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The Impact of Weight-Based Dosing on Pricing and Reimbursement Outcomes for Ultra-Rare Disease Treatments in the EU4

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OBJECTIVES

Many pharmaceutical treatments for severe, ultra-rare diseases have weight-based dosing regimens. When the indication covers both paediatric and adult patients, this can result in significant variation in drug utilisation and costs per patient. For these high-cost treatments, this introduces additional complexity and uncertainty in price determination by payers. This analysis aims to understand how weight-based dosing impacts pricing and reimbursement outcomes across Germany, France, Italy and Spain.

METHODS

Treatments with marketing authorisation from 2014 onwards were extracted from Orpha.net. Criteria for inclusion were weight-based dosing; prevalence ≤10 per million; paediatric and adult indication; chronic treatment; first approved in indication. Drug prices and reimbursement outcomes were collected from the relevant health technology assessment (HTA) body website.

RESULTS

Overall, 7 drugs were identified. All 7 drugs were reimbursed in all EU4 markets, except for vestronidase alfa in France and elosulfase alfa, asfotase alfa, velmanase alfa and olipudase alfa in Spain where these treatments were not recommended for reimbursement (Table 1).

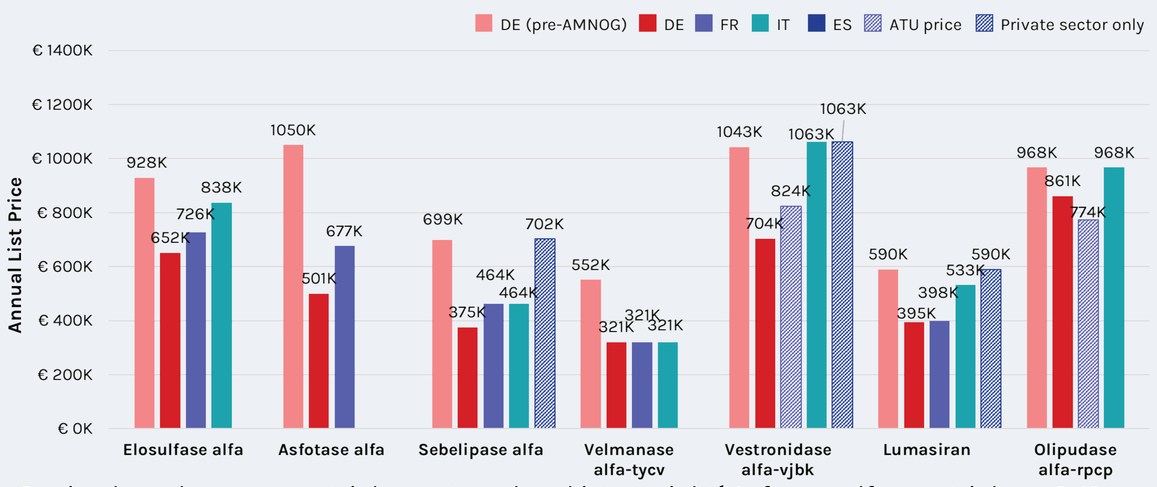
TABLE 1. REIMBURSEMENT OUTCOMES OF IDENTIFIED DRUGS

Drug, indication (prevalence)	DE	FR	IT	ES
Elosulfase alfa *MPS IVA (3 per 1M)*	Nov '14 & Mar '18: **Minor added benefit**	Oct '14: **SMR substantial, ASMR III** Jun '23 (OLE data): **SMR substantial, ASMR IV**	Jul '15: **Reimbursed, class H** Restricted to hospital only	Jun '16: **Not recommended** for public reimbursement
Asfotase alfa *Hypophosphatasia (10 per 1M)*	Mar '17: **Non-quantifiable added benefit** Apr '20 (exceeded OD sales threshold): **Unquantifiable** in subset with improved mortality; **No added benefit** in subset	Mar '16: **SMR substantial, ASMR II** Restricted to specialist centres	Not assessed	Jul '18: **Not recommended** for public reimbursement
Sebelipase alfa *LAL deficiency (6 per 1M)*	Mar '16: **Non-quantifiable added benefit** Jun '21 (with OLE data): **Minor added benefit**	Aug '17: **SMR important, ASMR III** in subset with rapid progression and infantile onset; **SMR low, ASMR V** in subset Restricted to specialist centres, patient monitoring	Dec '17: **Reimbursed, class H** Restricted to hospital only, patient registry	Sep '18: **Recommended** per label *(no price agreement)*
Velmanase alfa-tycv *a-Manniosidosis (2 per 1M)*	Dec '18: **Non-quantifiable added benefit**	Dec '18: **SMR moderate, ASMR IV** Jan '22 (manufacturer request based on Ph2 paediatric data): **SMR substantial, ASMR IV**	Jun '18: **Excluded from reimbursement list** Aug '20: **Reimbursed, class A** Restricted to specialist centres	Aug '21: **Not recommended** for public reimbursement
Vestronidase alfa-vjbk *MPS VII (4 per 1M)*	Mar '19: **Non-quantifiable added benefit**	May '19 & Jun '20: **SMR insufficient, not reimbursed** *(available through EAP)*	Nov '18: **Excluded from reimbursement list** Aug '21: **Reimbursed, class H, cond. innovation** Restricted to hospital only	Sep '20: **Not recommended** for public reimbursement May '21 & May '22: **Recommended**
Lumasiran *PH1 (2 per 1M)*	Jul '21: **Non-quantifiable added benefit**	Apr '21: **SMR substantial, AMSR III**	Mar '22: **Reimbursed, class H, innovative** Restricted to hospital, patient registry, OBA	Jul '22: **Recommended** Restricted to last line; *(no price agreement)*
Olipudase alfa-rpcp *ASMD (0.4 per 1M)*	Mar '23: **Non-quantifiable added benefit**	Dec '22: **SMR substantial, ASMR III** Aug '23: **SMR substantial, ASMR V**	Nov '23: **Reimbursed, class H, innovative** Restricted to hospital only, patient registry	Oct 23, Dec 23 & Jan 24: **Not recommended** for public reimbursement

ASMD: acid sphingomyelinase deficiency; EAP: early access programme; LAL: lysosomal acid lipase; MPS IVA: mucoploysaccharidosis type IV A; MPS VII: mucoploysaccharidosis type VIII; OBA: outcomes-based agreement; OD: orphan drug; OLE: open-label extension; PH1: primary hyperoxaluria type 1

Annual list prices ranged from €321K per patient for velmanase alfa to €1.1 million for vestronidase alfa and were lowest in Germany (post-AMNOG) for 5 out 7 drugs (Figure 1).

Figure 1. Annual List Prices of Identified Drugs



Dosing based on average trial ages translated into weight.[1] Asfotase alfa avg. trial age 3-12 years, translating to 28.5 kg; elosulfase alfa, sebelipase alfa, vestronidase alfa-vjbk avg. trial age 13-17 years, translating to 50 kg; velmanase alfa-tycv, lumasiran avg. trial age 18-30, translating to 62.5 kg; olipudase alfa-rpcp avg. trial age 31-60 years, translating to 70 kg. Dosing assumptions taken from each product's summary of product characteristics: Elosulfase alfa: 2 mg/kg/week; asfotase alfa: 2 mg/kg 3x a week; sebelipase alfa: 1 mg/kg every 2 weeks; velmanase alfa-tycv : 1 mg/kg/week; vestronidase alfa-vjbk: 4 mg/kg every 2 weeks; lumasiran: 3 mg/kg every 3 months; olipudase alfa-rpcp: 3 mg/kg every 2 weeks. ATU: temporary authorisation

In Germany, all drugs had a list price reduction following the end of the pre-AMNOG free-pricing period (mean: 26.3%, min, max: 11.0%, 35.7%; Table 2).

TABLE 2: ANNUAL LIST PRICE REDUCTION OF IDENTIFIED DRUGS IN GERMANY

Drug	Pre-AMNOG	Post-AMNOG	Price Decrease
Olipudase alfa-rpcp	€967,902	€861,160	11%
Elosulfase alfa	€1,067,364	€899,464	16%
Vestronidase alfa-vjbk	€1,303,897	€939,549	28%
Lumasiran	€885,179	€621,838	30%
Velmanase alfa-tycv	€551,698	€388,991	29%
Sebelipase alfa	€932,471	€614,066	34%
Asfotase alfa	€1,050,196	€675,644	36%

CONCLUSION

Although most treatments were reimbursed in all markets at a relatively high list price, it is likely that significant confidential discounts would have been required, as suggested by price reductions following negotiations in Germany. The high number of treatments not recommended for reimbursement in Spain suggests payer uncertainty due to high costs and weight-based dosing in this budget-focused market. It is important for payers and manufacturers to work together to manage the uncertainty of weight-based dosing to reach an agreement that satisfies all stakeholders and enables access for patients in need.

REFERENCES

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