the heart (such as QTc interval prolongation, an alteration of the electrical activity of the heart) and the liver. The CHMP also noted that some bacteria already show a level of resistance to the antibiotic even before it is in general use.
Nenad	Restless Legs Syndrome. **What documentation did the company present to support its application to the CHMP?** The effects of Nenad were first tested in experimental models before being studied in humans. The company presented results of one main study of 309 patients with moderate-to-severe restless legs syndrome. The patients were given Nenad, ropinirole (another medicine for restless legs syndrome) or placebo (a dummy medicine). The main measure of effectiveness was the change in the rating of the patients' symptoms after 12 weeks using the International Restless Legs Syndrome rating scale (IRLS) score. The 210 patients who completed the first 12 weeks were also offered the opportunity to continue treatment in an extension study. The company had also provided results on studies involving patients with Parkinson's disease. The evaluation had finished and the CHMP had given a negative opinion. The company withdrew before the European Commission had issued a decision on this opinion. **What was the recommendation of the CHMP at that time?** Based on the review of the data and the company's response to the CHMP lists of questions, at the time of the withdrawal, the CHMP had given a negative opinion, recommending that the marketing authorisation for Nenad be refused. The CHMP noted that, while the short-term effectiveness of Nenad for the treatment of restless legs syndrome had been shown, there was not enough evidence to demonstrate its long-term effectiveness. Since restless legs syndrome is often a lifelong disease, long-term data were considered essential. The Committee was also concerned that a large proportion of

	patients in the study stopped treatment with Nenad because of skin irritation, making the patch unsuitable for long-term use. There were also problems with the patches not sticking well enough to the skin. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Nenad in the treatment of restless legs syndrome did not outweigh its risks.
Oncophage	Renal cell carcinoma **What documentation did the company present to support its application to the CHMP?** The effects of Oncophage were first tested in experimental models before being studied in humans. The company presented results of a study involving 818 adults with localised renal cell carcinoma that had been surgically removed and who had a high risk of the cancer coming back. The study compared the patients who were given Oncophage with those who were not. The main measure of effectiveness was how long the patients lived without the cancer coming back. The evaluation had finished and the CHMP had given a negative opinion. The company withdrew before the European Commission had issued a decision on this opinion. **What was the recommendation of the CHMP at that time?** Based on the review of the data and the company's response to the CHMP lists of questions, at the time of the withdrawal, the CHMP had given a negative opinion, recommending that the marketing authorisation be refused for Oncophage for use as an add-on treatment after surgery for localised renal cell carcinoma at high risk of coming back. The CHMP was of the opinion that the main study did not show that Oncophage was effective at prolonging the length patients lived without the cancer coming back. The Commitee also noted that the company had provided insufficient information on the contents of the medicine and on the manufacturing process. There was also not enough information to clarify the way Oncophage works in renal cell carcinoma and to determine the appropriate dose of the medicine. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Oncophage did not outweigh its risks. Hence, the CHMP recommended that Oncophage be refused marketing authorisation.
Zactima	Non-small cell lung cancer **What documentation did the company present to support its application to the CHMP?** The effects of Zactima were first tested in experimental models before being studied in humans. The company presented results of two main studies in 1,927 patients with NSCLC that was advanced or had spread to other parts of the body. The patients had previously received anticancer treatment. Patients were given docetaxel or pemetrexed (other anticancer medicines used in NSCLC) together with either Zactima or placebo (a dummy treatment). The main measure of

	effectiveness was how long the patients lived without their disease getting worse. The application was at day 96 when the company withdrew. The CHMP was evaluating the initial documentation provided by the company and had not yet made any recommendations.
Cerepro	Glioma **What documentation did the company present to support its application to the CHMP?** The effects of Cerepro were first tested in experimental models before being studied in humans. Cerepro has also been studied in 36 patients with high-grade glioma. The study compared the effects of adding Cerepro and ganciclovir sodium to standard treatment with the effects of standard treatment alone. The main measure of effectiveness was how long the patients survived after the first operation. The evaluation had finished and the CHMP had given a negative opinion. The company had requested a re-examination of the negative opinion, but this had not yet finished when the company withdrew. **What were the main concerns of the CHMP?** The CHMP had concerns that a benefit of Cerepro had not yet been shown. It was concerned over the low number of patients included in the main study of Cerepro, which prevented a benefit of the medicine being demonstrated. The Committee also had concerns over the ways in which the study had been carried out, which made it difficult to interpret the results. In addition, the CHMP considered there to be insufficient information on the safety of Cerepro, and, since the benefits of the medicine had not been demonstrated, that its risks, when used in combination with ganciclovir, could be of concern. Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Cerepro had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.
Ethyl Eicosapent	Huntington's disease **What documentation did the company present to support its application to the Agency?** The effects of Ethyl Eicosapent soft gelatin capsules were first tested in experimental models before being studied iin humans. The company also presented data on experimental models from the scientific literature. In three main studies involving 741 patients with Huntington's disease, the medicine was compared with placebo (a dummy medicine). The main measure of effectiveness was the reduction in symptoms affecting patients' movements after six months or one year. The application was withdrawn at 'day 120'.

	What was the recommendation of the CHMP at that time? Based on the review of the data, at the time of the witdrawal, the CHMP had some concerns and was of the provisional opinion that Ethyl Eicosapent soft gelatin capsules could not have been approved for the long-term stabilisation of symptoms in patients with Huntington's disease. The CHMP noted that results from the three main studies failed to show that the medicine is effective. There was also insufficient information provided on what would happen to the medicine in the body. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Ethyl Eicosapent soft gelatin capsules did not outweigh its risks.
Recothrom	Hemostasis **What documentation did the company present to support its application to the Agency?** The effects of Recothrom were first tested in experimental models before being studied in humans. The company presented results of one main study involving 463 patients undergoing different types of surgeries. The study compared Recothrom with another medicine containing thrombin and the main measure of effectiveness was the number of patients whose bleeding stopped within 10 minutes. The application was withdrawn at 'day 180'. **What was the recommendation of the CHMP at that time?** Based on the review of the data and the company's response to the CHMP list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Recothrom could not have been approved for use in stopping bleeding during surgery where standard surgical techniques are insufficient. The CHMP was concerned that the company provided evidence from specialised surgeries, whereas Recothrom was intended for more general use. The Committee also noted that because the sponge and spray worked differently and should have been studied separately, there was not enough to determine the effects of the spray. In addition, not enough evidence was presented to show that Recothrom used with a gelatin sponge was more effective than a sponge alone. Finally, there were concerns about the medicine that Recothrom was compared with (the comparator) in the main study. According to EU requirements, Recothrom should have been compared with a standard treatment that did not contain thrombin.
Sliwens	Chronic insomnia. **What documentation did the company present to support its application?** The effects of Sliwens were first tested in experimental models before being studied in humans.

	The company presented results of four main studies involving over 3,000 adults who had difficulty staying asleep. The studies compared Sliwens with placebo (a dummy treatment). The main measures of effectiveness were based on the amount of time the patients spent awake after they had first fallen asleep and improvements in the quality of sleep over the first four to 12 weeks of treatment. A fifth study involving 283 adults compared Sliwens with lormetazepam (another medicine used to treat insomnia) looked at how sleepy the patients were the morning after taking Sliwens. The application was withdrawn at 'day 180'. **What was the recommendation of the CHMP at that time?** Based on the review of the data and the company's response to the CHMP list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Sliwens could not have been approved. The CHMP considered the effect of Sliwens on sleep to be small. There was also a lack of information comparing the long-term use of Sliwens with placebo. The Committee was also concerned about the risk of diverticulitis (inflammation in little sacs or pouches in the intestines) in patients taking the medicine.

ANNEX 2

Characteristics of extension of indications - outcome in 2009. Tables II.1 to II.3

II.1 – Extensions of indications with an outcome in 2009 (n=49)

Table 1

Product name (variation number)	INN	Accumulated Active time	Accumulated Clock-stop	SAG/ Expert group	Scientific advice	Outcome
Abilify	aripiprazole	269	217	Yes	No	Update of 4.1
Abilify	aripiprazole	219	114	Yes	Yes	Withdrawn prior to opinion
Aclasta	zoledronic acid	223	194	No	Yes	Update of 4.1
Adcirca	tadalafil	203	158	No	No	Update of 4.1
Alimta	pemetrexed	154	61	No	No	Update of 4.1
Angiox	bivalirudin	222	94	No	Yes	Update of 4.1
Aptivus	tipranavir	205	156	No	No	Update of 4.1
Avastin	bevacizumab	220	113	Yes	No	Update of 4.1
Avastin	bevacizumab	187	146	Yes	Yes	Negative opinion
Celsentri	maraviroc	152	90	No	No	Update of section 5.1
Corlentor/ Procoralan	ivabradine	216	89	No	No	Update of 4.1
Cymbalta/Xeristar	Duloxetine hydrochloride	240	93	No	No	Update of 4.1
Dynastat	Parecoxib sodium	163	46	No	No	Update of section 5.1
Efficib/ Janumet/Velmetia	Sitagliptin/metformin hydrochloride	153	28	No	No	Update of 4.1
Efficib)/ Janumet/ Velmetia	Sitagliptin/metformin hydrochloride	154	27	No	No	Update of 4.1
Erbitux	cetuximab	190	125	Yes	No	Negative opinion after re-examination
Gardasil	Human papilloma virus recombinant vaccine	284	107	No	Yes	Update of section 5.1
Glivec	imatinib mesilate	176	59	Yes	Yes	Update of 4.1
Herceptin	trastuzumab	82	6	No	No	Update of 4.1
Isentress	raltegravir	198	74	No	Yes	Update of 4.1
Januvia/ Tesavel/ Xelevia	sitagliptin phosphate monohydrate	153	28	No	No	Update of 4.1
Januvia/ Tesavel/ Xelevia	sitagliptin phosphate monohydrate	151	35	No	Yes	Update of 4.1
Januvia/ Tesavel/ Xelevia	sitagliptin phosphate monohydrate	124	27	No	No	Update of 4.1
Keppra	levetiracetam	200	161	No	No	Update of 4.1
Lyrica	pregabalin	245	146	Yes	Yes	Negative opinion after re-examination
MabThera	rituximab	157	22	No	No	Update of 4.1
MabThera	rituximab	147	32	No	No	Update of 4.1
Kinzalmono/ Micardis/	telmisartan	209	96	Yes	Yes	Update of 4.1

Pritor						
Myozyme	alglucosidase alfa	236	153	No	No	Update of 4.1
Orencia	abatacept	187	174	No	No	Update of 4.1
Pandemrix	split influenza virus	152	35	No	No	Update of 4.2 and 5.1
PegIntron/ ViraferonPeg	peginterferon alfa-2b	241	183	No	No	Update of 4.1
PegIntron/ ViraferonPeg	peginterferon alfa-2b	208	178	No	No	Update of 4.1
Prepandemic influenza vaccine	Prepandemic influenza vaccine (H5N1)	152	35	No	No	Update of 4.1
Prepandrix	prepandemic influenza vaccine (H5N1)	152	35	No	No	Update of 4.1
Prezista	darunavir	92	0	No	No	Update of 4.1
Protopic	tacrolimus	231	130	No	No	Update of 4.1
Rebetol	ribavirin	241	183	No	No	Update of 4.1
Rebetol	ribavirin	127	259	Yes	No	Update of 4.1
Revatio	sildenafil citrate	152	7	No	No	Update of 4.1
Stalevo	Levodopa/carbidopa/entacapone	200	113	No	Yes	Withdrawn prior to opinion
Tamiflu	oseltamivir	10	0	No	No	Update of 4.1
Tamiflu	oseltamivir	9	0	No	No	Update of 4.1
Thelin	sitaxentan sodium	184	149	No	No	Update of 5.1
Thyrogen	thyrotropin alfa	207	93	No	No	Update of 4.1
Torisel	temsirolimus	271	272	No	Yes	Update of 4.1
Xolair	omalizumab	151	35	No	Yes	Update of 4.1
Yondelis	trabectedin	215	62	No	No	Update of 4.1
Zometa	Zoledronic acid	202	89	No	No	Update of section 5.1

II.2 Information on approved extensions of indications (update of section 4.1) during 2009 – (n=38)

(Further information is available on the EMEA web: www.emea.europa.eu/index/indexh1.htm)

Product	**New indication**
Abilify	Extension of indication for Abilify to include treatment of schizophrenia in adolescents 15 years and older.
Aclasta	Extension of Indication to include treatment of -osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk for fracture.
Adcirca	Change of the indication of Adcirca from erectile dysfunction to the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.
Alimta	Extension of indication to include monotherapy maintenance treatment of locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) other

	than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.
Angiox	Extension of the current indication to include patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI.
Aptivus	Extension of indication to include the treatment of HIV-1 infection in highly pretreated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.
Avastin	Extension of the indication for the treatment of metastatic breast cancer in combination with paclitaxel or docetaxel.
Corlentor/Procoralan	Amendment of the indication for the use of ivabradine in combination with beta-blockers in patients inadequately controlled with an optimal betablocker dose and with a heart rate > 60 bpm.
Cymbalta/Xeristar	Extension of indication to include treatment of major depressive disorder.
Efficib/Janumet/Velmetia	Extension of indication to include use in combination with a PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
Efficib/Janumet/Velmetia	Extension of indication for the treatment of Efficib/Janumet/Velmetia as add on to insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dosage of insulin and metformin alone do not provide adequate glycaemic control.
Glivec	Extension of indication to include the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
Herceptin	Extension of the indication for use in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.
Isentress	To extend the indication to include antiretroviral therapy naïve adult patients.
Januvia/Tesavel/Xelevia	Extension of indication to include use in combination with a PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
Januvia/Tesavel/ Xelevia	To extend the indication of Januvia for the use as monotherapy in patients for whom metformin is not an option, due to either contraindication or intolerance.
Januvia/Tesavel/Xelevia	Extension of indication for the treatment of sitagliptin as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control.

Keppra	Extension of indication for the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old.
Kinsalmono/Micardis/ Pritor	Extension of indication to add "Reduction of cardiovascular morbidity in patients with (i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or (ii) type 2 diabetes mellitus with documented target organ damage" based on the results of 3 clinical trials (ONTARGET, TRANSCEND, PRoFESS).
Mabthera	Extension of indication to include MabThera in combination with chemotherapy for the first-line treatment of patients with chronic lymphocytic leukaemia.
Mabthera	Extension of indication to include MabThera in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL). Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy.
Myozyme	Update of section 4.1 of the Summary of Product Characteristics to amend the statement on the benefits of Myozyme in Late-onset Pompe Disease patients.
Orencia	Extension of the therapeutic indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.
PegIntron/ViraferonPeg	Extension of the therapeutic indication of peginterferon alfa-2b in combination with ribavirin in the treatment of adult patients with chronic hepatitis C who are positive for serum HCV-RNA to include patients with compensated cirrhosis based on the results of the IDEAL study.
PegIntron/ ViraferonPeg	Extension of the therapeutic indication of combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population based on the results of Study P02538.
Prepandemic influenza vaccine	To extend the therapeutic indication to include treatment in subjects aged 61 years and above based on clinical trial data.
Prepandrix	To extend the therapeutic indication to include treatment in subjects aged 61 years and above based on clinical trial data.
Prezista	Extension of indication for Prezista 300 mg and 600 mg film-coated tablet to include the treatment of HIV-1 infection in ARV treatment experienced adolescents and children of 6 years and above and with a body weight of more than 20 kg.
Protopic	Extension of Indication to include 'maintenance treatment' of moderate to severe atopic dermatitis further to completion of one study in adult patients (FG-506-06-40) and one in paediatric patients (FG-506-06-41).
Rebetol	Extension of the therapeutic indication of peginterferon alfa-2b in

	combination with ribavirin in the treatment of adult patients with chronic hepatitis C who are positive for serum HCV-RNA to include patients with compensated cirrhosis based on the results of the IDEAL study.
Rebetol	Extension of the therapeutic indication of combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population based on the results of Study P02538.
Revatio	Extension of indication in patients with Pulmonary Arterial Hypertension classified as WHO functional class II.
Tamiflu	Extension of the therapeutic indication to include treatment of children between 6 and 12 months of age in case of pandemic influenza following the assessment of data falling under the frame of the Article 45 of the Paediatric Regulation (No 1901/2006) and further to the Article 5(3) procedure dated May 2009.
Tamiflu	Extension of the therapeutic indication to include treatment of children between 0 and 6 months of age and prophylaxis for children less than 1 year of age in case of pandemic influenza following the assessment of data falling under the frame of the Article 45 of the Paediatric Regulation (No 1901/2006) and further to the Article 5(3) procedure dated May 2009.
Thyrogen	To extend the ablation of thyroid tissue remnants indication of Thyrogen from low risk patients to patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer.
Torisel	Extension of Indication to add treatment of adult patients with relapsed and/or refractory mantel cell lymphoma (MCL).
Xolair	To extent the indication to children (6 to <12 years of age) as add-on therapy to improve allergic asthma control.
Yondelis	Addition of a new indication of Yondelis in combination with pegylated liposomal doxorubicin (PLD) in the treatment of patients with relapsed platinum-sensitive ovarian cancer.

II.3 Information on not approved (withdrawn or with a negative opinion) extensions of indications during 2009 (n= 5).

(Further information is available on the EMEA web: www.emea.europa.eu/index/indexh1.htm)

Product	**Therapeutic area and main concerns of the Committee**
Abilify	Withdrawn prior to opinion Major depressive episodes. **What documentation did the company present to support its application to the CHMP?** The company presented the results of three short-term and one long-term study to support its application. The short-term studies involved patients with major depressive episodes that had not responded to up to three previous

	antidepressant treatments. At the start of the study, the patients were put on an eight-week course of an antidepressant (escitalopram, sertraline, venlafaxine, fluoxetine or paroxetine). Each patient received an antidepressant that they had not previously taken for the current depressive episode. The 1,090 patients who did not respond to this antidepressant then added either Abilify or placebo (a dummy treatment). The main measure of effectiveness was the change in symptoms over the six weeks of dual treatment. The short-term studies were 'double-blind', which means that neither the patients nor the investigators knew which patients were receiving Abilify and which were receiving placebo. The long-term study looked at the maintenance of Abilify's effects when added to an antidepressant. The study lasted up to a year and involved 1,076 patients, some of whom had completed one of the three short-term studies. Abilify was not compared with any other treatments in this study and the patients knew which medicines they were taking. **What was the recommendation of the CHMP at that time?** Based on the review of the data and the company's responses to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Abilify could not have been approved for the treatment of resistant major depressive episodes. The CHMP was concerned over the patients included in the studies, as it was not clear whether they all had resistant depression, defined as failure to respond to at least two previous antidepressants. The Committee was also concerned that there was no long-term information from 'double-blind' studies looking at the maintenance of Abilify's effects and its ability to prevent depression coming back. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Abilify in the treatment of major depressive episodes did not outweigh its risks.
Avastin	Negative opinion **G**lioblastoma **What documentation did the company present to support its application to the CHMP?** The company presented the results of one main study involving 167 patients with glioblastoma that had come back after one or two previous courses of treatment. Half of the patients received Avastin alone and the other half received Avastin together with irinotecan. There were two main measures of effectiveness: the number of patients whose tumours had responded to treatment ; and 'progression-free survival' (the number of patients who were still alive and whose disease had not got worse) after six months of treatment. The study also looked at how long the patients survived. **What were the major concerns that led the CHMP to recommend the refusal of the change to the marketing authorisation?** The CHMP was concerned that the company had not provided sufficient evidence of the medicine's benefits, because the number of patients who responded to treatment was not dramatic and because response rates may not be a suitable measure of the medicine's effectiveness. In addition, the CHMP could not interpret the findings on survival because the study did not compare Avastin

	directly with any other treatments. Therefore, at that point in time, the CHMP was of the opinion that the balance of benefits and risks of Avastin in the treatment of glioblastoma after relapse could not be established. Hence, the CHMP recommended that the change to the marketing authorisation be refused.
Eribitux	Negative opinion after re-examination Non-small cell lung cancer **What documentation did the company present to support its application to the CHMP?** The company presented the results of two main studies involving a total of 1,801 adults with advanced, metastatic or recurrent non-small cell lung cancer who had not been treated before. In both studies, the combination of Erbitux with platinum-based chemotherapy was compared with platinum-based chemotherapy without Erbitux. The main measures of effectiveness were how long the patients survived and how long they lived without their cancer getting worse. **What were the major concerns that led the CHMP to recommend the refusal of the change to the marketing authorisation?** In July 2009, the CHMP was concerned that the benefits of adding Erbitux to standard platinum-based chemotherapy were modest in terms of survival times, and that the medicine did not have a convincing effect on how long patients lived without their cancer getting worse. Severe side effects were seen in some lung cancer patients who received Erbitux - these were similar to the side effects seen in patients treated with Erbitux for other types of cancer. In November 2009, following the re-examination, the CHMP added a further concern over the ways in which the studies' results were analysed after they can be completed. These 'subgroup analyses' attempted to identify a group of patients that would benefit from treatment. The CHMP was also concerned over discrepancies in the studies' findings between the two main measures of effectiveness. Therefore, the CHMP was of the opinion that the benefits of Erbitux in the treatment of non-small cell lung cancer did not outweigh its risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused.
Lyrica	Negative opinion after reexamination Fibromyalgia **What documentation did the company present to support its application to the CHMP?** The company presented the results of five main studies involving over 3,000 adults with fibromyalgia. Most of the patients included in the studies came from outside the European Union (EU). Four of the studies compared the short-term effects of Lyrica at doses between 150 and 600 mg per day with those of placebo (a dummy treatment) in a total of 2,757 patients. The main measure of effectiveness was the change in pain levels over eight to 14 weeks of treatment. The fifth study compared the long-term effects of Lyrica with those of placebo in

	566 patients who had responded to an initial six weeks of treatment with Lyrica. In this study, the main measure of effectiveness was how long it took until the patient's pain came back. The study lasted for six months. **What were the major concerns that led the CHMP to recommend the refusal of the change to the marketing authorisation?** The CHMP was concerned that the benefits of Lyrica in fibromyalgia had not been shown in either the short or the long term. There were no consistent or relevant reductions in pain or other symptoms in the short-term studies, and the maintenance of Lyrica's effect was not shown in the longer study. The Committee was also concerned that the safety and effectiveness of Lyrica had not been shown in patients from the EU. At that point in time, the CHMP was of the opinion that the benefits of Lyrica in the treatment of fibromyalgia did not outweigh its risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused. The CHMP refusal was confirmed after re-examination.
Stavelo	Withdrawn prior to opinion Parkinson's disease **What documentation did the company present to support its application to the CHMP?** The company presented the results of one study involving 423 adults with Parkinson's disease who needed to start treatment with levodopa. The study compared Stalevo with a combination of levodopa and carbidopa (but without entacapone, the extra enzyme blocker included in Stalevo). The patients were not told which treatment they were taking. The main measure of effectiveness was the change in symptoms after 39 weeks of treatment. **What were the main concerns of the CHMP?** The CHMP was concerned that the benefits of Stalevo over the combination of levodopa and carbidopa without entacapone were too small to be relevant for patients starting levodopa treatment. In addition, the benefits of Stalevo over levodopa and carbidopa were mainly seen in patients taking Stalevo who had discoloration of the urine, which is a known side effect of entacapone, the extra component in Stalevo. There was no explanation for the improvement in this group of patients, which was more marked than in patients taking Stalevo who did not have urine discoloration. This could mean that some patients were able to guess which treatment they were taking, making the results of the study less convincing. Stalevo was also linked to side effects affecting the stomach and gut, such as diarrhoea and weight loss. Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Stalevo in the treatment of adults with Parkinson's disease who are starting levodopa treatment had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.