WebLog Journal of Pharmacology and Therapeutics

Review Article
Published: 11 Jun, 2026

Adverse Drug Reaction Monitoring of Semaglutide in India: Impact of Expanding Formulations and Generic Market Entry

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WebLog Open Access Publications
Article ID : wjpt.2026.f1104
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Abstract

Semaglutide has become a key therapy for the management of Type 2 Diabetes Mellitus and obesity. In India, the rising burden of metabolic diseases has led to a rapid increase in its use. Recently, with the expiry of patent protection, generic semaglutide has been officially introduced in the Indian market, leading to wider accessibility and reduced cost. Multiple pharmaceutical companies are now offering different formulations, including pre-filled pens, multi-dose pens, vials, and oral tablets. While this expansion improves patient access, it also introduces challenges related to drug safety and consistency. Adverse drug reactions (ADRs) associated with semaglutide are mainly gastrointestinal, but serious reactions such as pancreatitis, renal impairment, gallbladder disease, and worsening diabetic retinopathy have also been reported. In India, factors such as polypharmacy, self-medication, off-label use for weight loss, and variability among generic formulations further increase the risk of ADRs. Differences in drug concentration, delivery systems, and excipients among various generic products may result in variability in pharmacokinetics and pharmacodynamics. This can lead to inconsistent therapeutic outcomes and increased risk of adverse effects, especially when patients switch between brands without proper medical supervision.

The Pharmacovigilance Programme of India (PvPI) plays a vital role in monitoring ADRs; however, underreporting remains a major limitation. With the official launch of multiple generic semaglutide products, there is an urgent need to strengthen ADR monitoring systems.

This review highlights the importance of pharmacovigilance in the Indian context, focusing on formulation variability, generic expansion, and patient safety. Continuous monitoring, regulatory vigilance, and healthcare professional awareness are essential to ensure safe use of semaglutide in India.

Keywords: Semaglutide; Adverse Drug Reactions; India; Pharmacovigilance; Generics; GLP-1 Receptor Agonist; Drug Safety

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Received Date: *05 May 2026*
Accepted Date: *09 Jun 2026*
Published Date: *11 Jun 2026*

Citation:
Lakshmi Prasanna T, Aruna T, Brattiya K. Adverse Drug Reaction Monitoring of Semaglutide in India: Impact of Expanding Formulations and Generic Market Entry. WebLog J Pharmacol Ther. wjpt.2026.f1104. https://doi.org/10.5281/zenodo.20951128

Introduction

India has earned the unfortunate title of the "diabetes capital of the world," with over 77 million adults currently living with type 2 diabetes mellitus (T2DM), a figure projected to rise to 134 million by 2045 [9]. The prevalence of obesity has also surged, driven by urbanization, sedentary lifestyles, and dietary transitions, creating a dual epidemic of diabetes and obesity [7]. These conditions significantly elevate the risk of cardiovascular disease, chronic kidney disease, and other metabolic complications [8].

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as a transformative therapy due to its dual benefits: glycemic control and weight reduction. Clinical trials such as SUSTAIN-6 and STEP have demonstrated its efficacy in reducing HbA1c, promoting weight loss, and lowering cardiovascular risk [1, 2]. Following patent expiry, generic versions have entered the Indian market, improving affordability and access. However, increased availability raises concerns about misuse, inappropriate prescribing, and adverse drug reactions (ADRs). Effective

pharmacovigilance is therefore critical to safeguard patient safety.

Pharmacology of Semaglutide

GLP-1 Physiology

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and reduces appetite [3]. These mechanisms collectively improve glycaemic control and promote weight loss.

Mechanism of Action

Semaglutide is a long-acting GLP-1 RA with structural modifications that confer resistance to dipeptidyl peptidase-4 (DPP-4) degradation and extend half-life to ~7 days, enabling once-weekly dosing [4]. Its actions include:

1. Insulinotropic effect: Enhances insulin secretion in a glucose-dependent manner.
2. Glucagon suppression: Reduces hepatic glucose output.
3. Gastrointestinal modulation: Slows gastric emptying, reducing postprandial glucose excursions.
4. Central appetite regulation: Acts on hypothalamic pathways to decrease food intake.

Clinical Benefits

HbA1c reduction of 1.5–2.0% [1].

Weight loss up to 15% in obesity trials [2].

Cardiovascular risk reduction (SUSTAIN-6 trial).

Potential renal protective effects [5].

Indian Market Scenario and Generic Expansion

Patent Expiry and Generic Entry

The expiry of semaglutide's patent has catalysed generic launches by multiple Indian pharmaceutical companies. This has:

1. Increased competition.
2. Reduced prices by 40–60%.
3. Expanded access to middle-income populations.

Available Formulations

1. Injectable pens (pre-filled, multi-dose).
2. Vials for hospital use.
3. Oral tablets (semaglutide co-formulated with absorption enhancers).

Market Challenges

1. Confusion due to multiple brands.
2. Variability in device usability.
3. Patient adherence issues.

Formulation Variability and Clinical Impact

Variability Factors

1. Strength differences (0.25 mg, 0.5 mg, 1 mg).
2. Device design (ease of use, dose accuracy).
3. Stability under Indian climatic conditions.

Clinical Implications

1. Dose errors due to unfamiliar devices.
2. Variable bioavailability in oral formulations.
3. ADR risk from improper storage and administration.

Adverse Drug Reactions (ADRs)

Common ADRs

1. Gastrointestinal: nausea, vomiting, diarrhea, constipation.
2. Injection site reactions.

Serious ADRs

1. Acute pancreatitis [6].
2. Gallbladder disease.
3. Acute kidney injury.
4. Diabetic retinopathy worsening [1].

Indian-Specific Risk Factors

1. Polypharmacy: Common in elderly diabetics.
2. Self-medication: Driven by OTC culture.
3. Off-label use: For weight loss in non-diabetics.
4. Poor storage: Cold-chain challenges in rural areas.
5. Brand switching: Confusion between innovator and generics.

Importance of ADR Monitoring

Pharmacovigilance ensures:

1. Detection of rare ADRs.
2. Guidance for prescribers.
3. Regulatory interventions.

Pharmacovigilance in India

The Pharmacovigilance Programme of India (PvPI), under CDSCO, coordinates ADR monitoring.

Functions

1. Collect ADR reports *via* VigiFlow.
2. Analyse safety signals.
3. Issue regulatory alerts.

Challenges

1. Underreporting (estimated <10% of ADRs reported).
2. Limited awareness among physicians.
3. Infrastructure gaps in rural areas.

Comparative Table: Innovator *vs* Generic

See Table 1.

ADR Reporting Pathway in India

See Figure 1.

Strategies to Improve ADR Monitoring

1. **Awareness Campaigns**

Table 1:

Parameter	Innovator Product	Generic Products
Manufacturing	Standardized	Variable
Delivery device	Pre-filled pen	Pens, vials, tablets
Dose accuracy	High	May vary
Bioavailability	Consistent	Variable
Cost	High	Lower
Stability	Controlled	May vary
ADR risk	Known profile	Uncertain

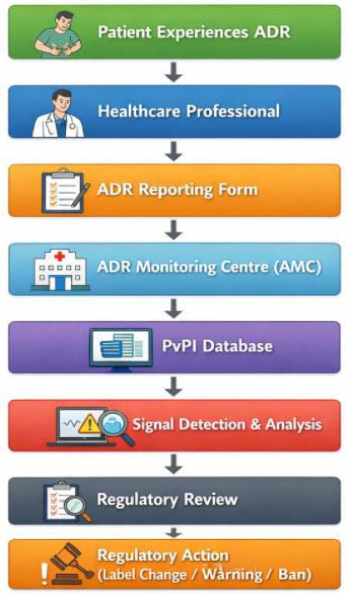

Figure 1:

Conduct regular awareness programs among healthcare professionals and the general public to emphasize the importance of reporting Adverse Drug Reactions (ADRs), including mild and unexpected events.

2. **Training Programs for Healthcare Providers**

Organize continuous medical education (CME) sessions, workshops, and hands-on training to improve the knowledge and skills of doctors, pharmacists, and nurses in identifying and reporting ADRs effectively.

3. **Patient Education Initiatives**

Educate patients on recognizing possible ADRs and encourage them to actively report any unusual symptoms experienced during treatment.

4. **Utilization of PVPI Initiatives**

Maximize the use of tools and resources provided by the Pharmacovigilance Programme of India to enhance ADR reporting, such as:

Toll-free helpline (1800-180-3024) for easy reporting by healthcare professionals and patients.

Mobile applications (e.g., ADR PvPI app) for quick and user-friendly submission of ADRs.

Online reporting forms available on the Indian Pharmacopoeia Commission website.

Email and SMS-based reporting systems to improve accessibility and convenience.

Encouraging widespread adoption of these platforms can significantly strengthen the ADR reporting ecosystem in India.

Discussion

The introduction of generic semaglutide in India represents both an opportunity and a challenge. On one hand, it democratizes access to a highly effective therapy for diabetes and obesity, conditions that are reaching epidemic proportions in the country. On the other hand, the proliferation of multiple formulations and brands increases the risk of dosing errors, misuse, and adverse drug reactions (ADRs).

Several key themes emerge:

1. Clinical Effectiveness *vs.* Real-World Use: While randomized controlled trials (RCTs) demonstrate robust efficacy of semaglutide in glycaemic control and weight reduction [1, 2], real-world outcomes in India may differ due to patient heterogeneity, comorbidities, and inconsistent adherence. Polypharmacy and self-medication practices further complicate outcomes.

2. Formulation Diversity and Patient Confusion: The availability of injectable pens, vials, and oral tablets is beneficial but can lead to confusion among patients and healthcare providers. Device usability, dose titration, and storage requirements vary, increasing the likelihood of administration errors.

3. Pharmacovigilance Gaps: India's Pharmacovigilance Programme (PvPI) has made progress, but underreporting remains a major barrier. Studies suggest that less than 10% of ADRs are reported, limiting the ability to detect rare but serious events such as pancreatitis or diabetic retinopathy worsening [6, 10].

4. Socioeconomic and Cultural Factors: Cost reduction through generics improves access, but affordability does not guarantee safe use. Cultural practices of self-medication, reliance on informal healthcare providers, and limited patient education exacerbate risks. Moreover, cold-chain storage challenges in rural areas may compromise drug stability.

5. Regulatory Oversight: The Central Drugs Standard Control Organization (CDSCO) must balance rapid market entry of generics with stringent quality control. Variability in bioavailability and device accuracy among generics underscores the need for post-marketing surveillance.

6. Global Comparisons: Lessons can be drawn from pharmacovigilance systems in Europe and North America, where digital ADR reporting platforms and mandatory reporting by healthcare professionals have improved safety monitoring. India could adapt similar models to strengthen its system.

7. Ethical Considerations: Off-label use of semaglutide for cosmetic weight loss in non-diabetic individuals raises ethical concerns. Regulatory bodies must ensure that prescribing practices align with evidence-based indications.

Conclusion

Semaglutide has revolutionized the management of type 2 diabetes and obesity, offering dual benefits of glycaemic control

and weight reduction. In India, the entry of generics has expanded access, but it has also introduced variability in formulations, dosing, and patient experiences. The potential for misuse, dosing errors, and ADRs is heightened in a healthcare environment characterized by polypharmacy, self-medication, and limited pharmacovigilance infrastructure.

To ensure safe and effective use, India must prioritize:

1. Strengthening Pharmacovigilance: Enhancing ADR reporting through digital platforms, awareness campaigns, and mandatory reporting mechanisms.

2. Healthcare Professional Training: Equipping providers with knowledge about formulation differences, dosing protocols, and ADR management.

3. Patient Education: Empowering patients with information on proper administration, storage, and recognition of ADRs.

4. Regulatory Vigilance: Ensuring quality control of generics, monitoring bioequivalence, and enforcing labelling standards.

5. Ethical Prescribing: Preventing off-label misuse and promoting evidence-based practice.

Ultimately, semaglutide's promise in India can only be realized if affordability is matched with safety. A robust pharmacovigilance framework, coupled with regulatory oversight and patient-centred education, will be critical in safeguarding public health while harnessing the therapeutic potential of this modern drug.

Acknowledgment

The authors acknowledge National Coordination Centre (NCC) – Pharmacovigilance Programme of India (PVPI) for the technical support provided.

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