EU5 MARKET ACCESS FOR MEDICINES APPROVED UNDER EXCEPTIONAL CIRCUMSTANCES

Mycka J[1], Dellamano R[2], Lobb W[1], Dalal N[1], Dellamano L[2], Pereira E[1], Mora M[1], Pollere D[1], Khan O[1]

[1]Medical Marketing Economics, LLC, Montclair, NJ, USA; [2]ValueVector, Milan, Italy

OBJECTIVE

To examine market access timelines and HTA assessments for medicines approved under exceptional circumstances by the European Medicines Agency (EMA) between January 2009 and December 2017

BACKGROUND

- For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, EMA may grant a marketing authorisation in absence of comprehensive data under exceptional circumstances
- Reasons that medicinal products that would qualify without comprehensive data on the efficacy and safety could be because :
  - Indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
  - In the present state of scientific knowledge, comprehensive information cannot be provided, or
  - It would be contrary to generally accepted principles of medical ethics to collect such information.
- Unlike conditional marketing authorisation, where marketing approval is granted in the likelihood that the sponsor will provide such data within an agreed timeframe, authorisation under exceptional circumstances can be granted when comprehensive data cannot be obtained even after authorisation
  - Authorisation initially valid for 5 years (renewable), but the status of fulfilment of the specific obligations and the impact of the specific obligations' data on the benefit / risk balance is to be reassessed annually
  - This authorisation route normally does not lead to a standard marketing authorisation

Source: European Medicines Agency (accessed Sep 20, 2018)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196

METHODS

- Reviewed all drugs between January 2009 and December 2017 that were granted approval under exceptional circumstances by the European Medicines Agency (EMA)
- Analysed time to market and HTA assessments of drugs that retained approval under exceptional circumstances 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 the *Journal Officiel*)	*Haute Autorité de Santé* (HAS)
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

- 14 drugs approved by the EC between January 2009 and December 2017 under exceptional circumstances (Table 2)
  - Only 43% (n=6) are new active substances
  - Approximately 79% (n=11) of drugs have an orphan designation
  - Only 1 drug (dinutuximab beta) has an oncology indication
- Only 21% of drugs (n=3) approved under exceptional circumstances have completed P&R negotiations in Spain and only 43% in France (n=6)- see Table 3
- Time to market for drugs approved under exceptional circumstances is substantially longer compared to national averages for all drugs across the EU5 countries (except Germany where timelines are similar)- see Table 3
- HTA assessments published so far for 11 drugs in France (79%), but only 7 in Germany (50%) and 6 in the UK (43%)
  - In Germany reasons for lack of G-BA assessments include known active substance, insignificant costs to sickness funds, blood products and in one case approval prior to AMNOG implementation
  - In the UK, guidance for 6 drugs is in development by NICE/NHS England (2 are being reviewed via Highly Specialised Technology-HST process)
- In France and Germany, level of incremental benefit assigned upon reviewing available evidence package tends to be low
  - Of the 11 drugs reviewed in France
    - 2 drugs have no ASMR assigned based on insufficient SMR
    - 7 drugs assigned ASMR IV/V
    - Only 2 drugs have ASMR of I or II
  - Germany: Only 7 drugs (50%) have G-BA assessment
    - 5 are assigned non quantifiable added benefit rating (71%)
    - 1 assigned no added benefit (no orphan designation in the approved indication) and
    - Only 1 has minor added benefit
- National agencies can make very different decisions upon reviewing the same clinical data
  - Two drugs with strong ASMR ratings in France (asfotase alfa and cholic acid) assigned non-quantifiable added benefit rating in Germany
- In the UK, positive recommendations/guidance are almost always based on a negotiated PAS or MAA
  - England: Except for one drug that is not recommended, all others reviewed are recommended for restricted use as per criteria, PAS or managed access scheme
  - Scotland: Only 6 drugs reviewed by the SMC, of which 4 are not recommended and 2 are accepted with PAS

Table 2: Drugs granted approval under exceptional circumstances by the EMA between January 2009 and December 2017

Generic Name	Brand name	Indication	Chemical type	EC approval date
tocofersolan*	Vedrop	Vitamin-E deficiency	Known active substance	24-Jul-09
amifampridine	Firdapse	Lambert-Eaton Myasthenic Syndrome	Known active substance	23-Dec-09
tafamidis	Vyndaqel	Amyloidosis	New active substance	16-Nov-11
lomitapide*	Lojuxta / Juxtapid	Hypercholesterolemia	New active substance	31-Jul-13
cholic acid (1)	Orphacol	Inborn Errors of Metabolism	Known active substance	12-Sep-13
defibrotide	Defitelio	Hepatic Veno-Occlusive Disease	Known active substance	18-Oct-13
afamelanotide	Scenesse	Protoporphyria, Erythropoietic	New active substance	22-Dec-14
asfotase alfa	Strensiq	Hypophosphatasia	New active substance	28-Aug-15
idebenone	Raxone	Leber Hereditary Optic Neuropathy	Known active substance	8-Sep-15
susoctocog alfa*	Obizur	Hemophilia A	New active substance	11-Nov-15
cholic acid (2)	Kolbam/Cholbam	Inborn Errors of Metabolism	Known active substance	20-Nov-15
chenodeoxycholic acid	Chenodeoxycholic acid Leadiant	Inborn errors of metabolism, xanthomatosis (CTX))	Hybrid medicinal product	10-Apr-17
dinutuximab beta	Qarziba	Neuroblastoma	Known active substance	8-May-17
cerliponase alfa	Brineura	Neuronal Ceroid-Lipofuscinoses	New active substance	30-May-17

**Non orphan drugs*

Known active substance | New active substance

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 approved under exceptional circumstances*** (n=14)	
	# 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%	81	43%
Germany (n=318)	18	89%	17	94%	18	86%
Italy (n=282)	78	79%	90	78%	108	71%
Spain (n=235)	67	65%	104	39%	112	21%
UK (n=311)	25	87%	30	87%	40	64%

*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 under exceptional circumstances as of March 1, 2018 (i.e. not suspended or withdrawn)

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 71% of drugs approved under exceptional circumstances, only 43% have reimbursed access (4 of the 10 drugs with a decree published are categorized as Class C)

CONCLUSIONS

- It is important to recognize that, while approval under exceptional circumstances may be a path to regulatory approval, it could be challenging from a market access perspective
  - In France and Spain, less than 50% of these drugs have completed P&R negotiations in the last nine years
  - Timelines for access are substantially longer especially in Italy and Spain
    - In Italy, this could be due to the high proportion of repurposed molecules that are not viewed favourably by authorities
  - HTA in Germany is often negative with potential impact on price negotiations, particularly when a drug does not have orphan designation
  - Lower percentage of drugs approved under exceptional circumstances are on the UK market with timelines for guidance development being long
    - Approximately 50% of the drugs have a NICE guidance in development
    - Final decisions result in restricted access with negotiated patient access schemes or managed access schemes/commercial agreements
- Closer interaction between regulators, HTA bodies and manufacturers is required to ensure that regulatory approval pathway can translate into a route to patient access

Medical Marketing Economics, LLC, 8 Hillside Ave Suite 301, Montclair, NJ 07042

Phone: (973) 744-2500 E-Mail: info@m2econ.com Internet: www.m2econ.com