

PBRER Safety Summary (Excerpt)

Product: Neurolex (modafinil extended-release)

Reporting Interval: 01 Apr 2025 - 31 Mar 2026

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1. Introduction

This excerpt summarizes key safety updates, signal evaluations, and benefit-risk conclusions for the current periodic safety update reporting interval.

2. Worldwide Exposure

Estimated patient exposure: 1.25 million patient-months (all indications). No significant changes in geographic distribution were observed compared with the previous PBRER.

3. Newly Identified Safety Concerns

3.1 Elevated Blood Pressure Events

Twenty-four spontaneous reports described sustained hypertension following dose escalation to 400 mg/day. Twenty cases resolved after dose reduction.

Review Point 1: Ensure MedDRA coding is harmonized (PT Hypertension vs PT Blood pressure increased) across the case series listed in Appendix 3.

3.2 Sleep Disturbance in Pediatric ADHD Use (Off-label)

Eight reports from Japan and South Korea indicated severe insomnia lasting more than 10 nights. Four cases involved concomitant methylphenidate.

Mitigation: Reinforce label guidance against evening dosing; issue Dear Healthcare Provider letter in affected regions.

4. Ongoing Safety Concerns

- **Serious skin rashes (SCAR):** No confirmed cases; monitoring continues.
- **Abuse potential:** Prescription monitoring data show slight increase (+4%) in early refill requests.

5. Signal Evaluation Summary

Signal	Cases Evaluated	Disposition
Hypertension	24	Requires label update
Insomnia (pediatric off-label)	8	Risk minimization action
Drug interactions (CYP3A4 inhibitors)	12	No new signal

6. Benefit-Risk Assessment

Current benefit-risk balance remains favorable for approved indications. Proposed label changes include addition of hypertension warning in Section 4.4 and clarification of off-label pediatric use.

7. Actions Planned and Taken

1. Submit variation application to include hypertension warning by August 2026.
2. Update Risk Management Plan (RMP) to reflect new pharmacovigilance activities.
3. Launch patient education leaflet emphasizing cardiovascular monitoring.

Review Point 2: Confirm RMP activity table references the latest MedDRA version (26.1) and cross-links to PMS study PV-302 milestone dates.

8. Appendices (Referential)

- Appendix 1: Line listings for hypertension cases.
- Appendix 2: Insomnia case narratives.
- Appendix 3: MedDRA coding reconciliation table.
- Appendix 4: Exposure data methodology.