Innovation in off-patent competitive environment: Key learnings from successes and failures

HPR123

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Objectives

- To **assess the main reasons for success and lack of success in HTA (Health Technology Assessment) and P&MA (Pricing and Market Access)** for new products launching into therapeutic spaces where the standard of care (SoC) is off-patent.
- To **review the types of evidence presented** as well as resulting decisions and P&R (Pricing and Reimbursement) outcomes in France, Germany, England, Canada, and Brazil.
- To **identify key success/unsuccessful stories** of analogues launching in spaces with off-patent SoC and review the payer value drivers and evidence presented.

Hypotheses

- P&MA outcomes for first-launches in indications with off-patent SoC are driven by the incremental clinical benefit in placebo (PBO) or active comparative trials.
- The impact on Quality of Life (QoL), mortality/morbidity, and challenges with trial design may be perceived differently across markets.

Methods and Analysis

Analogue Search Approach:

- Focused on products with first approved indication launched in a single indication (to isolate impact of differentiation).
- Therapeutic area (TA) agnostic, excluding oncology, imaging/diagnosis, and sexual disorders.
- Included small molecules or biologics (Cell & Gene Therapies excluded).
- Approved since 2011 in the EU (considering AMNOG assessments in Germany).
- Targeting all non-oncology products with first approval since 2011 in a single indication where the standard of care was genericised. Priority given to more recent launches.

Data Analysis:

- A targeted analogue analysis and secondary research of multi-country HTA recommendations and feedback, list prices over time, and National reimbursement restrictions using the 'Nuro' business intelligence platform.
- Success measured based on HTA outcomes with multi-indication approvals and launches.
- In-depth analysis of list price changes, price change timings, indication-specific evidence, and public-domain HTA decisions was conducted.
- Payer value was determined by separating products with ASMR III or "Considerable added benefit" (or better) versus those with ASMR VI/V or "no added benefit."

Brand (Analogue)	Indication	Orphan Designation at Launch	Earliest Regulatory Approval	Trial Design	Price Level at Launch (vs. Comparator)	Success/ Unsuccessful Status
Camzyos	Cardiomyopathy	NO	Apr 2022	Placebo-controlled	**Premium** vs. generic Beta blockers, Calcium channel blockers	Successful
Xenpozyme	Acid sphingomyelinase deficiency	YES	June 2022	Placebo-controlled	**Premium** vs. generic Best Supportive Care (BSC)	Successful
Giapreza	Hypotension	NO	Dec 2017	Placebo-controlled	**Discount** vs. generic Vasopressors (norepinephrine, epinephrine)	Unsuccessful
Ravicti	Urea cycle disorders	YES	Feb 2013	Active-controlled	**Discount in EU5** vs. generic Sodium Phenylbutyrate (NaPBA)	Unsuccessful
Aimovig	Preventive Migraine	NO	May 2018	Placebo-controlled	**Premium** vs. generic Triptans, Botox	Unsuccessful
Veltassa	Hyperkalaemia	NO	Oct 2015	Placebo-controlled; Non-comparative	**Premium** vs. generic Sodium bicarbonate, sodium polystyrene sulfonate, insulin	Unsuccessful
Spevigo	Pustular Psoriasis	YES	Sep 2022	Placebo-controlled	**Premium** vs. generic Systemic Corticosteroids	Unsuccessful

Note: Spevigo is categorised as an 'unsuccessful' analogue due to negative HTA outcomes in some markets, despite achieving a price premium as indicated in the table

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Conclusions

- Globally, payers acknowledged a **high unmet need for effective and better-tolerated treatment options** and/or due to disease severity during assessments for several analogues, including Camzyos, Giapreza, Aimovig, Spevigo, Xenpozyme, and Veltassa.
- However, **several products failed to gain positive value assessments in off-patent environments due to various trial design limitations** that were perceived unfavourably by global payers (e.g., Camzyos, Ravicti, Giapreza, Aimovig, and Veltassa).
- Payers consistently **expect incremental clinical benefit across primary endpoints.**

Key Learnings & Trends Identified

A. Incremental Clinical Efficacy on Primary Endpoints & Unmet Need are Paramount

Payer Expectation: Payers expect **incremental clinical benefit across primary endpoints in placebo-controlled or Head-to-Head (H2H) trials**. Improvements in Quality of Life (QoL) and other secondary endpoints are considered "value-adds".

Success Stories:

- **Camzyos** demonstrated **superiority on clinical endpoints as well as QoL** in a placebo-controlled trial, resulting in **favourable HTA outcomes and a price premium** against generic beta blockers and calcium channel blockers.
- **Xenpozyme** showed **clinical efficacy on morbidity endpoints along with significant improvement in QoL** compared to placebo, leading to a **price premium** against generic SoC.

- **High Unmet Need:** Success was limited to a few analogues (e.g., Camzyos, Xenpozyme) supported by **high unmet need and significant clinical/QoL benefit, even without direct impact on mortality/morbidity**. Global payers acknowledged high unmet need for several analogues (Camzyos, Giapreza, Aimovig, Spevigo, Xenpozyme, Veltassa).
  - Examples include lack of efficacious treatment options (Camzyos), need for more effective treatment for non-responders (Giapreza), disease severity (Aimovig, Spevigo), and need for effective and better-tolerated treatments (Xenpozyme, Veltassa).
  - **Orphan products** generally face lesser payer scrutiny due to high unmet needs and low prevalence.

- **Safety Profile:** A **favourable safety profile remains key**; added safety concerns (e.g., Ravicti) resulted in negative payer outcomes in France.

- **Unsuccessful Outcomes:**
  - **Giapreza** (partial clinical efficacy) and **Ravicti** (non-inferior efficacy in active-controlled trials) faced **unfavourable P&MA outcomes**, exacerbated by a **lack of data on QoL** for both, and safety concerns for Ravicti.

B. Issues with Trial Design May Pose Significant Challenges in P&MA Outcomes

- **Payer Preferences for Trial Type:**
  - Global payers **prefer Head-to-Head (H2H) trials**.
  - However, global payers (except Germany's G-BA) are **expected to accept placebo-controlled trials if clinical superiority is demonstrated** through payer-accepted endpoints.
  - The **G-BA specifically highlighted the absence of H2H data** in assessments for Aimovig, Giapreza, and Veltassa.

- **Methodological Limitations Perceived Unfavourably:** Global payers highlight concerns over methodological limitations in trial design, which **adversely impacted HTA outcomes**. Common concerns include:
  - **Lack of long-term safety and efficacy data** (e.g., Camzyos).
  - **Limited follow-up or long-term data** (e.g., Ravicti).
  - **Uncertainties regarding the generalisability of clinical trial data** to real-world practice (e.g., Giapreza, Camzyos, Aimovig, Veltassa).
  - **Short-term clinical data** (e.g., 12-weeks for Aimovig, 8-weeks for Veltassa).

- **Impact on Market Access:** Several products, including Camzyos, Ravicti, Giapreza, Aimovig, and Veltassa, faced **negative value assessments due to these perceived trial design limitations**.

- **Best Practice: Trial design should be validated with payers** to avoid major methodological limitations and concerns over the transferability of study results to real practice.

- **Successful Trial Design Example: Xenpozyme's placebo-controlled trial for 52 weeks was acceptable to payers** without any objections or concerns.

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