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Original Article

Approvals of drugs with uncertain benefit–risk profiles in Europe

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ABSTRACT

Purpose: This paper examines conditional approvals that allow the marketing of medicines with unsettled benefit–risk profiles in the European Union.
Methods: We identified medicines that had received conditional approval from the European Medicines Agency in the period January 2006–June 2015. We searched the reasons and bases for approvals, the median time to address the specific obligations imposed in order to cover the information gap and allow regular authorisations, and their extent of fulfilment.
Results: Of the 26 products conditionally authorised two were withdrawn for commercial reasons, ten were switched to regular approval, and 14 are still under conditional approval. Conditional approval was granted mainly to medicinal products intended for seriously debilitating disease or life-threatening disease. The median time to address the specific obligations was four years (range 0.2 to 7.7). There were delays or discrepancies in the fulfilment of these obligations in more than one third of the authorisation procedures.
Conclusions: In most cases there was limited evidence supporting the positive benefit–risk balance at the time of approval. Delays or discrepancies in the fulfilment of obligations allow medicinal products with unsettled benefit–risk profiles onto the market for several years. This should be taken into account when further early or step-wise licensing strategies are considered.

1. Introduction

Early access to new medicinal products is a controversial matter [1,2]. Regulatory agencies are often criticised by pharmaceutical companies and patients' advocacy groups for delaying access to promising therapies [3,4]. However, shrinking the premarketing development procedures may increase the risks of approving drugs that are ineffective, unsafe, or both [5,6]. The European Medicines Agency (EMA), which is responsible for centralised approvals in Europe (Box 1), has implemented two different procedures to grant marketing authorisations on the basis of incomplete data, with a view to meeting "unmet medical needs of patients and in the interests of public health" [7]. Unlike approvals passed under exceptional circumstances, conditional approvals are granted when the risk–benefit balance is based on preliminary, not yet full, evidence (Box 2) [7,8]. The marketing authorisation holder is given obligations, such as a requirement for further studies, which in principle should fill the information gaps so as to permit a marketing authorisation that is no longer subject to specific obligations. Depending on the fulfilment of these requirements over time, conditional approval may benefit patients by making innovative treatments available sooner but, on the other hand, medicines may be authorised with incomplete information, which may jeopardise rather than benefit public health.

This cross-sectional study examined the conditional approval procedure after its establishment in 2006 [8], and tracking the follow-up of the specific obligations, including the switch to regular approval.

2. Methods

We searched the EMA website to identify products that had received conditional marketing authorisation in the period January 2006–June 2015. From the European Public Assessment Report (EPAR) on the relevant drugs, we retrieved data on the pivotal studies supporting the marketing authorisation, the reasons for granting conditional approval, and the specific obligations imposed by the EMA. To track the specific obligations and the status of the marketing authorisation (still conditional or converted to regular), we thoroughly searched two sections of the EPAR headed "Procedural steps taken and scientific information after authorisation" and "Specific obligations to complete post-authorisation measures for the conditional marketing authorisation" (the EPAR Annex II). We focused on specific obligations, i.e. post-approval commitments to be fulfilled by the marketing authorisation holder within an agreed timeframe, but excluded follow-up measures and other commitments that apply to most marketing authorisations, not just conditional approvals.

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Box 1
European centralised procedure for granting new drugs marketing authorisation.
Regulatory agencies are responsible for the assessment and monitoring of medicines that are marketed. Any medicinal product should show a positive benefit–risk profile in order to be placed on the market. In Europe, medicinal products should not be authorised if their quality, safety or efficacy have not been adequately or sufficiently demonstrated [49–51]. Once a new drug is developed and its dosage, efficacy, and tolerability assessed in properly designed and conducted clinical trials, these results are submitted to drug-approval agencies to obtain marketing authorisation for a given indication. In Europe, the EMA is responsible for the centralised procedure for human and veterinary medicines to be used in the EU. This procedure results in a single marketing authorisation that is valid in the European Union (EU) and associated countries. The Agency's Committee for Human Medicinal Products (CHMP) evaluates the applications for marketing authorisations, and issues an opinion on whether the medicine should be marketed or not. The European Commission is the ultimate authority for granting marketing authorisations in the EU [49]. Any medicinal product to be placed on the market should show a positive benefit–risk ratio. In Europe, marketing authorisation will be refused only if the quality, safety or efficacy of the medicinal product has not been adequately or sufficiently demonstrated by the applicant [49–51]. According to current legislation, in order to meet "unmet medical needs of patients and in the interests of public health", it may sometimes be necessary to grant marketing authorisations on the basis of incomplete data [7]. These authorisations are subject to specific obligations to be addressed by the marketing authorisation holder, which are periodically re-assessed by the EMA.

As the majority of commitments refer to clinical studies, we extensively searched trial registries (e.g. EU Clinical Trial Registry, Clinicaltrial.gov, and pharma-companies' registries), and MedLine to see whether the studies committed (clinical trials, observational studies, etc.) had been planned and started, whether their results had been published in medical journals or public registries, and submitted to and assessed by the EMA (i.e., mentioned in the post-authorisation documents on the Agency website).

For each medicinal product, we recorded the interval between initial marketing authorisation and delivery date of the last specific obligation in order to estimate how long medicinal products were on the market with incomplete information about their benefit–risk profile.

All the searches were done in December 2014 and kept updated until June 2015 by one author and data were checked independently by a second author. Discrepancies were solved by consensus.

3. Results

Out of 490 medicinal products authorised by the EMA between 2006 and June 2015 (excluding generics and biosimilars), 26 were granted

Box 2
EMA procedures to grant marketing authorisations when data are incomplete.

	Exceptional circumstances	Conditional approval
Defined by	EC regulation 726/2004 Article 14(8) [7]	EC regulation 726/2004 Article 14(7) [7]
Since	1995	2006
Relevant guidance	Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14(8) of EC regulation 726/2004 [7]	EC regulation 507/2006 [8]
Ground for applicability	Inability to provide comprehensive data on the efficacy and safety under normal conditions	To meet unmet medical needs of patients and in the interests of public health
Conditions	• The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. • In the present state of scientific knowledge, comprehensive information cannot be provided. • It would be contrary to generally accepted principles of medical ethics to collect such information.	• Treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases. • Medicinal products to be used in emergency situations in response to public health threats recognised either by the World Health Organisation or by the EU. • Orphan medicinal products.
Specific obligations	Aimed at the provision of information on the safe and effective use of the product (normally not leading to completion of a full dossier).	To confirm that the risk–benefit balance is positive and resolving any questions relating to the quality, safety and efficacy of the product (the authorisation is not intended to remain conditional indefinitely).
Re-assessment of benefit–risk profile	Annual	Annual
Renewal of the marketing authorisation	After five years (like the regular marketing authorisation)	Annual
Accelerated assessment procedure	Yes	Yes

conditional approval (5.3%). We excluded two vaccines approved during the H1N1 pandemic influenza outbreak that the authorisation holder subsequently withdrew from the market for commercial reasons. Of the remaining 24, none was subsequently withdrawn by the Agency, ten were switched to regular approval and 14 are still under conditional approval (Fig. 1). Table 1 lists key information on the conditionally approved products, including summaries of the pivotal studies which formed the basis of the first approval and the specific obligations required then. Two out of 26 marketing authorisation applications were supported by controlled trials versus active comparators and less than half by blinded studies. The median sample size of the pivotal studies was 315.

With regard to the categories laid down by the European legislator [8], conditional approval was granted to 20 medicinal products intended for seriously debilitating or life-threatening disease. Nine of these were also orphan drugs. Three other drugs received conditional approval just because of their orphan status. Fourteen conditional approvals were for antineoplastic agents (54%), eight for anti-infective drugs, and three for neurological diseases. The EMA granted the first European marketing authorisation, under conditional approval, to an advanced therapy medicinal product to treat limbal stem cell deficiency due to physical or chemical burns to the eye(s) in adults [9]. The specific obligations requested by the EMA at the time of the conditional approval are reported in Appendix A.

Overall, the median time allowed to address the specific obligations is four years (range 0.2–7.7, data on 24 medicinal products). The median time to fulfil obligations for drugs still conditional is nearly twice that of those converted (data not shown).

3.1. Medicinal products still under conditional approval

Of the 14 medicinal products still under conditional approval, nine have specific obligations whose timeframes go beyond 2015. We were able to track the status of almost all the studies required, which are mainly ongoing clinical trials or trials in the long-term follow-up phase. However, there were some delays or discrepancies. The confirmatory phase III clinical trial required to provide additional efficacy and safety data for bedaquiline for pulmonary multidrug-resistant (MDR) tuberculosis was terminated before enrolment started because of a change in the marketing authorisation holder's development plan [10,11]. For delamanid, also approved for MDR tuberculosis, we could not find the trial required to compare two dosage regimens (100 mg

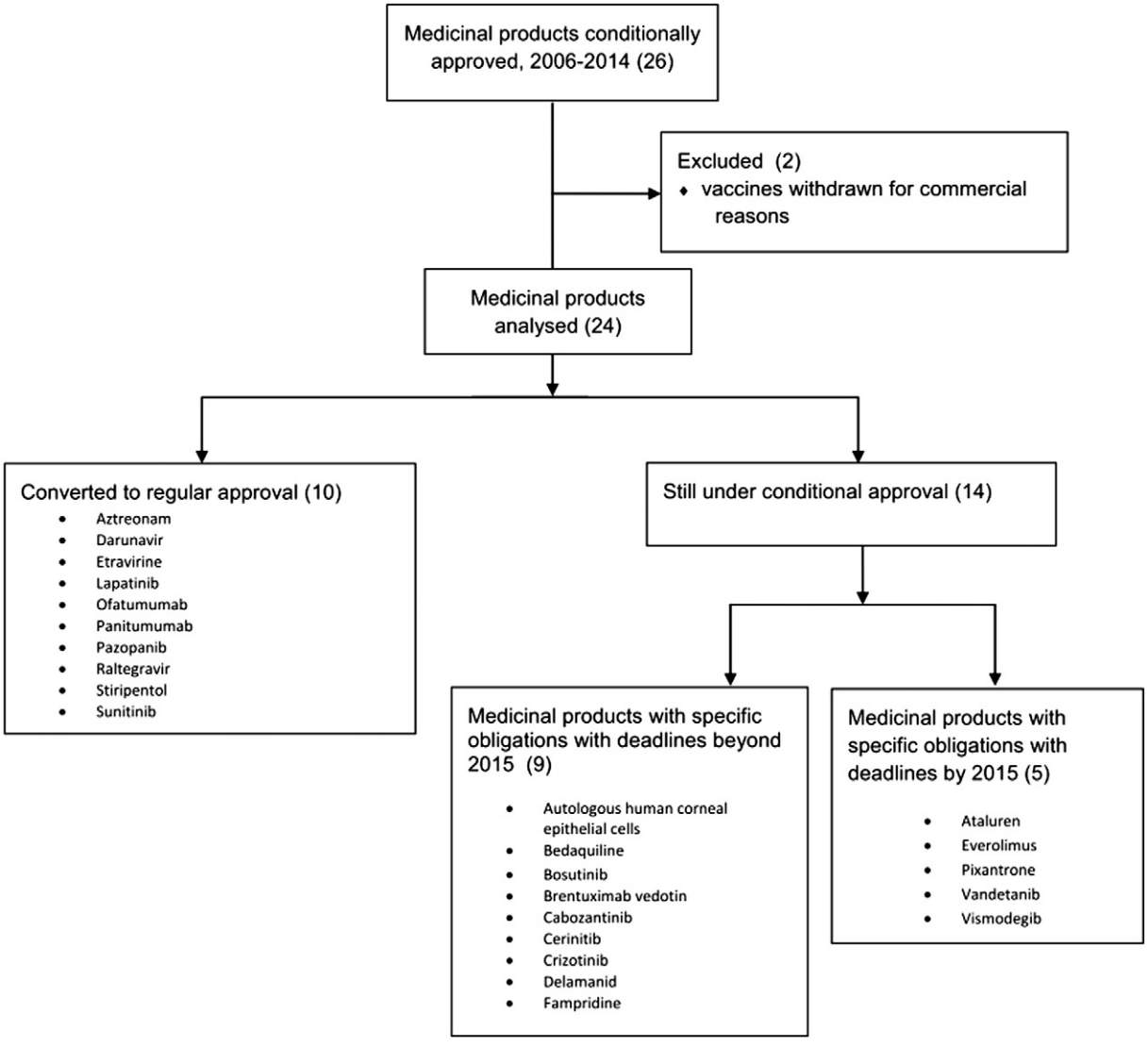

Fig. 1. Flow chart of the medicinal products.

twice daily for two months followed by 200 mg as a single daily dose for four months versus 400 mg single daily dose for six months).

We were not able to find information on the start of a multinational, uncontrolled interventional study to test the efficacy and safety of autologous human corneal epithelial cells containing stem cells for the treatment of corneal damage.

Among the more "mature" conditional approvals in this group, i.e., those with specific obligations to be completed in 2015 or before, we noticed some delays. Two of the three specific obligations for vismodegib for advanced basal-cell carcinoma were delayed; the third is currently in progress [12] but its deadline has been recently extended to 2016. Similarly, the specific obligation for pixantrone for non-Hodgkin B-cell lymphomas [13] has been postponed for more than one year. In the case of everolimus for astrocytoma, two of the three specific obligations were fulfilled more than one year after the agreed deadline, while the long-term follow-up of the two pivotal studies [14,15] is ongoing at the time of this analysis.

3.2. Medicinal products switched to regular marketing authorisation

The median time for the ten conditional approvals switched to regular marketing authorisations was five years (range 1–8). For five products (aztreonam, etravirine, raltegravir, pazopanib, sunitinib), we were able to track the fulfilment of all the specific obligations through the EMA documents.

We found discrepancies and delays in the post-authorisation history of three anticancer drugs (lapatinib, ofatumumab, panitumumab). These drugs were in fact converted into regular approvals in the first months of 2015 but were still flagged as conditional approvals on the EMA website at the time of this analysis. Some of the specific obligations required, e.g. incidence of brain metastases as the site of relapse for lapatinib in breast cancer [16], robust data on efficacy and safety of ofatumumab in chronic lymphocytic leukaemia [17] and the unsettled questions of RAS testing (rat sarcoma oncogen) for panitumumab in colorectal neoplasm [18] were defined differently over time and were submitted later than expected to the Agency.

Full information was not available for stiripentol and darunavir. Stiripentol for the treatment of juvenile myoclonic epilepsy was conditionally authorised in 2007. Then EMA requested a "placebo-controlled trial of stiripentol as an add-on therapy in paediatric patients with Dravet's syndrome not adequately controlled with clobazam and valproate" to be done by end-2009 [19]. This specific obligation was downgraded to "robust observational study to support stiripentol to control clonic seizure or tonic–clonic seizure in Dravet's syndrome over the short and long term". We could not find the observational data in the EMA documents [20] that led to regular authorisation. Possibly two studies (an uncontrolled trial in 27 Japanese children [21] and a retrospective survey on 82 US children [22]) convinced the EMA that there were no remaining grounds for maintaining the conditional status.

In the post-authorisation information on darunavir, we found no clear reference to the final reports of the three pivotal trials [23–25]. Possibly a pooled analysis of these results satisfied the specific obligation, providing information on the resistance to darunavir in HIV patients heavily treated with other antiretroviral drugs. Similarly, we could not find any clear statement on the submission of an open-label extension of previous studies in combination with low-dose ritonavir.

4. Discussion

EMA conditional approval is a regulatory tool developed for granting European marketing authorisations to medicinal products on the basis of incomplete data with a view to allowing early access to new treatments [8]. Conditional approval is usually granted to drugs intended to address unmet medical needs, i.e. "any seriously debilitating or life-threatening condition for which there exists no satisfactory […] treatment authorised" [8]. The benefit to public health of immediate availability of those drugs is believed to outweigh the risks of limited clinical information. This may be no more than a guess when the evidence comes from uncontrolled trials involving few tens or hundreds of patients and addressing surrogate endpoints with questionable clinical value, such as tumour response (Table 1). The lack of a robust evidence package at the time of approval is not only an issue for conditional approvals but also for regular authorisations, as has repeatedly been pointed out [26–30].

The application of this process to unmet medical needs is justifiable. However, any situations in which additional benefit is presumed, as for instance in a subset refractory to standard treatments, can be configured as an unmet need. Assuming that medicines granted conditional approval in spite of uncertain efficacy and safety can benefit patients with severe diseases and no available treatment, it is hard to agree that their immediate availability can outweigh the risks of the limited clinical information in conditions for which there are already effective treatments. This is the case with the indications of several conditionally approved medicines, such as breast and colorectal cancer. In most of these conditions additional benefit over the available therapies needs to be demonstrated, rather than approving products with no clearly defined place in therapy.

It should be stressed that any regulatory framework which allows the applicant to complete the evidence package after the marketing authorisation can only work if the additional evidence is going to be generated reliably and in a reasonable time.

The smaller the evidence package at the time of approval, the greater the challenge to produce the missing data after licensing. The requirement for specific obligations to be fulfilled only after several years (up to seven in the case of bedaquiline) allows a medicinal product onto the market with limited information on its efficacy and safety for almost as long as its patent lasts.

The requirement for extended follow-up for assessing long-term efficacy and safety of drugs to be used in chronic conditions is reasonable. However, it is questionable whether it is worth assessing the long-term efficacy of drugs that did not even offer a robust efficacy profile in the short term. For instance, fampridine was conditionally approved on the basis of a marginal benefit over placebo on a surrogate outcome, i.e. an absolute improvement of about 30% in the 25-foot walking speed.

Some of the specific obligations regard clinical data that are hard to produce once the drug is approved. For instance, updated survival data from pivotal trials frequently requested for anticancer drugs whose approval is based on proxy measures of survival, such as progression-free survival (PFS) or time to progression (TTP). When the drug is licensed on the basis of PFS or TTP, trial participants who are still involved in the follow-up phase may decide to cross over from the control to the intervention arm [5,31]. Cross-over is allowed for ethical reasons as, in principle, both patients and physicians trust that drugs approved by regulators are efficacious. It will therefore never be possible to assess the overall survival because of the contamination of the two treatment groups. In our sample, this limitation was clear for lapatinib [32] and crizotinib [33] for advanced breast cancer and non-small-cell lung cancer respectively.

4.1. Our findings in relation to other studies

To our knowledge, this is the first study that has systematically examined EMA conditional approvals and post-authorisation fulfilment of specific obligations required at the time of marketing authorisation. Previous studies examined the introduction of conditional approval of HIV and anticancer drugs [34] and compared conditional approvals and approvals under exceptional circumstances as regulatory instruments for stimulating drug innovation in Europe [35]. Other studies focused on post-approval safety, reporting post-authorisation studies generally to comply with the EMA requirements [36] and early approvals (either under exceptional circumstances or conditional) led to

Table 1
EMA conditional approvals (January 2006–June 2015).

Active substance (Name)	Year of conditional approval	Therapeutic area	Basis for approval (pivotal studies)	Specific obligations at the time of approval	MA holder
Still conditional (14)					
Everolimus (Votubia)[a]	2011	Astrocytoma associated with tuberous sclerosis	Phase II, single-arm, open-label, 28 SEGA associated with tuberous sclerosis pts. Median primary SEGA lesion reduction at 6 mo: 0.80 cm^3 (range 0.06–6.25) Preliminary data phase III RCT vs. placebo, 117 pts. RR: 34.6 Vs. 0%; 95% CI 15.1 to 52.4	1) Follow-up of duration of response and TTP from pivotal studies 2) Interim and final analyses of the phase III pivotal study 3) Population PK of everolimus in children	Novartis Europharm Ltd.
Fampridine (Fampyra)	2011	Multiple sclerosis	Two short-term, double-blind RCTs vs. placebo, 424 multiple sclerosis pts with walking impairment WSI: 37.2 vs. 8.9%; 95% CI 22.1 to 34.2	1) Long-term study addressing a clinically meaningful endpoint in terms of walking ability and the early identification of responders	Biogen Idec Ltd.
Brentuximab vedotin (Adcetris)[a]	2012	Hodgkin and systemic anaplastic large-cell lymphoma	Two single-arm studies relapsed/refractory HL (102 pts) and relapsed/refractory sALCL (58) HL: ORR 75%, sALCL: ORR 86%	1) OS follow up from pivotal studies 2) PASS in HL and sALCL (500, including at least 50 sALCL pts) 3) Single-arm study in sALCL 4) Single-arm study in relapsed/refractory HL not eligible for ASCT	Takeda Pharma A/S
Crizotinib (Xalkori)	2012	Anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer	Phase I, single-arm study, 125 ALK-NSCLC pts. ORR: 60%, 95% CI 51 to 69 Preliminary data, phase II single arm 261 pts ORR: 136/261 (53%), 95% CI 47 to 60 Preliminary data from a phase III RCT vs. 2nd-line standard chemotherapy, 318 pts. Median PFS increase 4.0 mo, HR 0.49, 95% CI 0.37 to 0.64	1) OS final analysis of the phase III pivotal study and its safety analysis	Pfizer Ltd.
Pixantrone dimaleate (Pixuvri)	2012	Non-Hodgkin B-cell lymphomas	Phase III, open-label RCT vs. physician's choice of specified single-agent therapies 140 pts relapsed/refractory NHL CR: 20 Vs. 5.7% ($p = 0.021$)	1) Phase III RCT pixantrone–rituximab vs. gemcitabine–rituximab in aggressive B-cell NHL (2nd to 4th lines)	CTI Life Sciences Limited
Vandetanib (Caprelsa)	2012	Medullary thyroid cancer	Phase III, double-blind RCT vs. placebo, 331 unresectable locally advanced/metastatic MTC pts. Median PFS increase: 11.2 mo; HR 0.46, 95% CI, 0.31 to 0.69	1) Open label trial of vandetanib in RET negative and RET positive sporadic MTC	Astra Zeneca AB
Bosutinib (Bosulif)[a]	2013	Chronic myelogenous leukaemia	Phase I/II, open-label, single arm study, 52 Ph + CML pts pre-treated with TKI or unsuitable for TKI. MCyR: 14/52 (27%)	1) Single-arm study of bosutinib Ph + CML pre-treated with TKI or unsuitable for TKI	Pfizer Ltd.
Vismodegib (Erivedge)	2013	Advanced basal-cell carcinoma	Single-arm, two-cohort, 100 advanced/metastatic BCC pts. Advanced BCC, ORR: 30/63 (48%) Metastatic BCC, ORR: 11/33 (33%)	1) Safety update of pooled safety populations 2) Final analysis of pivotal study 3) Single-arm study of vismodegib (500 pts, at least one-year follow up)	Roche Registration Ltd.
Ataluren (Translarna)[a]	2014	Duchenne muscular dystrophy	Phase IIb, double-blind RCT vs. placebo, 174 nonsense-mutation Duchenne and Becker muscular dystrophy pts 6MWD, week 48: −0.1 m, 95% CI −30.4 to 30.2	1) Double-blind RCT of ataluren 10, 10, 20 mg/kg daily vs. placebo	PTC Therapeutics Limited
Bedaquiline fumarate (Sirturo)[a]	2014	Pulmonary multi-drug resistant tuberculosis	Phase IIb RCT vs. placebo as add-on to a background regimen, 160 MDR or pre-XDR TB pts. TCC week 24: HR 2.44, 95% CI 1.57 to 3.80	1) Confirmatory phase III trial of bedaquiline in different treatment regimens vs. regimens without bedaquiline	Janssen-Cilag International N.V.
Cabozantin (Cometriq)[a]	2014	Metastatic medullary thyroid carcinoma	Interim data, Phase III, double-blind, RCT vs. placebo, 330 unresectable locally advanced/metastatic MTC pts. Median PFS increase: 7.2 mo; HR 0.29, 95% CI 0.19 to 0.49	1) OS data from pivotal study and subgroup analyses 2) Dose-comparison study (140 vs. 60 mg)	TMC Pharma Services Ltd.
Delamanid (Deltyba)[a]	2014	Pulmonary multi-drug resistant tuberculosis	Phase II, double-blind RCT vs. placebo, 481 MDR-TC pts. SCC: delamanid 100 mg BID: 45.4% ($p = 0.0083$ vs. placebo); delamanid 200 mg BID: 41.9% ($p = 0.0393$ vs. placebo); placebo: 29.6%	1) Phase III trial of delamanid 100 mg BID 2 mo + 200 mg QD 4 mo as add-on to background regimen 2) Comparative study of different delamanid regimens	Otsuka Novel Products GmbH
Autologous human corneal epithelial cells (Holoclar)	2015	Corneal lesions	Retrospective analysis of 133 pts. enrolled in two case series-based studies. CNV: 72% (main study); 60% (supportive study) Improvements of ocular symptoms and visual acuity	1) Multinational, multicentre, prospective, open-label, uncontrolled interventional study to assess efficacy and safety	Chiesi Farmaceutici S.p.A
Ceritinib (Zikadia)	2015	Anaplastic--lymphoma-kinase--positive advanced non-small-cell lung cancer	Phase I uncontrolled, open label dose escalation trial, 255 locally advanced or metastatic NSCLC pts. with genetic abnormalities in ALK, that has progressed despite standard therapy, or for which no effective standard therapy exists. ORR: 60%, 95% CI 52.4 to 67.2, DOR: 8.3 months Preliminary data from two ongoing phase II uncontrolled studies.	1) Final results of the phase III efficacy study comparing ceritinib to chemotherapy 2) Final results of open label single arm phase II study	Novartis Europharm Ltd.

Table 1 (*continued*)

Active substance (Name)	Year of conditional approval	Therapeutic area	Basis for approval (pivotal studies)	Specific obligations at the time of approval	MA holder
No longer conditional (10)					
Sunitinib (Sutent)[a]	2006	Gastrointestinal stromal tumours, renal cell carcinoma	GIST: Double-blind RCT vs. placebo (312 pts) Median TTP increase: 20.9 wks, HR: 0.33, 95% CI 0.23 to 0.47 RCC: single-arm, open label trial (106 pts) OR: 25.5%, 95% CI 17.5 to 34.9	1) Results of ongoing study in cytokine-naive patients with metastatic RCC	Pfizer Limited
Darunavir (Prezista)	2007	HIV infection	Two RCTs with ritonavir vs. other ritonavir-boosted protease inhibitor combinations (596 pts) VR: 70% vs. 21%	1) Final study reports of POWER 1, 2, 3 studies 2) Final study report ongoing RCT darunavir with low-dose ritonavir vs. lopinavir/ritonavir in treatment-experienced pts 3) Final study reports of ongoing interaction studies 4) Data from the darunavir treatment arm that do not receive the candidate NNRTI in trials on heavily-treated pts. 5) Open-label trial of darunavir with low-dose ritonavir in pts from phase II trials or sponsor-selected phase I trials 6) Safety study of darunavir with low-dose ritonavir and other AVRs in highly treated pts with limited or no treatment option	Janssen-Cilag International NV
Raltegravir (Isentress)	2007	HIV infection	Two double-blind, RCTs vs. placebo 699 reduced susceptibility to NNRTI, NRTI and PI pts. VR OR: 10.6; 95% CI 5.60 to 20.25 and 9.6 (5.02 to 18.25).	1) Clinical data on long-term viral suppression, safety profile and resistance pattern 2) Monitoring of resistance and risk for tumours	Merck Sharp & Dohme Ltd.
Stiripentol (Diacomit)[a]	2007	Myoclonic epilepsy, juvenile	Two double-blind RCTs as add-on therapy, 65 Dravet's syndrome not adequately controlled paediatric pts. 50% Seizure reduction: 71.4% vs. 5% and 66.7% vs. 9.1%	1) Placebo-controlled trial stiripentol as an add-on therapy in children with Dravet's syndrome not controlled with clobazam and valproate, then changed to "robust observational study" 2) Bioavailability of two 500 mg formulations (capsule and sachet)	Biocodex
Panitumumab (Vectibix)	2007	Colorectal cancer	Phase III, open-label RCT vs. best supportive care, 463 metastatic CRC pts after failure of chemotherapy. Median PFS increase: 0.7 wks, HR 0.54; 95% CI 0.44 to 0.66	1) Final data of phase II trial FOLFIRI + panitumumab or bevacizumab as 2nd line in pts with wild-type KRAS CRC 2) Results from ongoing studies (1st line + FOLFOX and 2nd line + FOLFIRI) 3) Confirmatory trial of panitumumab monotherapy 4) Additional data on QoL using a validated scale 5) Resolution of uncertainties on RAS testing in practice	Amgen Europe B.V.
Lapatinib (Tyverb)	2008	Breast cancer	Phase III, open-label RCT lapatinib + capecitabine vs. capecitabine alone, 399 ErbB2 over-expressing, progressive, locally advanced/metastatic breast cancer pts. Median TTP increase: 8.5 wks, HR 0.57; 95% CI 0.43 to 0.77	1) Phase III RCT lapatinib-containing regimen vs. trastuzumab-containing control arm to compare the incidence of brain metastases as the site of relapse 2) Updated analysis of survival in the pivotal study 3) Comparative data on the incidence of brain metastases from other ongoing studies	Glaxo Group Ltd.
Etravirine (Intelence)	2008	HIV infection	Two 48-week, double-blind RCTs vs. placebo, 1203 pts with genotypic resistance to currently available NNRTI. VR (pooled): 248 (41.1%) vs. 353 (58.9%). Significant in the "not de novo ENF" main subgroup.	1) Characterization of clinical efficacy of etravirine with boosted protease inhibitors other than darunavir (data from EURESIST cohort and other appropriate sources)	Janssen-Cilag International NV
Aztreonam (Cayston)[a]	2009	Respiratory tract infections cystic fibrosis	Two phase III, short term, double-blind RCTs vs. placebo, 375 CF pts with pulmonary *Pseudomonas aeruginosa* Time antibiotics needed: 92 vs. 71 days CF-specific QoL measure: 37.3 vs. 56.3	1) RCT aztreonam vs. tobramycin in pts 6 years and older 2) Review of all paediatric data from controlled studies	Gilead Sciences International Ltd.
Ofatumumab (Arzerra)[a]	2010	Chronic lymphocytic leukaemia	Preliminary data single arm, open-label, 154 CLL pts. RR in refractory CLL: 58%; 99% CI 40 to 74 RR in CLL refractory bulky lymphadenopathy: 47%; 99% CI 32 to 62	1) Confirmatory data from phase III trial in earlier settings 2) Study ofatumumab vs. physicians' choice in pts with fludarabine refractory CLL 3) Phase IV observational study of efficacy and safety	Glaxo Group Ltd.
Pazopanib (Votrient)	2010	Renal carcinoma, soft tissue sarcoma	Phase III, double-blind, RCT vs. placebo, 435 locally advanced and/or metastatic renal carcinoma pts. Median PFS increase: 5.2 mo; HR: 0.46, 95% CI, 0.34 to 0.62	1) Study pazopanib vs. sunitinib in pts with locally advanced and/or metastatic RCC 2) Pooled analysis of data from studies in Caucasian and Asian pts.	Glaxo Group Ltd.

no increase in serious safety issues, though the small number of such approvals calls for caution on this point [37].

Outside Europe, one analysis evaluated Canadian conditional prescription [38] and another the Notice of Compliance with conditions policy [39]. The latter showed that serious safety warnings were more likely for drugs approved under the conditions policy than for those approved with a standard review. Several papers focused on the four FDA approaches for speeding up the availability of drugs for serious diseases (priority review, breakthrough therapy, accelerated approval, and fast track) [5,40–44]. A recent review of expedited approval by the FDA reported that the proportion of new drugs subject to post-approval obligations rose from 30% in the early 1980s to approximately 80% in the early 2000s [5].

4.2. Limitations of the study

As the introduction of conditional approval is quite recent, about half the medicinal products in our analysis were approved between 2011 and 2015, which is not long enough for adequate post-marketing history or firm conclusions. These commitments will be monitored in the future. We did our best to collect information on conditional approvals through manual searches of the EMA documents, including reports and press releases. However, we might have underestimated the number of medicinal products that were given conditional approval initially, then regular marketing authorisation. This is because while medicinal products currently licensed with conditional approval are flagged in the EMA website, those switched to regular approval are not highlighted anymore and cannot be automatically retrieved in the EMA database. However, three conditional approvals switched to regular were still flagged at the time of this analysis. In addition, not all the EPARs we analysed clearly reported the specific obligations and we may have misinterpreted some. Similarly, tracking the specific obligation status in the documents issued by the EMA after licensing was not always straightforward. Traceability of changes in the marketing authorisation may improve with the publication of annual re-assessment reports, the introduction of links to publications and trial registries, or the establishment of a repository of post-marketing measures, like the FDA's [45]. We did not contact EMA to obtain the information we could not retrieve in the public documents. This may be seen as a limitation; however, these details should be clearly reported and accessible to any health professional. Finally, our approach to data collection (one extractor and a second independent person checking the quality of the extracted data) may not have been sufficient to prevent errors in data extraction.

5. Conclusions

Our analysis of conditional approvals granted by the EMA highlights inconsistencies with regard to the fulfilment of the criteria for this kind of authorisation and the specific obligations imposed at the time of approval. The benefit–risk profile of medicines conditionally allowed onto the market is rarely reassuring and strong enough to make the expected public health advantage outweigh the risks of limited clinical information.

The regulatory tools adopted to grant marketing authorisation on the basis of incomplete evidence packages need to be analysed promptly as the experience with conditional approvals may anticipate the outcome of the recently proposed adaptive-licensing (adaptive pathway) which could potentially open many more doors to approvals with low evidence thresholds. Adaptive licensing is proposed as a prospectively-planned process, with iterative phases of data gathering and regulatory evaluation [46–48]. Early authorisation of a few medicines with unsettled benefit–risk profiles could pave the way to further marketing authorisation strategies allowing general access to medicines whose clinical value is still not fully established.

Learning points

- Though advocated by pharmaceutical companies and patient groups, early access to new medicinal products may increase the risks of approving drugs that are ineffective, unsafe, or both.
- Regulatory authorities have adopted tools that favour early access to the market of medicines with still unsettled benefit–risk profiles, while hoping to fill the gaps promptly.
- Since 2006 the “conditional approvals” have been intended to serve this purpose in Europe.
- Analysis of the EMA conditional approvals highlights inconsistencies and delays in the fulfilment of the specific obligations imposed at the time of approval.
- Early authorisation of medicines allows access to medicines whose clinical value is not fully established clinical value for long periods, with possible risks for patients.

Authors' contributions

SG proposed a systematic assessment of the EMA procedure to grant early marketing access to medicines in Europe. RB and VB planned the analysis and RB, CG, VB extracted the data and verified their accuracy. RB drafted the initial manuscript and all the authors commented the drafts, contributed to the final text and approved it. All authors had full access to all the data. SG served as a member and VB as an expert on the Committee for Proprietary Medicinal Products at the EMEA (now Committee for Human Medicinal Products at the EMA) up to 2004. SG is the guarantor of the article.

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Conflict of interests

None of the authors have financial or non-financial personal competing interests to be declared.

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Notes to Table 1:
6MWD: Change in 6-minute walk distance; ALK: anaplastic large cell lymphoma; ASCT: autologous stem cell transplant; AVR: anti-retrovirals; BCC: basal-cell carcinoma; BID: twice a day; CA: conditional approval; CF: cystic fibrosis; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CML: chronic myelogenous leukaemia; CNV: corneal neovascularisation; CR: complete response; CRC: colorectal cancer; DOR: duration of response; ENF: enfuvirtide; GIST: gastrointestinal stromal tumours; HL: Hodgkin lymphoma; HR: hazard ratio; MA: marketing authorisation; MDR: multi-drug resistant KRAS: Kirsten rat sarcoma viral oncogene homolog; MCyR: major cytogenetic response; MDR-TC: pulmonary multi-drug resistant tuberculosis; mo: months; MTC: medullary thyroid carcinoma; NHL: non-Hodgkin B-cell lymphomas; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTI: nucleoside/nucleotide reverse transcriptase inhibitors; NSCLC: non-small-cell lung cancer; ORR: overall response rate; OS: overall survival; PASS: post-authorisation safety study; PFS: progression-free survival; PI: protease inhibitors; PK: pharmacokinetics; Pre-XDR TB: pre-extensively drug-resistant tuberculosis; pts: participants; QD: once daily; QoL: quality of life; RCT: randomised controlled trial; RET: rearranged during transfection receptor (proto-oncogene); RR: relative risk; sALCL: systemic anaplastic large-cell lymphoma; SCC: sputum culture conversion; SEGA: subependymal giant cell astrocytoma; TKI: tyrosine kinase inhibitor(s); TTP: time to progression; wks: weeks; VR: viral response; WSI: walking speed improvement.
[a] Orphan drug.

Appendix

EMA conditional approvals (2006–June 2015) total = 26; still conditional = 14, update June 2015.

	Name/active substance	Date of issue of MA	Therapeutic area	MA holder	Specific obligations to be fulfilled by the MA holder[b]	Studies aimed at resolving the specific obligations	Specific obligation status
1	Everolimus Votubia[a]	2011 (+2012 and 2013 extensions)	Astrocytoma associated with tuberous sclerosis	Novartis Europharm Ltd.	1) Long-term follow-up on duration of response and time to progression for studies C2485 and M2301 by March 2015	1) C2485 (NCT00411619) and M2301 (NCT00789828) Ended, published in Krueger 2010 [1], 2013 [2] + Franz 2013 [3] + results on clinicaltrial.gov	Not yet resolved (late) Interim data submitted November 2013 (X/0008/G), December 2014 (var. II/28)
					2) Complete the ongoing pivotal clinical study M2301 and provide the interim and final safety and efficacy results including analysis of adverse event incidence as a function of plasma drug concentration with and without inducer stratified by age, readdress the starting dose strategy Interim CSR due by December 2011; final CSR due by September 2012	2) M2301 (NCT00789828) Ended, published in Franz 2013 [3] + results on clinicaltrial.gov	Resolved (late) November 2013 (X/0008/G)
					3) To document the population PK of everolimus in children by December 2012.	3) PK substudy of the Pivotal (M2301)	Resolved (late) June 2014 (II/20)
2	Fampridine Fampyra [re-examination after a negative opinion]	2011	Multiple sclerosis	Biogen Idec Ltd.	1) Double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary end-point clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment (by June 2016)	1) ENHANCE (NCT02219932) Recruiting, no publication Extension of pivotal studies published in Goodman 2015 [4]	Ongoing
3	Brentuximab vedotin Adcetris[a]	2012	Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL)	Takeda Pharma A/S	1) OS follow up of the patients included in study SG035-0003 (by 2015) and SG035-0004 (by 2016)	1) SG035-003 (NCT00848926) annual reports; SG035-0004 (NCT00866047) Ended, published in Pro 2012 (tumour response) [5], Younes 2012 [6], Gopal 2015 (PFS, OS) [7] + results on clinicaltrial.gov	Partially resolved August 2014 (var. II/11) OS and PFS from study SG035-0003
					2) PASS in both HL and sALCL patient populations (n = 500) including a sufficient number of sALCL patients (i.e. at least n = 50, study MA25101). Interim analysis by April 2016. Final study report by December 2018.	2) MA25101 (ARROVEN) Observational study Ongoing, no publication	Ongoing
					3) Single-arm study in a similar patient population as the sALCL population investigating RR, duration of response, rate of (second) ASCT (Study C25006) Protocol sub. by Q4 2012. Final study report: by Q1 2016	3) Study C25006 (NCT01909934) (EudraCT number: 2012-004128-39) Recruiting, no publication	Ongoing
					4) Single-arm studying r/r HL population not eligible for ASCT investigating RR, PFS, OS, proportion of patients proceeding to transplant and safety (n = 60) (Study C25007) Protocol: Q1 2013. Final study report: Q2 2016	4) Study C25007 (NCT01990534) (EudraCT number: 2013-000232-10) Recruiting, no publication	Ongoing
4	Crizotinib Xalkori	2012	Anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).	Pfizer Ltd.	1) OS status of study A8081007 and provide the final data within 9 months after the required 238 OS events have been reached. The CSR should also include a detailed safety analysis (by Q1 2016).	1) A8081007 (NCT00932893) Recruitment ended, published in Shaw 2013 [8] + results on clinicaltrial.gov + phase I study on other tumour. (NCT01121588)	Ongoing
5	Pixantrone dimaleate Pixuvri	2012	Non-Hodgkin B-cell lymphomas (NHL)	CTI Life Sciences Limited	1) A randomised controlled Phase III study (PIX 306) of pixantrone-rituximab vs. gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for ASCT (2nd line) or failed ASCT (3rd or 4th line) by June 2015 (June 2015: by November 2016)	1) PIX 306 (NCT01321541) EudraCT number: 2012-001790-86 Recruiting, no publication	Ongoing (late)
6	Vandetanib Caprelsa	2012	Medullary thyroid cancer (MTC)	AstraZeneca AB	1) Open label trial comparing RET negative and RET positive patients	1) NCT01945762 Observational study	Ongoing

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Appendix (*continued*)

	Name/active substance	Date of issue of MA	Therapeutic area	MA holder	Specific obligations to be fulfilled by the MA holder[b]	Studies aimed at resolving the specific obligations	Specific obligation status
					with sporadic MTC treated with vandetanib (approximately 60% of patients who receive vandetanib within the EU) (by December 2015).	Recruiting, no publication	
7	Bosutinib Bosulif[a]	2013	Chronic myelogenous leukaemia (CML) in patients where other TKI are not appropriate	Pfizer Ltd.	1) Single-arm open label, multi-centre efficacy and safety study of bosutinib in patients with Ph + CML previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (by Sept. 2018)	1) NCT02228382 EudraCT number: 2013-003250-25 Recruiting, no publication	Ongoing
8	Vismodegib Erivedge	2013	Advanced basal-cell carcinoma (BCC)	Roche Registration Ltd.	1) Safety update of the pooled safety population (by June 2014).	1) Pooled safety population, a final SHH4476g pivotal study and an interim analysis of study MO25616.	Resolved (late) May 2015 (Var. II/08)
					2) Final SHH4476g (pivotal study) (by June 2014).	1) SHH4476g (NCT00833417) Recruitment ended, published in Sekulic 2012 [9] + results on clinicaltrial.gov EudraCT number: 2008-004945-27	Resolved (late) May 2015 (Var. II/08)
					3) study MO25616 of 500 patients with a potential one year follow up. Interim analysis by June 2014; final analysis by June 2015. Reworded: further data on safety and data on efficacy from the final analysis of MO25616 by (Q1 2016).	2) MO25616 (NCT01367665) EudraCT number: 2011-000195-34 Recruiting, no publication (final data for primary outcome Sept 2016)	Ongoing
9	Ataluren Translarna[a]	2014	Duchenne muscular dystrophy	PTC Therapeutics Limited	1) Multicentre, randomised, double-blind, placebo-controlled confirmatory study to examine efficacy and safety of Ataluren 10, 10, 20 mg/kg daily in patients with non-sense mutation Duchenne muscular dystrophy (Study PTC124-GD-020-DMD) by 4Q 2015	1) PTC124-GD-020-DMD (NCT01826487) EudraCT number: 2012-004527-20 Ongoing, but not recruiting participants, no publication + phase III extension of PTC124-GD-020-DMD (NCT02090959)	Ongoing
10	Bedaquiline fumarate Sirturo[a]	2014	Pulmonary multidrug resistant (MDR) tuberculosis	Janssen-Cilag International N.V.	1) Additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory phase III) 1Q 2018: Interim analysis when half of the patients reach W68; 1Q 2021: W92 analysis — Clinical Study Report; November 2021: W132 final analysis	1) TMC207-C210 (NCT01600963) EudraCT number: 2011-000653-23 Withdrawn prior to enrolment	No information
11	Cabozantinib Cometriq[a]	2014	Metastatic medullary thyroid carcinoma (MTC)	TMC Pharma Services Ltd.	1) OS analysis of study XL184-301 including subgroup analyses on relevant demographic and baseline tumour characteristics and potential confounding effect of post-study therapies (by April 2015).	1) EXAM study (NCT00704730) Recruitment ended, published in Elisei 2013 [10] + results on clinicaltrial.gov	Ongoing
					2) Study XL-184-401 dose-comparison (140 vs. 60 mg) in 112 patients with hereditary or sporadic MTC (by March 2019).	2) XL-184-401 (NCT01896479) Recruiting, no publication	Ongoing
12	Delamanid Deltyba[a] [re-examination after a negative opinion]	2014	Pulmonary multi-drug resistant tuberculosis (MDR-TC)	Otsuka Novel Products GmbH	1) A phase III trial on delamanid 100 mg BID for 2 months + 200 mg QD for 4 months as add-on of optimal background regimen (study 242-09-213) (by 2Q 2017)	1) Study 242-09-213 (NCT01424670) Ongoing, but not recruiting participants, no publication, no results on clinicaltrial.gov	Ongoing
					2) A controlled study of the efficacy, safety and PK of delamanid 100 mg BID for 2 months followed by delamanid 200 mg in single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary MDR-TC (by 4Q 2018)	2) Not found in clinicaltrial.gov, EU Clinical Trials Register, PubMed, Otsuka website	No information
13	Autologous human corneal epithelial cells containing stem cells Holoclar[a]	2015	Corneal lesions	Chiesi Farmaceutici S.p.A	1) Multinational, multicentre, prospective, open-label, uncontrolled interventional study to assess efficacy and safety (by December 2020)	Not found in clinicaltrial.gov, EU Clinical Trials Register, Chiesi website	No information

Appendix (*continued*)

	Name/active substance	Date of issue of MA	Therapeutic area	MA holder	Specific obligations to be fulfilled by the MA holder[b]	Studies aimed at resolving the specific obligations	Specific obligation status
14	Ceritinib Zikadia	2015	ALK-positive locally advanced or metastatic NSCLC	Novartis Europharm Ltd.	1) Final results of the phase III efficacy study comparing ceritinib to chemotherapy by September 2018	1) A2303 (NCT01828112) Recruiting, no publication	Ongoing
					2) Final clinical study report of phase II study (A2201) by June 2016	2) A2201 (NCT01685060) ongoing, but not recruiting participants	Ongoing

MA: marketing authorization; BID: twice a day; QD: once daily; CA: conditional approval; SCC: sputum culture conversion; SO: specific obligation; PASS: Post-authorisation safety study; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; ASCT: autologous stem cell transplant; ALK: anaplastic large cell lymphoma; PK: pharmacokinetics; RET: Rearranged during Transfection receptor (proto-oncogene); CR: complete response; RR: response rate; PRT-TB: Pre-extensively resistant tuberculosis; 6MWD: Change in 6-minute walk distance; TKI: tyrosine kinase inhibitor(s).

[a] Orphan drug.

[b] If the specific obligations listed in the EPAR at the time of the first approval and that in the annex II of the EPAR do not match we report in the table the former.

EMA conditional approvals (2006–June 2015) total = 26, converted to regular = 10, update June 2015.

	Active substance/ name	Date of issue of MA	Therapeutic area	MA holder	Specific obligation to be fulfilled by the MA holder	Fulfilment of the specific obligation	Switched to regular approval
1	Sunitinib malate Sutent[a]	2006	Gastrointestinal Stromal Tumours (GIST) Carcinoma, Renal Cell	Pfizer Limited	1) To provide results of an ongoing study in cytokine-naive patients with metastatic renal cell carcinoma (by September 2006)	1) Study A6181034 (NCT00083889) published in Motzer 2007 [11], Cella 2010 [12] + results on clinicaltrial.gov	January 2007 (variation II/01)
2	Darunavir Prezista	2007	HIV Infection	Janssen-Cilag International NV	1) Final reports from the studies POWER 1, 2, 3	1) Not clear when it has been addressed Pooled analysis submitted in 2008 (variation II/12) Katlama 2007 (POWER 1) [13]; Haubrich 2007 (POWER 2) [14]; Molina 2007 (POWER 3) [15] Additional studies supporting extensions to the paediatric population: TMC 114-C230 (DIONE, NCT00915655), TMC114-C176 (NCT01308658) TMC114-C228 (NCT00919854), TMC 114-C212 (NCT00355524) + other extensions TMC114-C229 (ODIN, NCT00524368)	September 2013 (renewal R/0055)
					2) The final report from the ongoing randomised, controlled, open-label study C214 to compare the efficacy, safety and tolerability of darunavir with low dose of ritonavir versus lopinavir/ritonavir in treatment-experienced HIV-1 infected subjects (TITAN study);	2) Addressed in 2008 (II/14) and 2009 (variation II/26) TITAN study (NCT00110877), published in Madruga 2007 [16] + var II/27 naïve patients ARTEMIS (NCT00258557), published in Mills 2009 [17]	
					3) Final study reports from the ongoing interaction studies with rifabutin and didanosine and analysis assessing the effect of coadministered nevirapine and efavirenz on darunavir from study C214	3) Addressed in 2007 (variation II/04, didanosine) + 2008 (variation II/10, rifabutine) + 2011 (variation II/32, efavirenz) No mention of interaction with nevirapine	
					4) Data from the darunavir treatment arm that do not receive the candidate NNRTI for	4) 2008 (variation II/12) C206 and C216 (NCT00359021) DUET studies on etravirine	
					5) C208: open label trial of darunavir with low dose of ritonavir in HIV-1 infected subjects randomised in the trials C201, C207 or in sponsor selected Phase I trials	5) C208 (NCT02187107) not clear when it has been addressed No publication, summary results available on clinicaltrial.gov	
					6) C209: open-label safety study of darunavir in combination with low dose RTV and other ARVs in highly experienced HIV-1 patients with limited or no treatment options	6) C209 (NCT00115050) not clear when it has been addressed No publication, clinical study report available on clinicaltrial.gov	
3	Raltegravir Isentress	2007	HIV Infection	Merck Sharp & Dohme Ltd.	1) Comprehensive clinical data up to 48 weeks on long-term viral suppression, safety profile and resistance pattern	1) Addressed in 2009 (variation II/01) P018 (NCT00293267) and P019 (NCT00293254) Ended, published in Steigbigel 2010 [18], Steigbigel 2008 [19], Cooper 2008 [20], Eron 2014 [21] + results on clinicaltrials.gov	July 2009 (renewal)
					2) Further monitoring of resistance to raltegravir and the risk for malignancies	2) Addressed in 2009 (variation II/09, carcinogenicity study in mice) + data on long term safety submitted addressed in	

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Appendix (*continued*)

	Active substance/ name	Date of issue of MA	Therapeutic area	MA holder	Specific obligation to be fulfilled by the MA holder	Fulfilment of the specific obligation	Switched to regular approval
						2009 (variation II/01) Additional study supporting extension of indication to the paediatric population (IMPAACT, NCT00485264)	
4	Stiripentol Diacomit[a]	2007	Myoclonic Epilepsy, Juvenile	Biocodex	1) A placebo-controlled using stiripentol as an add-on therapy in paediatric patients with Dravet's syndrome not adequately controlled with clobazam and valproate by 2009 Then changed into "robust observational study to support stiripentol to control clonic seizure or tonic-clonic seizure in Dravet's syndrome over the short and long term"	1) No trial on clinicaltrial.gov. US retrospective analysis? Willer 2013 [22] Additional data from a Japanese study published in Inoue 2014 [23]	January 2014 (renewal R014)
					2) Bioavailability study of stiripentol after single oral adm. of two 500 mg formulations (capsule and sachet) in 24 healthy male volunteers by 2007	2) Addressed in 2009 (variation II/0004) (the study was negative)	
5	Panitumumab Vectibix [re-examination after a negative opinion] [still flagged as conditional]	2007 (+2011 extension)	Colorectal Neoplasms	Amgen Europe B.V.	1) To submit the clinical study summary report of the SPIRITT study including the safety-efficacy analysis in relation with KRAS by September 2012;	1) SPIRITT study (20060141, NCT00418938) Ended, results on clinicaltrial.gov, no publication Not clear if and when it was submitted II/0050 (July 2013)	January 2015 (renewal 0064)
					2) To provide results of ongoing studies 20050181 and 20050203	PRIME study (20050203, NCT00364013) first line + FOLFOX Ended, published in Douillard 2013 and 2014 [24,25] and 2010 [26] and Weeraratne 2011 [27] + results on clinicaltrial.gov II/0017 (March 2011), NCT00339183 (20050181, NCT00339183) second line combination with FOLFIRI Ended, published in Peeters 2010 [28] and 2014 [29] + results on clinicaltrial.gov Variation II/63	
					3) To complete a Confirmatory trial examining panitumumab monotherapy in licensed indication by December 2012;	3) 20080763, ASPECTT trial (NCT01001377) Ended, published in Price 2014 [30] + results on clinicaltrial.gov Panitumumab vs. cetuximab	
					4) Additional data on Quality of life using a validate scale	Mentioned at pages 33, 34 of the variation II/17 report	
					5) To resolve the uncertainties about RAS testing (range and performance of diagnostic tests conducted in clinical practice, compliance of physicians with the recommend use of Vectibix in wild-type tumours) by Sept. 2014/March 2015;	Addressed March 2015 (Var. II/63): study 20050181 confirmed previous results showing that the benefit of panitumumab is confined to wild-type RAS tumours	
6	Lapatinib Tyverb [still flagged as conditional]	2008 (+2013 and 2010: extensions)	Breast neoplasms	Glaxo Group Ltd.	1) Phase III RCT to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with trastuzumab-containing control arm (by March 2013)	1) NCT00820222 (EGF111438) Ended, results on clinicaltrial.gov, no publication Interim data submitted in 2012 (var II/27)	February 2015 (var. II/37)
					2) Update analysis of survival data for study EGF100151	2) NCT00078572 (EGF100151) Ended, published in Cameron 2008 [31], 2010 [32], Geyer 2006 [33] Not clear if and when data on OS have been submitted	
					3) [added in 2014] provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO) by December 2014	3) EGF108919 (NCT00667251), EGF105485 (NCT00374322), EGF106708 (NCT00490139) Ended, results on clinicaltrial.gov TEACH published in Goss 2013 [34] Addressed in February 2015 (var. II/37)	
7	Etravirine Intelence	2008	HIV Infection	Janssen-Cilag International NV	1) To conduct a study with the objective of further characterizing the clinical efficacy of etravirine with other boosted protease inhibitors than darunavir/r. The analysis will be	1) Addressed in November 2013 (variation II/0031) (retrospective observational cohort study including 1115 subjects treated by etravirine plus protease inhibitors)	November 2013 (var. II/31)

Appendix (*continued*)

	Active substance/ name	Date of issue of MA	Therapeutic area	MA holder	Specific obligation to be fulfilled by the MA holder	Fulfilment of the specific obligation	Switched to regular approval
					based on the data from the EURESIST cohort and other appropriate sources of similar data by September 2012	No study on clinicaltrials.gov, EURESIST cohort Oette 2012 [35] Additional study supporting extension of indication to the paediatric population PIANO study (NCT00665847) Tudor-Williams 2014 [36]	
8	Aztreonam lysine Cayston[a]	2009	Respiratory Tract Infections Cystic Fibrosis (CF)	Gilead Sciences International Limited	1) to submit the results of study GS-US-205-0110 (ages 6 years and older): open-label, randomised Phase 3 study to evaluate the efficacy and safety of AZLI versus Tobramycin Nebulizer Solutions in an intermittent aerosolized regimen in patients with CF by September 2010	1) Study GS-US-205-0110 (NCT00757237) Ended, published in Assael 2013 [37] + results on clinicaltrial.gov	February 2011 (renewal R015)
					2) Review of all paediatric data from controlled studies by September 2010	2) Data submitted in the renewal R/0015 Study GS-US-205-0160 (NCT01404234) Ended, results on clinicaltrial.gov, no publication Additional study supporting the extension of indication and committed in the paediatric plan: CP-AI-006 (NCT00128492) Ended, published in Oermann 2011 [38] + results on clinicaltrial.gov, GS-US-205-0117 (NCT00712166) Ended, published in Wainwright 2011 [39] + results on clinicaltrial.gov GS-US-205-0162 (ALPINE, NCT01375049) Ended, published in Tiddens 2015 [40] + results on clinicaltrial.gov	
9	Pazopanib Votrient	2010	Carcinoma, Renal Cell, Soft Tissue Sarcoma	Glaxo Group Ltd.	1) Study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma (VEG108844) by February 2012	1) Var II/25 (2014): final study report for VEG108844 (NCT00720941) confirms the non-inferiority of pazopanib vs. sunitinib. Published: Motzer et al. 2014 [41] + results on clinicaltrials.gov ongoing, but not recruiting participants published in Motzer 2013 [42] + results on clinicaltrial.gov	June 2013 (renewal R/017) on the basis of PFS and preliminary OS
					2) Pooled analysis of data from study VEG108844 and VEG113078 (a sub study of VEG108844 in Asian subjects with locally advanced and/or metastatic renal cell carcinoma) by June 2012	2) Var II/25 (2014): final study report for VEG108844 (NCT00720941) var II/18 (2013) VEG108844 (NCT00720941) safety data and VEG113078 (NCT01147822) var II/08 (2011) results of final overall survival from study VEG 105192 (NCT00387764) Additional study supporting extension of indication VEG-110727 (NCT00753688), published in van der Graaf 2012 [43] + results on clinicaltrial.gov	
10	Ofatumumab Arzerra[a] [still flagged as conditional]	2010 (+2014: Extens.)	Chronic lymphocytic leukaemia (CLL)	Glaxo Group Ltd.	1) Comprehensive clinical data from the phase III trial in earlier settings (OMB110911)	1) OMB110911 (NCT00748189) May 2014, var II/23 Poster presentation 2013	April 2015 (var. II/0035)
					2) Open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory CLL (by December 2014)	2) NCT01313689 Ongoing, but not recruiting participants, no publication, results on clinicaltrial.gov Addressed in April 2015 (Var. II/0035)	
					3) Phase IV observational study to provide data on the clinical efficacy and safety (by June 2013)	3) NCT01453062 No publication, results on clinicaltrial.gov Not clear if and when it was submitted. No more mentioned in 2014.	

AZLI: Aztreonam for Inhalation Solution; CA: conditional approval; MA: marketing authorization; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; SO: specific obligation.

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