Orphan Drugs – How Will the New Proposed European Union (EU) Commission Pharmaceutical Regulation Impact Therapies for Rare Diseases?

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OBJECTIVES

To analyze the implications of the new proposed legislation and its impact on orphan drugs (OD), and to compare these changes to the existing OD legislative landscape

METHODS

We conducted a comprehensive assessment of the pharmaceutical legislation within the EU. Using Darzalex® as an analogue due to its recent successes in multiple myeloma and recent expansion into AL amyloidosis, we compared the proposed new legislation with the current legislation governing the environment. The impact of the shortened exclusivity period on OD access in the EU was assessed via analysis of Darzalex® availability and reimbursement across EU Member States (MS) as well as by internet searches on supply issues.

PROPOSED NEW LEGISLATION[1]

- Aim is to increase availability, accessibility and affordability of medicines
- New legislation is a merger of the Orphan (EC 141/2000) and Paediatric Regulations (EC 1901/2006)
- All medicines with marketing authorization (MA) via the centralized procedure must be supplied in all 27 MS within 2 years (although an individual MS can waive this condition)
- An orphan designation shall be valid for 7 years
- All new orphan medicinal products will receive an Unmet Medical Need (UMN) designation, where at least one indication relates to a life-threatening or severely debilitating condition. Some orphan products will be designated as High Unmet Medical Need (HUMN) where there is an absence of satisfactory diagnosis, prevention or treatment for the condition, or if the product provides exceptional therapeutic advancement and benefit.
- Standard duration for orphan market exclusivity (OME) is proposed to be 9 years with variations, which can increase up to 13 years:
  - Additional year for HUMN
  - A new indication generates a 1-year extension (for a maximum of two indications) on the orphan medicine exclusivity (OME) period
  - Supply to all MS within 2 years (3 years for small and medium-sized enterprises (SMEs)) of MA generates an additional year extension

RESULTS

Orphan Drug Analogue: Darzalex®

Current Regulations

Table 1. Market authorization and access across all MS

Indication Order	Indication	EMA MA Date	MS Access[2]
1st	Multiple Myeloma (MM)	20/05/2016[3]	16/28 (57%)
2nd	AL Amyloidosis	21/06/2021[4]	8/27 (30%)

- **Access:** AL Amyloidosis available in first MS within 8 months[2] of EMA MA
- **Supply Issues**: Not reported

Proposed New Regulations

Under new legislation, if launched now and based on historic performance, Darzalex® would achieve a net OME of 10 years

Table 2. Potential Darzalex® OME under new regulations

Elements affecting OME	Darzalex® OME
MM indication potentially designated as UMN rather than HUMN	9 years
Unlikely to achieve the 1-year extension for continuous supply to all MS within 2 years	0 years
2nd indication AL-Amyloidosis (likely designated as HUMN)	1 year
Total	**10 years**

- For AL Amyloidosis, achieving MA 5 years after the 1st indication launch with time to market + 8 months remains less than 5 years to maximize sales revenue

IMPLICATIONS

Member States: Health Systems

- Potential for increased consistency across MS
- Potential for consistent drug supply across MS
- MS may find there is a longer wait for new orphan / rare disease drugs to become available within the continent
- Manufacturer uncertainty may lead to higher price levels and limited research into additional indications

Manufacturer

May be discouraged from investing in orphan / rare disease drug development due to:

- Uncertainty about which potential indications to pursue first to achieve:
  - HUMN vs UMN
  - Highest price
  - Largest patient population
  - Sufficient evidence for access in all MS
- Potential for reduced returns on investment
  - Shorter OME
    - OME extensions limited to two additional indications
  - Faster price erosion post-OME

May reconsider European MS as first wave launch markets

Key: Negative Impact; Neutral or Mixed Impact; Positive Impact

CONCLUSIONS

The new proposed EU pharmaceutical regulations appear to promise alignment, consistency of process and availability of new orphan drugs across the MS. However, as demonstrated by the hypothetical example of Darzalex® being launched under the proposed regulations, the uncertainty that manufacturers would experience are likely to negate some of these benefits.

If manufacturers perceive the EU as hindering their ability to generate returns on their investment in orphan and rare diseases, the continent may find that the availability of new drugs could be delayed for all MS.

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