EU5 MARKET ACCESS FOR MEDICINES WITH CONDITIONAL MARKETING AUTHORISATIONS

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OBJECTIVE

To examine market access timelines and HTA assessments for medicines authorized by the European Medicine Agency (EMA) conditional approval pathway between January 2009 and December 2017

BACKGROUND

- Conditional marketing authorisation may be granted by the EMA for medicines that address unmet medical needs of patients and where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required
- Medicines for human use are eligible if they belong to at least one of these categories:
  - Aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases;
  - Intended for use in emergency situations
  - Designated as orphan medicines
- Conditional marketing authorisations are valid for one year and can be renewed annually
- Renewal is given on the basis of confirmation of the benefit–risk balance, taking into account the specific obligations and the timeframe for their fulfilment
- Once comprehensive data on the product has been obtained, the marketing authorisation may be converted into a "standard" marketing authorisation. Initially, this is valid for 5 years, but can be renewed for unlimited validity

Source: European Medicines Agency (accessed Sep 20, 2018)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

METHODS

- Reviewed all drugs between January 2009 and December 2017 that were granted a conditional marketing authorisation by the European Medicines Agency (EMA)
- Analysed time to market and HTA assessments of drugs that retained conditional marketing authorisation as of March 1, 2018
  - Data gathered from EMA, national Health Technology Assessment (HTA) agencies and Pricing and Reimbursement (P&R) bodies
  - Sources for launch date and HTA information provided in Table 1:

Table 1: Launch date and HTA information in the EU5

Country	Launch date information	HTA information
France	P&R decision (date published in Journal Officiel),	Haute Autorité de Santé
Germany	Product availability/introduction (ABDATA),	Gemeinsamer Bundesausschuss (G-BA)
Italy	First P&R Decree publication on Official Gazette - Analysis of launch date does not consider initial approval in Class C-nn	Not applicable
Spain	Date of commercialization (Portalfarma)	Not applicable
UK	Launch date/availability not considering HTA (MIMS/NHS SPS/NHS DMD)	National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium

RESULTS

- A total of 27 medicines were granted conditional marketing authorization by the EMA between January 2009 and December 2017 (Table 2). As of March 1, 2018:
  - 10 were converted to standard marketing authorization (no association between EC approval date and conversion to standard marketing authorization)
  - 17 retained conditional authorization
- Majority of the drugs that still have conditional approval are new active substances (16 of the 17 drugs); only one known substance is included (parathyroid hormone)

Table 2: Drugs granted conditional marketing authorization by the EMA between January 2009 and December 2017

Generic Name	Indication	EC approval date	Date converted to full MA
aztreonam	Cystic fibrosis	21-Sep-09	5-Sep-11
ofatumumab	Chronic B-Cell Leukemia, Lymphoma	19-Apr-10	3-Jul-14
pazopanib	Renal Cell Carcinoma	14-Jun-10	14-Jun-13
fampridine	Multiple Sclerosis	20-Jul-11	22-May-17
everolimus	Tuberous Sclerosis	2-Sep-11	16-Nov-15
crizotinib	Non Small Cell Lung Cancer	23-Oct-12	11-Nov-16
vismodegib	Basal Cell Carcinoma	12-Jul-13	14-Nov-16
ceritinib	Non Small Cell Lung Cancer	6-May-15	22-May-17
osimertinib mesylate	Non Small Cell Lung Cancer	2-Feb-16	24-Apr-17
daratumumab	Multiple Myeloma	20-May-16	24-Apr-17
vandetanib	Thyroid Neoplasms	17-Feb-12	
pixantrone dimaleate	Non-Hodgkin Lymphoma (NHL)	10-May-12	
brentuximab vedotin	Hodgkin disease, NHL	25-Oct-12	
bosutinib	Myeloid leukemia	27-Mar-13	
bedaquiline fumarate	Multidrug-Resistant Tuberculosis	5-Mar-14	
cabozantinib	Thyroid neoplasm	21-Mar-14	
delamanid	Multidrug-Resistant Tuberculosis	28-Apr-14	
ataluren	Duchenne Muscular Dystrophy	31-Jul-14	
ex vivo expanded autologous human corneal epithelial cells containing stem cells	Corneal Diseases, Stem cell transplantation	17-Feb-15	
blinatumomab	Lymphoblastic Leukemia-Lymphoma	23-Nov-15	
allogeneic T cells genetically modified with a retroviral vector	Hematopoietic Stem Cell Transplantation; GVHD	18-Aug-16	
olaratumab	Advanced soft tissue sarcoma	9-Nov-16	
ixazomib citrate	Multiple Myeloma	21-Nov-16	
venetoclax	Chronic lymphocytic leukaemia	5-Dec-16	
obeticholic acid	Biliary Liver Cirrhosis	12-Dec-16	
parathyroid hormone	Chronic hypoparathyroidism	24-Apr-17	
avelumab	Merkel cell carcinoma	18-Sep-17	

Converted to standard MA as of March 1, 2018 | Drugs with conditional approval as of March 1, 2018

- Of the 17 drugs with conditional approval as of March 1, 2018
  - 88% (n=15) have an orphan designation
  - 59% (n=10) are indicated for oncology
  - 47% (n=8) have an orphan designation and are indicated for oncology
- Further analysis of time to market for these 17 drugs suggests access issues in both France and Spain (Table 3)

  Completed P&R procedure by only 24% in Spain (n=4) and 41% in France (n=7)
  - Time to launch is substantially longer in both markets compared to existing national averages
    - France: 101 weeks vs. 74 weeks (all general medicines) and 86 weeks (orphan drugs)
    - Spain: 135 weeks vs 67 weeks (all general medicines) and 104 weeks (orphan drugs)
- Italy is the only market where access for drugs with conditional approval seems more favourable compared to other drugs (Table 3)
  - P&R decree is published for 88% of drugs with conditional MA compared to 79% for all other drugs
  - Time to launch is quicker at 74 weeks for drugs with conditional approval vs. 78 weeks for general medicines and 90 weeks for orphan drugs
- From an HTA perspective, some interesting observations can be made
  - In France and Germany, level of incremental benefit assigned upon reviewing available evidence package tends to be low; primarily due to quality of data and clinical uncertainty
    - Of the 13 drugs reviewed by HAS in France only 2 were assigned ASMR III (no ASMR I or II ratings)
      - 11 were assigned ASMR IV or V (2 of these drugs had ASMR III in one subgroup)
    - Of the 12 drugs reviewed by the GB-A in Germany
      - 7 were rated as having only a non-quantifiable or no added benefit (similar to most orphan drugs)
      - 3 were rated as having minor added benefit
      - Only 2 were rated as having important added benefit
    - National agencies can make very different decisions based upon the same clinical data, for instance Brentuximab vedotin was assigned ASMR III/IV in France but a non-quantifiable added benefit in Germany
  - UK: Positive recommendations/guidance are almost always based on a negotiated PAS or MAA. NICE seems more receptive to commercial arrangements compared to the SMC
    - England: All drugs with conditional approval reviewed by NICE were recommended and for oncology drugs:
      - 50% of recommendations were based on MAA and
      - 40% were recommended within the new Cancer Drug Fund (CDF)
    - Scotland: Only one non-oncology drug with conditional MA was reviewed and accepted by the SMC; no SMC guidance available for most

Table 3: Number of weeks to launch post regulatory approval in the EU5 for drugs approved between January 2009 to December 2017 and on the market as of March 1, 2018

Country	All drugs* (n=359)		Orphan drugs** (n=83)		Drugs with Conditional marketing authorization*** (n=17)	
	# of Weeks	*% of all EC approved drugs*	*# of Weeks*	*% of all EC approved orphan drugs*	*# of Weeks*	*% of all EC approved orphan drugs*
France (n=193)	74	53%	86	49%	101	41%
Germany (n=318)	18	89%	17	94%	17	100%
Italy (n=282)	78	79%	90	78%	74	88%
Spain (n=235)	67	65%	104	39%	135	24%
UK (n=311)	25	87%	30	87%	27	94%

*All drugs approved by EC between Jan 2009 and Dec 2017 on the market as of March 1, 2018 (i.e. not suspended or withdrawn)
**All orphan drugs approved by EC between Jan 2009 and Dec 2017 on the market as of March 1, 2018 (i.e. not suspended or withdrawn)
**All drugs approved by EC between Jan 2009 and Dec 2017 via conditional approval route that have retained conditional approval status on the market as of March 1, 2018 (i.e. not converted to full MA)

Date of publication of P&R decree is used as indication of launch date. This does not necessarily mean reimbursed access.
-For example, in Italy although a P&R decree was published for 88% of drugs with conditional approval; only ~70% are reimbursed (3 drugs assigned Class C, i.e. not reimbursed)

CONCLUSIONS

- It is important to recognize that while conditional approval pathway may result in quicker regulatory approval for new drugs, market access challenges may be great in some countries
  - In France and Spain, in particular, standard P&R procedures take substantially longer for these drugs with limited access
- Market access for drugs with conditional approval seems consistent with general process in Germany
- Environment seems more favourable in Italy and the UK where most drugs are available and recommended for reimbursement
  - This is likely a result of both countries being open to reimbursement based on post-launch data collection, patient registries and managed access agreements
- Closer interaction between regulators and HTA agencies and more flexible reimbursement approaches could further facilitate patient access for drugs with conditional regulatory approval

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