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Marketing authorisation pathways and clinical evidence supporting approval of orphan medicinal products in EU between January 2015 and October 2021

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Declaration of interest: This study was performed under the umbrella of Copenhagen Centre for Regulatory Science (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organisations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related.

Introduction

Background

Under normal market conditions, the pharmaceutical industry has little incentive to develop and market medicinal products to treat rare diseases. The objective of the European Orphan regulation (Regulation (EC) No 141/2000) is to facilitate that patients with rare diseases have access to the same quality of treatment as any other patient in the EU. The regulation incentivises the industry to develop and market designated Orphan Medicinal Products (OMP). Incentives include Protocol assistance, ten years of market exclusivity and fee reductions. Designated OMPs are also eligible for Conditional Market Authorisation (CMA). Still, generating evidence for the safety and efficacy of medicines indicated for orphan diseases may be both logistically and ethically challenging due to the low prevalence and severity of orphan diseases.

Aims

The objective of this study is to characterise the clinical evidence supporting marketing authorisation (MA) of orphan medicinal products and to explore if there is an association between the rarity of disease and type of MA granted and the strength of clinical evidence, respectively.

Methods

Data collection

We identified all OMPs granted MA between January 2015 and October 2021, cross-referencing the European Medicine Agency (EMA) “download table of all EPARs for human and veterinary medicines” and the “EMA download table of all orphan designation” on the EMA homepage. All included OD were categorised as rare or ultra-rare based on the prevalence of the condition (rare: ≤ 5/10,000 and > 1/100,000 and ultra-rare: ≤1/100,000) as stated in the public summary of the opinion of the OD. The OMP was categorised by therapeutic area based on the product ATC code anatomical main group.

We retrieved the European Public Assessment Report (EPAR) for all included OD. We collected information about the initial marketing authorisation type (standard MA, conditional MA (CMA) or exceptional circumstances MA (EC MA)), as well as information about pivotal (main) clinical studies supporting the MA. Information collected includes the number of pivotal trials, study design (randomisation, blinding) and use of clinical or surrogate endpoints as primary endpoints. The FDA Downloadable Table of Surrogate Endpoints was consulted to identify surrogate endpoints.

Statistical Analyses

MA type and the therapeutic area were reported in absolute numbers and percentages of total number of approved ODs. Analysis for MA type was also stratified by the rarity of disease. Study design and use of clinical endpoints or only surrogate endpoints were reported in absolute numbers and percentages to the total number of clinical trials and stratified by rarity of disease.

Association between rarity of disease and MA type and use of blinded randomised clinical trials, respectively, was tested using Chi-square test of independence.

Results

A total of 109 ODs were granted MA during the period corresponding to 94 OMPs. The majority of the ODs (76%) were for ultra-rare diseases, and 24% were for rare diseases. An absolute majority (72%) was granted standard MA, 17% CMA, and 11% EC MA (Table 1). There was no statistically significant difference in MA type between rare and ultra-rare diseases (p-value = 0.351).

Table 1. MA type and rarity of orphan disease

	Rare disease (N = 26)	Ultrarare disease (N = 83)	Total (N = 109)
Standard MA	19 (73%)	59 (71%)	77 (72%)
Conditional MA	6 (23%)	13 (16%)	21 (17%)
Exceptional circumstances	1 (4%)	11 (13%)	12 (11%)

The top three types of medicinal products with an OD were Antineoplastic and immunomodulating agents (32%), followed by medicinal products for alimentary tract and metabolism disorders (23%), and the third was medicinal products which act on the nervous system (15%) (Figure 1).

MA was supported by min. one (max 4) pivotal clinical trial for all approved ODs, except for 3 OD (for ultra-rare diseases). The majority (82%) included one pivotal clinical trial in the MA application. One of the three with no pivotal clinical trials was SomaKit TOC®; this product was approved under “well-established medicinal use supported by bibliographic literature” (Directive 2001/83/EC Article 10a). Chenodeoxycholic acid Leadiant ®, a hybrid medicinal product, and Obiltoxaximab SFL®, an anti-anthrax drug, were granted EC MA. For both, it was considered unethical to collect clinical efficacy data.

Hundred-twenty-four pivotal clinical trials supported the authorisation of 106 ODs. Half of the pivotal trials (52%) were double-blinded randomised clinical trials, and 47% of the trials used clinical endpoints; 53% only used surrogate endpoints as the primary endpoints (Table 2). There was no significant difference between rare and ultra-rare diseases and study design (p-value = 0.272) or between rarity of disease and use of clinical endpoints (p-value = 0.818).

Of the 53% (66) pivotal trials using only surrogate endpoints as the primary endpoints, 24 were for anti-cancer treatments. Commonly used surrogate endpoints for this group were progression-free survival (PFS) and overall response rate (ORR).

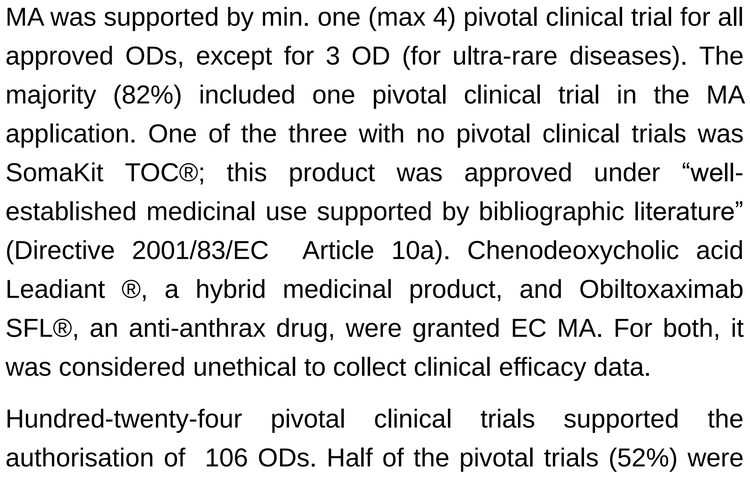

Figure 1. Distribution of therapeutic area of the medicinal products for the 109 orphan designation approved in EU between January 2015 and Oct 2021.

Table 1. Pivotal studies supporting MA

	Rare disease (N = 31)	Ultrarare disease (N = 91)	Total (N = 124)
Blinding			
Blinded	20 (61%)	45 (49%)	65 (52%)
Open label	13 (39%)	46 (51%)	59 (48%)
Randomisation			
Randomised	25 (76%)	62 (68%)	87 (70%)
Non randomised	8 (25%)	29 (32%)	37 (30%)
Primary endpoint			
Clinical endpoint	16 (48%)	42 (51%)	58 (47%)
Only surrogate	17 (52%)	49 (49%)	66 (53%)

Discussion

A majority OMPs approved in the study period the ODs were granted for ultra-rare diseases. One-third of the products were Antineoplastic and immunomodulating agents. Most ODs were granted a standard MA, a bit less than one-fifth was granted CMA, and around one in ten EC MA. While there were no statistically significant differences in MA type between rare and ultra-rare diseases, all (12) except one EC MA granted were for an ultra-rare disease. Comparing our results with the results of Westermark, et al. 2011 suggests that orphans designation is less common than earlier uses of the EC MA, in their study they found that, in the first ten years of the EU orphan regulation, 38% of OMPs were granted EC MA.[1] EC MA can be granted when comprehensive data cannot be obtained even after MA.

Similar to what has been observed in previously studies[2,3] most of the approvals of OMP were based on evidence from a single pivotal clinical trial. The study by Morant & Vestergaard 2018 found that orphan drugs are more likely to only include one pivotal clinical study compared to non-orphan medicinal products.[2] Only half of the clinical trials were double-blinded randomised studies, similar results from earlier period was observed in Pontes, et al. 2018.[3] We did not find any statistically significant difference in study design between rare and ultra-rare diseases.

We found that surrogate endpoints were frequently used as the only primary endpoint in pivotal trials. While the use of surrogate endpoints is becoming more common,[4] a study of orphan drugs approved in the first 15 years of the EU orphan drug regulation also found a high reliance on surrogate endpoints in the clinical evidence supporting MA.[3] The use of surrogate endpoints may decrease clinical development time. In cancer use of surrogate endpoints is estimated to reduce development time by 11 months. However, there may also be drawbacks to the use of surrogate endpoints. Surrogate endpoints may prove difficult in health technology bodies’ decision-making as well as clinical decision-making and may be poor predictors of clinical effectiveness.[5]

Conclusion

The majority of orphan medical product authorisations between January 2015 and October 2021 were granted for ultra-rare diseases, and most were granted a standard MA. No association between type of MA or clinical evidence supporting MA and rarity of disease was found.

[1] Westermark, et.al. Nat Rev Drug Discov 2011;10(5):341-9, DOI: 10.1038/nrd3445, [2] Morant & Vestergaard CPT. 2018;104(1)169-77. DOI:10.1002/cpt.900, [3] Pontes, et al. Orphanet J Rare Dis. 2018;13(1):206.DOI:10.1186/s13023-018-0926, [4] Brown, et al. J Health Polit Policy Law. 2022. DOI: 10.1215/03616878-10041093, [5] Dawoud, et al. BMJ. 2021. DOI: 10.1136/bmj.n2191