HPR116

Expediting Reimbursement and Access for Novel Drug Indications in Europe: A Case Study on Glucagon-like Peptide 1 (GLP-1) agonists

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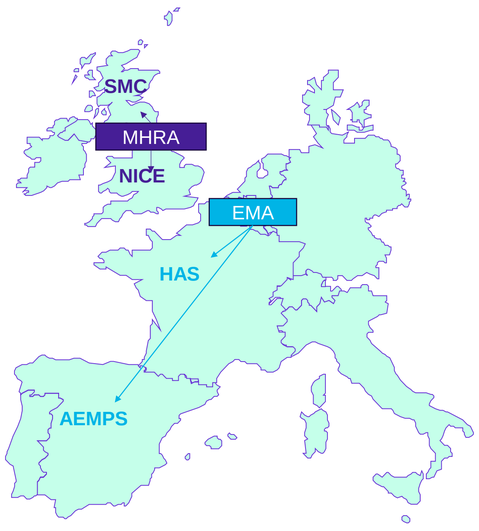
Background

- In recent years, the accelerated development of innovative medicines and the expansion of labels to cover new indications has significantly improved health outcomes. However, the extraordinary wealth of the industry pipeline can only generate value when patients have access to new treatment options.
- Following years of research and development, new treatments in Europe need to reach the following milestones prior to patients receiving access[1]:
  - **Step 1:** Marketing authorisation confirming the quality, safety and efficacy of the therapy, granted by the European Medicines Agency (EMA) in the European Union (EU) and by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK).
  - **Step 2:** Securing reimbursement at national and regional levels.
  - **Step 3:** Post-reimbursement positioning of the therapy within relevant treatment guidelines in accordance with its labels.
- In June 2024 it was estimated that only 43% of 167 innovative medicines with central marketing authorisation between 2019 and 2022 reached the indicated populations across 36 EU and European Economic Area countries.[2] Further, the average time from receiving marketing authorisation to patient access ranged from 126 days in Germany to >804 days in Poland, indicating a wide variability across countries.[2]
- In practice, as marketing authorisation deems the treatment to be safe to use, medical professionals can prescribe it to patients. However, until *Step 2* is completed, the treatment is available only for private patients who are willing to pay the full price. As a result, access inequalities based on economic status can represent an additional challenge.
- Such is the case of glucagon-like peptide-1 agonists (GLP-1s), which emerged as targets for glycaemic control in type 2 diabetes (T2D) treatment over 15 years ago. GLP-1s showed later that receptor activation may also lead to significant weight loss by suppressing appetite, or by producing a rapid satiating effect during a meal. Widespread access to this information has led to increasing off-label use for weight management. The main concern with such use has been issues with intermittent supply and ongoing shortages of GLP-1s for patients with T2D.

Methods

- The EMA and the MHRA websites were consulted to identify GLP-1s authorised for treating T2D and weight management.
- Subsequently, the websites of health technology assessment (HTA) bodies in England and Wales (NICE), France (HAS), Scotland (SMC) and Spain (AEMPS) were reviewed to determine the time between EMA and MHRA approval and positive recommendations within their healthcare systems (**Figure 1**).
- Lastly, Embase and Medline were searched for data on off-label use of GLP-1s in European cohorts.

Figure 1. Bodies included in this review



Key: AEMPS – Agencia Española de Medicamentos y Productos Sanitarios; EMA – European Medicines Agency; HAS – Haute Autorité de Santé; MHRA – Medicines and Healthcare products Regulatory Agency; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium.

Objective

- The objective of this review was to estimate patient access to GLP-1s in selected European countries by analysing their availability and off-label use post-market authorisation.

Results

- The EMA and MHRA have approved three classes of GLP-1s for adults with T2D: liraglutide injections (Victoza®), semaglutide (injections [Ozempic®] and tablets [Rybelsus®]) and tirzepatide injections (Mounjaro®). At higher dosages, tirzepatide under the same name (Mounjaro) was later licensed for weight management, while liraglutide and semaglutide were licensed under different brand names for weight management (Saxenda® and Wegovy®, respectively) (**Table 1**).
- The time to expand the EMA label to include weight management was reduced from 6 years (2009-2015) for liraglutide to 4 years (2018-2022) for semaglutide, and most recently to just 2 months (July-September 2022) for tirzepatide (**Table 1**).
- The average time from EMA or MHRA marketing authorisation to positive recommendation by the four HTA bodies is presented in **Table 1**. Of note, the average time from marketing authorisation to availability of GLP-1s in France and Spain (estimated at 345 and 420 days, respectively) was notably below the country-specific averages of 527 days and 661 days, respectively.[2] In contrast, the UK exhibited longer timelines, with reimbursement decisions taking, on average, 830 days in Scotland and 860 days in England and Wales, more than twice the country averages of 368 days and 344 days, respectively.[2]
- The real-world off-label use of GLP-1s in European cohorts was rarely reported in the medical literature, but available evidence suggests that it has increased over time (**Figure 2**). Semaglutide is predominantly used off-label for weight loss; limited evidence exists for liraglutide, while no evidence is available for tirzepatide as it was approved simultaneously for both indications.

Table 1. Time from marketing authorisation to reimbursement decision by European HTA bodies

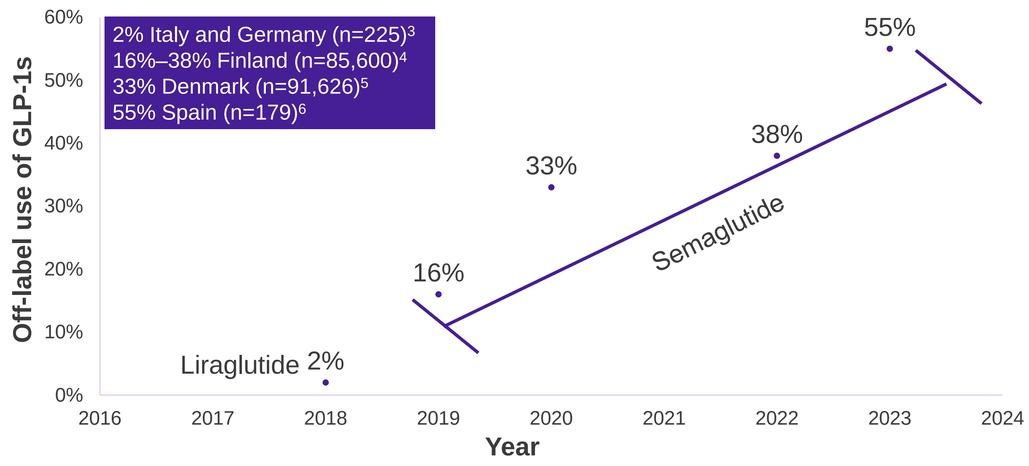
GLP-1 active ingredient	Brand name	EMA			AEMPS		HAS	MHRA[a]	NICE	SMC
		Marketing authorisation	Main indication	Population[b]	Commercial authorisation	Therapeutic positioning report[c]	Opinion	Public assessment report	Technology assessment	Advice
Liraglutide	Victoza®	30/06/2009	T2D	Adults and children >10 yo	0.3	--	5.1	EMA license	15.9	5.2
	Saxenda®	23/03/2015	Weight management[d]	Adults	13.5	--	--	EMA license	68.5	85.5
	Saxenda®	25/03/2021	Weight management[d]	Adults + adolescents >12 yo	--	--	--	EMA license	8.2	--
Semaglutide	Ozempic®	08/02/2018	T2D	Adults	5.8	16.1	12.4	11/01/2022	Awaiting development	35.9
	Rybelsus®	03/04/2020	T2D	Adults	1.1	21.1	17.1	EMA license	--	5.1
	Wegovy®	06/01/2022	Weight management[d]	Adults	6.8	19.6	11.5	24/09/2021	17.5	24.5
	Wegovy®	30/03/2023	Weight management[d]	Adults + adolescents >12 yo	--	--	--	EMA license	3.4	--
	Wegovy®	26/07/2024	Weight management[d] and CVD[e]	Adults[e] + adolescents >12 yo	--	--	--	EMA license	Under development	--
Tirzepatide	Mounjaro®	21/07/2022	T2D	Adults	21.3	14.8	--	26/09/2022	13.0	18.4
	Mounjaro®	15/09/2022	Weight management[d]	Adults	19.5	23.1	--	26/09/2022	Expected publication Dec 2024	20.5
				Average (months)	13.6		11.5	Average (months)	28.7	27.9

Reimbursed without restriction
Reimbursed with restriction
Not recommended
-- Not available

[a] MHRA replaced EMA as regulatory agency for the UK since its exit from the EU.
[b] BMI of 30 or more or BMI between 27 and 30 and weight-related complications such as diabetes, abnormally high levels of fat in the blood, high blood pressure or obstructive sleep apnoea.
[c] AEMPS started producing reports in 2018; prior to that, reimbursement followed EMA's approval.
[d] as an adjunct to healthy nutrition and increased physical activity.
[e] risk reduction of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).

Key: AEMPS – Agencia Española de Medicamentos y Productos Sanitarios; BMI – body mass index; EMA – European Medicines Agency; GLP-1 – glucagon-like peptide 1; HAS – Haute Autorité de Santé; HTA – health technology assessment; MHRA – Medicines & Healthcare products Regulatory Agency; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium; T2D – type 2 diabetes; yo – years old.

Figure 2. Off-label use of GLP-1s reported in European cohorts



Discussion and conclusions

- Despite established efficacy of GLP-1s in weight management through clinical trials and real-world off-label utilisation, obtaining reimbursement for extended indications has been a prolonged process. This delay may have contributed to the existing challenge of intermittent supply and ongoing shortages of GLP-1 medications for patients with T2D.
- Recently, the European Federation of Pharmaceutical Industries and Associations highlighted various factors contributing to delays and unavailability of medicines, including slow regulatory processes, delayed market access assessments, redundant evidence requirements, reimbursement delays, and local formulary decisions.[1] The implementation of the European Regulation on Health Technology Assessment (EU2021/2282, HTAR), set to be applied starting from January 2025, holds promise for establishing a streamlined system for joint clinical assessments and scientific consultations on new medicines in Europe, potentially expediting patient access to innovative treatments.[1] Future assessments will be crucial in evaluating the delivery and impact of these regulatory changes on patient access.

References

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