Navigating the complex landscape of GLP-1 receptor agonists: Barriers, opportunities, and future directions in the Indian pharmaceutical market

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Abstract

This study explores the key obstacles to the adoption of GLP-1 receptor agonists in India, focusing on economic, cultural, and healthcare infrastructure barriers. Economically, GLP-1 receptor agonists are significantly more expensive than traditional antidiabetic medications, which poses a major barrier, particularly for the substantial portion of the Indian population living below the poverty line and the prevalence of out-of-pocket healthcare expenditure. Additionally, the absence of generic versions keeps prices high and limits accessibility. Culturally, Indian patients generally prefer oral medications over injectables, and the injectable nature of GLP-1 receptor agonists deters acceptance due to fear of needles and associated discomfort. Furthermore, many patients rely on traditional medicine practices like Ayurveda and homeopathy, leading to resistance against newer, scientifically advanced treatments. In terms of healthcare infrastructure, rural areas often lack adequate healthcare facilities and specialists who can prescribe and manage GLP-1 receptor agonist therapy, and inadequate infrastructure for cold chain storage affects the availability and stability of these medications. The shortage of endocrinologists and diabetes specialists, especially in rural and semi-urban areas, further results in inadequate guidance and management of complex therapies. This analysis underscores the multifaceted challenges hindering the adoption of GLP-1 receptor agonists in India and emphasizes the need for comprehensive strategies to address these economic, cultural, and infrastructural barriers.

Keywords: Pricing Strategies; Economic Barriers; Cultural Barriers; Efficacy; Affordability

1. Introduction

The global pharmaceutical industry is a dynamic and complex sector, driven by significant profit motives that impact national economic development. Pricing in this industry is determined by the interplay of supply and demand, with several key factors influencing the strategies of global pharmaceutical companies in India:

- **Research and Development**: Significant investments in R&D lead to high-cost drugs aimed at achieving returns during the patent period.
- **Patient-First Model**: Prioritizing patient welfare involves substantial costs for high-quality medications and awareness initiatives.
- **Biosimilars**: The rapid introduction of biosimilars increases market competition and challenges pricing strategies.
- **Market Payment Models**: In India, many patients pay out-of-pocket due to limited insurance coverage, influencing their preference for lower-cost alternatives.
- **Innovative Technology**: Unique technologies in new products result in higher drug costs.
- **Disease Focus**: Drugs for rare diseases face higher cost barriers, while those for common diseases encounter fewer pricing challenges.

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These factors collectively shape the complex pricing strategies of pharmaceutical companies in India.

2. Key Obstacles to GLP-1 Adoption in India

2.1. Economic Barriers

- **High Cost**: GLP-1 receptor agonists are expensive compared to traditional antidiabetic medications. The high cost can be prohibitive for many patients in India, where a significant portion of the population lives below the poverty line. Limited insurance coverage and out-of-pocket healthcare expenditure are common in India, making it difficult for patients to afford these medications (Yang et al., 2021).

- **Lack of Generic Options**: As of now, GLP-1 receptor agonists are primarily available as branded medications. The absence of generic versions keeps prices high, limiting accessibility for a broader population (Alhiary et al., 2023).

2.2. Cultural Barriers

- **Preference for Oral Medications**: Indian patients generally prefer oral medications over injectables. GLP-1 receptor agonists are typically administered via injection, which can deter patients from accepting this treatment option. Fear of needles and discomfort associated with injections can reduce compliance and acceptance.

- **Traditional Medicine Practices**: Many patients in India rely on traditional medicine practices like Ayurveda and homeopathy. This preference can lead to resistance against adopting newer, more scientifically advanced treatments like GLP-1 receptor agonists.

2.3. Healthcare Infrastructure Barriers

- **Limited Access to Healthcare Facilities**: Rural areas in India often have limited access to healthcare facilities and specialists who can prescribe and manage GLP-1 receptor agonist therapy. Inadequate infrastructure for cold chain storage can affect the availability and stability of these medications (Eberly & Yang, 2021).

- **Shortage of Trained Healthcare Professionals**: There is a shortage of endocrinologists and diabetes specialists in India, particularly in rural and semi-urban areas. This can result in inadequate guidance and management of complex therapies like GLP-1 receptor agonists.

2.4. Upcoming GLP-1 in Indian Market & Current Unmet Needs for GLP-1 Data

GLP-1 agonist drugs transformed the weight loss and diabetes landscape in 2023, propelled by robust clinical trial results and a surge in endorsements from celebrities and influencers. While PD-1 antagonist drugs currently reign as the top-selling drug class, this status quo is poised for a shift. The ascent of GLP-1 agonists is anticipated to surpass PD-1 antagonists as the leading drugs on the market in 2024 (GlobalData, 2023).

Glucagon-like peptide 1 receptor (GLP-1R) is a GPCR drug target found in the pancreas and on neurons of the brain. GLP-1 agonists work by promoting insulin secretion, which helps maintain blood sugar levels among type 2 diabetics. GLP-1 agonists have also demonstrated the ability to promote weight loss by reducing appetite and delaying gastric emptying, leading to reduced food intake useful for people with obesity.

Looking ahead, the GLP-1 agonist market is poised for robust growth, anticipating a 19.2% compound annual growth rate (CAGR) from 2023 to 2029, reaching a substantial market size of $105 billion in 2029. In contrast, the PD-1 antagonist market forecasts a slower growth rate, projecting a 4.7% CAGR and a market size of $51 billion in 2029, nearly half of the GLP-1 agonist market.

The pharma landscape is undergoing a transformative shift, as GLP-1 agonists are poised to surpass PD-1 antagonists as the best-selling drugs from 2024 onward. This shift could reflect a changing demand away from oncology toward addressing metabolic disorders.

Leading the charge in the GLP-1 market are five key drugs: Mounjaro, Ozempic, Wegovy, Cagrisema, and Rybelsus, which are forecast to capture 83% of the GLP-1 agonist market by 2029. Eli Lilly's Mounjaro is predicted to lead in sales, generating an impressive $33.4 billion annually by 2029. However, Novo Nordisk is expected to emerge as the leading company, having a large portfolio of GLP-1 drugs, and is expected to capture 55% of the market share in 2029.
3. Remaining Unmet Needs

Though the value proposition of on-market GLP-1 and dual-agonists is strong, several key unmet needs still exist for incretin mimetics across diabetes and obesity, namely:

- Improved efficacy,
- Better tolerability,
- More convenient options/alternative routes, and
- Improved access and affordability.

3.1. Efficacy

Currently approved incretin mimetics are viewed as highly efficacious across diabetes and obesity. Unmet needs for better A1C control and additional weight loss still exist, but the bar is continuously being raised. Manufacturers are seeking to improve efficacy by developing new dual- and tri-agonists, studying combinations, and offering more potent doses. The dual- and tri-agonist approach is attracting attention due to Mounjaro’s success, and recent data for one of Lilly’s pipeline products – retartutide – are promising.

Retartutide is a subcutaneously injected tri-agonist (GLP-1/GIP/glucagon receptor) that demonstrated unprecedented levels of weight loss in a relatively short period of time. In a phase 2 obesity trial, the highest dose led to participants losing an average of 24.2% of their body weight over 48 weeks (a secondary endpoint). For reference, currently approved products offer around ~15–20% weight loss over a similar time period. A number of other manufacturers are developing dual- and tri-agonists (e.g., Amgen, Carmot, Zealand), setting the stage for a competitive market.

Beyond improvements in weight loss, increasing evidence is mounting of cardiovascular benefits of GLP-1s. Liraglutide, semaglutide, and dulaglutide have demonstrated cardiovascular benefits, and Wegovy recently added to this evidence base: in the SELECT trial, patients on Wegovy had a 20% lower incidence of heart attack, stroke, or death from heart disease compared to those on a placebo.

Combination approaches are also gaining traction in clinical development as a potential means to improve efficacy and address risk factors/comorbidities. For example, in November 2023 Novo announced a head-to-head phase obesity 3 trial (REDEFINE 4) evaluating CagriSema (fixed-dose combination of Wegovy and cagrilintide) against Lilly’s dual-agonist Zepbound. Novo is not alone in investing in combination approaches: in AstraZeneca’s 2023 announcement of its acquisition of Eccogene’s GLP-1 program, the manufacturer noted that they intend to combine the GLP-1 asset with other products in their portfolio (e.g., Farxiga, baxdrostat) in an effort to address obesity comorbidities (e.g., heart disease, kidney disease, metabolic syndrome).

3.2. Tolerability

While the side effect profile of incretin mimetics is relatively mild (low rates of severe AEs; most common AEs include nausea, vomiting, and diarrhea), room for improvement exists in improving GI tolerability and patient discontinuation due to AEs. For example, rates of nausea in incretin mimetic trials typically range from ~15% to 22% and discontinuation due to AEs range from ~3% to 8%. Opportunity exists for therapies with better tolerability profiles, though it may be difficult for an agent to achieve both enhanced efficacy and tolerability. That being said, different mechanisms may offer different side effect profiles, and it’s possible that future multi-agonists could yield improved tolerability profiles. Additionally, some novel GLP-1s hold promise for improved tolerability, as evidenced by Structure Therapeutics’ phase 2 data for GSBR-1290, which demonstrated encouraging results in terms of AEs and discontinuation rates.

3.3. Convenience/Administration

Oral therapies offer some promise as a more convenient option than the leading injectables. Oral GLP-1 agonists haven’t quite caught on yet, primarily due to (1) issues with absorption, which necessitates higher dosing than injectables and may impact efficacy, and (2) fasting restrictions (must be taken on an empty stomach). If manufacturers are able to develop orals that rival the clinical profile of injectables, the market could be flipped on its head. Companies including Pfizer, Eli Lilly, and Structure Therapeutics are leading the charge in developing novel orals.
3.4. Access and Affordability

Access and affordability challenges are a key factor preventing the GLP-1 market from reaching its peak potential, particularly in obesity where payer coverage is limited. Improvements in access will take time, and require generation of compelling data (e.g., pharmacoeconomics, impact on comorbidities) and savvy commercial strategy. In addition, some manufacturers are employing development strategies that may help address access issues. For example, Lilly is studying orforglipron, a daily oral non-peptide GLP-1 agonist which is easier and less costly to manufacture vs. traditional GLP-1 agonists. This has potential to alleviate supply shortages currently plaguing the class, and may provide an opportunity for Lilly to bring a lower-cost option to market, though Lilly's pricing strategy for orforglipron is unknown and likely to be dependent upon clinical results.

Another key development that may support access and affordability is the impending availability of generic liraglutide, which is expected to hit the market in the next 1-2 years. Generic liraglutide adoption may be aided by a lower price and potentially broader market access, but will be hindered by the need for daily injections.

3.5. How to Win in Diabetes and Obesity

The high volume of new entrants is likely to fragment the market moving forward. The massive size and heterogeneity of the diabetes and obesity patient populations offer ample opportunity for a range of products to simultaneously succeed. Manufacturers seeking to win in this space should consider how to address the following success factors:

3.6. Determine Whether to Go Broad or Target a Niche

Going broad has been an effective strategy to date, but this may change as the market fractures. To successfully employ an all-comers strategy moving forward, manufacturers need to ensure products have strong clinical and/or non-clinical differentiation, a robust data package that addresses a range of patient types and comorbidities, and well-funded physician and patient-facing marketing campaigns.

Creating niches to occupy will become increasingly important, especially for new players. This requires carefully designed clinical trials that account for commercial dynamics, as well as pre-launch disease education to prime market understanding regarding where new therapies fit in the treatment paradigm. For example, niches may be created by addressing specific unmet needs in certain patient types (e.g., patients who prefer not to inject, or who failed prior lines of GLP-1s), or by addressing specific access issues (e.g., developing a lower-cost option, securing broader payer coverage).

3.7. Generate Data That Addresses Unmet Needs in Diabetes and Obesity

Generating compelling data on comorbidities of diabetes and obesity, including cardiovascular and kidney outcomes, is critical to effectively competing with incumbents. Additionally, developing products with unique benefits that differentiate from the pack and address stakeholder needs may provide a path to success: for example, novel routes of administration, simplified titration schedules, or improved GI tolerability profiles.

Manufacturers relying solely on efficacy improvements to differentiate should be aware that in T2DM, current therapies are perceived to be efficacious enough to address the needs of many patients. Therapies that offer better efficacy could be saved for sicker diabetic patients. Therapies with improved efficacy would ideally not come at the cost of compromised tolerability, especially considering that patient discontinuation due to AEs is an important factor in physician decision-making in this space.

3.8. Deeply Understand Physician and Payer Dynamics, and Build Strategy Accordingly

Understanding the differences between primary care provider versus endocrinologist perceptions and prescribing behaviors (e.g., class preferences, route of administration preferences, etc.) is foundational to developing strategies that account for stakeholder-specific nuances (Lepkowski, Hurley, & Sadhu, 2021). Likewise, understanding payer dynamics and patient affordability, and building strategies that remove access obstacles for target customers (e.g., co-pay and cash pay assistance programs that enable affordability to more patients) are important to support the realization of the full potential of this market, especially considering the economic demographics of diabetes and obesity patients.
4. Opportunities Outside of Diabetes and Obesity

4.1. Additional Indications for Exploration

As new companies look to enter the incretin mimetic space, and existing players seek to expand their portfolios, it’s increasingly important to look beyond diabetes and obesity. The diabetes and obesity markets are massive, but are also intensely competitive and rapidly evolving.

As mentioned earlier, NASH is an area that has attracted a high level of manufacturer attention, as the liver disease is associated with metabolic syndrome and represents an area of large commercial opportunity with significant unmet medical need (Gores & Kirstie, 2023). Other therapeutic areas that are being heavily studied include kidney disease and cardiovascular disease, which are often comorbid with obesity and/or type 2 diabetes.

The potential versatility of incretin mimetics will be tested in coming years, with a long list of additional diseases being studied including short bowel syndrome, Alzheimer's disease, Parkinson's disease, and diabetic eye disease, just to name a few. These less crowded indications may offer high risk, high reward pathways for manufacturers who are looking to enter the GLP-1 arena without needing to fight for space in the competitive diabetes or obesity markets.

Yet to be explored disease areas that may soon attract interest include alcohol use disorder, other addictive disorders, and even oncology. Studies in rodents and primates have signaled that GLP-1 agonists may drive a reduction in intake of alcohol and drugs of abuse, and clinical trials have been initiated to investigate whether preclinical findings can be translated to humans. There's some scientific rationale supporting this possibility, as it has been hypothesized that GLP-1 agonists may decrease rewarding/reinforcing effects of alcohol and other drugs of abuse.

As companies consider whether to enter new therapeutic areas, they must carefully evaluate each to understand whether the risk/reward equation nets out positively. The opportunities in these indications can be assessed by deploying effective new product planning/opportunity assessment methodologies, including evaluating the following for each potential indication:

- Level of in-class/competitive activity.
- Likelihood of technical and regulatory success (i.e., based on scientific rationale and regulatory precedent).
- Level and nature of unmet needs for new therapies in the disease area of interest.
- Potential for GLP-1s to address these unmet needs.
- Commercial attractiveness of market.
- Potential speed to market.
- Alignment with individual manufacturer portfolio/strategy/capabilities.

5. Conclusion

Incretin mimetics have had an immense and growing impact on patient outcomes. This trend shows little signs of slowing. While the market is highly attractive to manufacturers, companies who aim to successfully commercialize therapies face a steep task: shifting sands necessitate carefully constructed development programs and product strategies.

To be successful, manufacturers should incorporate commercial considerations into early-stage clinical development decision-making and be quick to revise program and portfolio strategies as new data and products emerge. Smart manufacturers will implement iterative mechanisms to gather insights, aim to understand how new data and products impact customer perceptions and behaviors, and develop products and strategies that deliver on clearly defined unmet needs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.
References


GLP-1 agonists set to become the best-selling drugs in 2024: GlobalData." Express Pharma, 2024.


Access and affordability challenges are a key factor preventing the GLP-1 market from reaching its peak potential, particularly in obesity where payer coverage is limited. Improvements in access will take time, and require generation of compelling data." Express Pharma, 2024.