MADRAC Bulletin

For healthcare professionals only
Volume 58 | Issue 01/2026

In this issue

The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among healthcare professionals.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

Features

Signals

What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

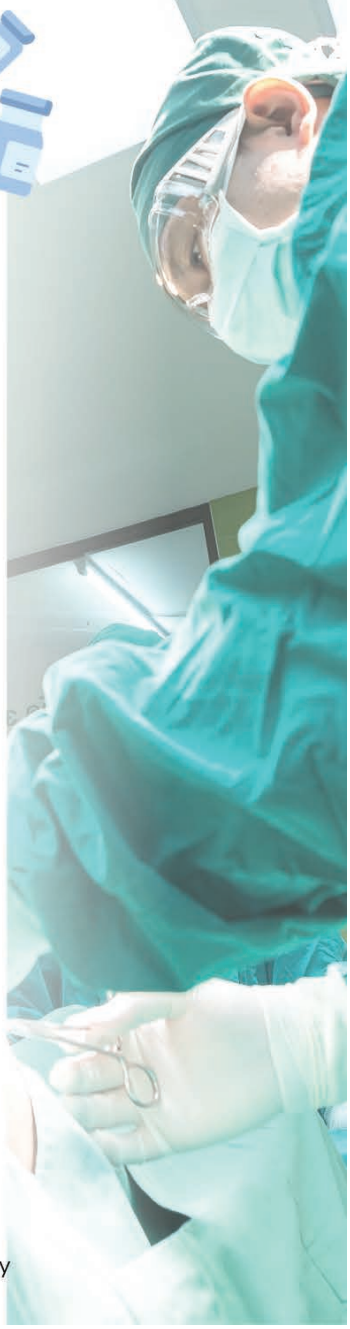
Features

New Infographic!

Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

For healthcare professionals

GLP-1 Receptor Agonists:
Aspiration risk during general anaesthesia or deep sedation



Background

GLP-1 receptor agonists (GLP-1 RAs) such as dulaglutide, liraglutide, lixisenatide, semaglutide, tirzepatide are approved in Malaysia for the management of Type 2 diabetes mellitus. Certain GLP-1 RAs are also indicated for chronic weight management.

Safety concern

- GLP-1 RAs are known to delay gastric emptying. Patients may have residual gastric contents even after routine preoperative fasting.
- Possible increased risk of pulmonary aspiration during general anaesthesia or deep sedation, which can lead to severe complications like aspiration pneumonia.

Advice for Healthcare Professionals

- Ask every patient specifically if they are taking any GLP-1 RA during pre-assessment before surgery.
- Counsel patients to inform their healthcare team that they taking a GLP-1 RA before any procedure requiring anaesthesia or sedation.
- Consider and manage the potential risk of aspiration in patients being treated with GLP-1 RAs

Please report

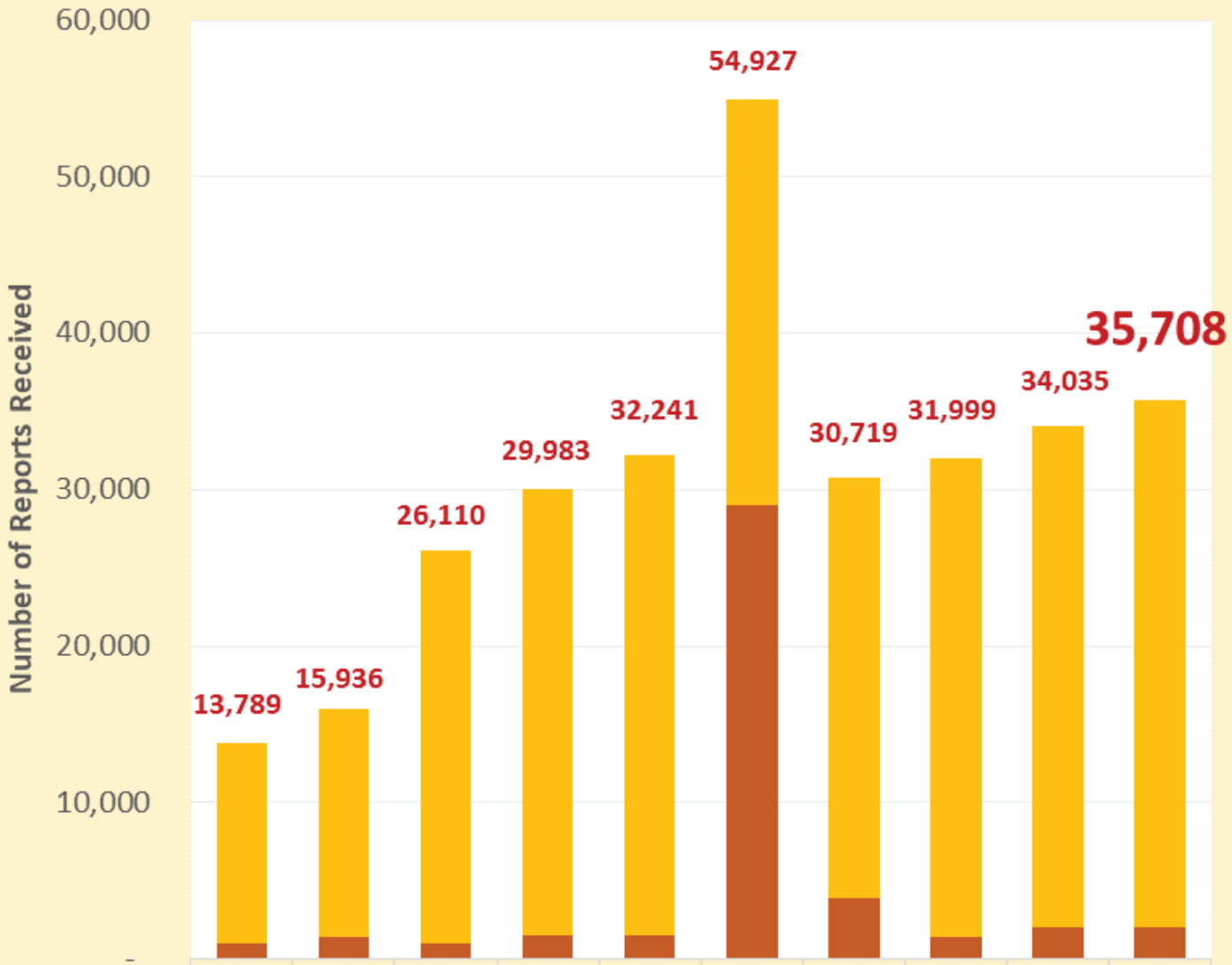
all **adverse events** suspected to be related to the use of GLP-1 RA-containing products to the **NPRA.**

www.npra.gov.my fv@npra.gov.my

Features

Adverse Event Reports Received 2016-2025

In 2025, the NPRA received a total of **35,708** adverse drug reaction (ADR) and adverse event following immunisation (AEFI) reports from across Malaysia, marking a 4.9% increase from the 34,035 reports recorded in 2024 (***Figure 1***).



	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
ADR Reports	12,834	14,590	25,127	28,505	30,746	25,951	26,829	30,584	32,072	33,744
AEFI Reports	955	1,346	983	1,478	1,495	28,976	3,890	1,415	1,963	1,964

Figure 1. Total Adverse Drug Reaction (ADR) and Adverse Event Following Immunisation (AEFI) Reports Received Annually (2016-2025)

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2]. The signals presented below are intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.*

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition[3], refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Lorlatinib and Hepatotoxicity

Written by Lee Sing Chet; Reviewed by Nora Ashikin Mohd Ali

Trigger of Signal [1,2]

During routine signal detection activity, quantitative analysis identified slight disproportionality in the reported terms concerning **liver-related investigations, signs, and symptoms associated with lorlatinib (IC_{025}=0.1)**. As of August 2025, NPRA has received six adverse reaction reports relevant to this safety concern. Reported terms included hepatic function abnormal, hypertransaminasaemia, hyperbilirubinaemia, blood bilirubin increased, aspartate aminotransferase (AST) increased, and alanine aminotransferase (ALT) increased.

Local Reports [1]

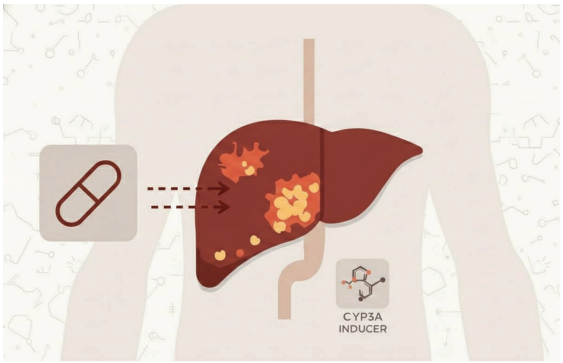
The six reports involved two males and four females aged 42 to 62 years (median age = 58 years). Time-to-onset was reported in two cases, with both events occurring at four weeks. Two cases were classified as 'serious' due to hospitalisation or prolonged hospitalisation, but further details were unavailable due to the absence of a narrative in the reports. Alectinib was co-suspected in one case, while concomitant drugs were not mentioned in the remaining reports. Therefore, it was not possible to assess potential drug-drug interactions with strong CYP3A inducers. Half of the cases were reported as resolved or resolving, whereas the outcomes for the other cases were not specified at the time of reporting.

Background

Lorlatinib is a selective third-generation inhibitor of anaplastic lymphoma kinase (ALK).[3] It is indicated for the treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC).[4]

Concomitant use of lorlatinib and strong cytochrome P450 3A (CYP3A) inducers is known to cause serious hepatotoxicity, specifically elevations in AST and ALT.[4] Such concomitant use is contraindicated, as noted in the local package insert. While the exact biochemical mechanism of hepatotoxicity is still being elucidated, one of the proposed mechanisms includes activation of the pregnane X receptor (PXR), a nuclear hormone receptor that is involved in the regulation of hepatic drug metabolism, by lorlatinib and rifampicin, both of which act as PXR agonists.[5,6]

Notably, even when used in the absence of strong CYP3A inducers, lorlatinib has been associated with AST and ALT elevations.[3] This was observed in the CROWN trial, although the incidence of Grade 3 or higher events was low, and no fatalities have been attributed to these elevations.



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Conclusion & Advice

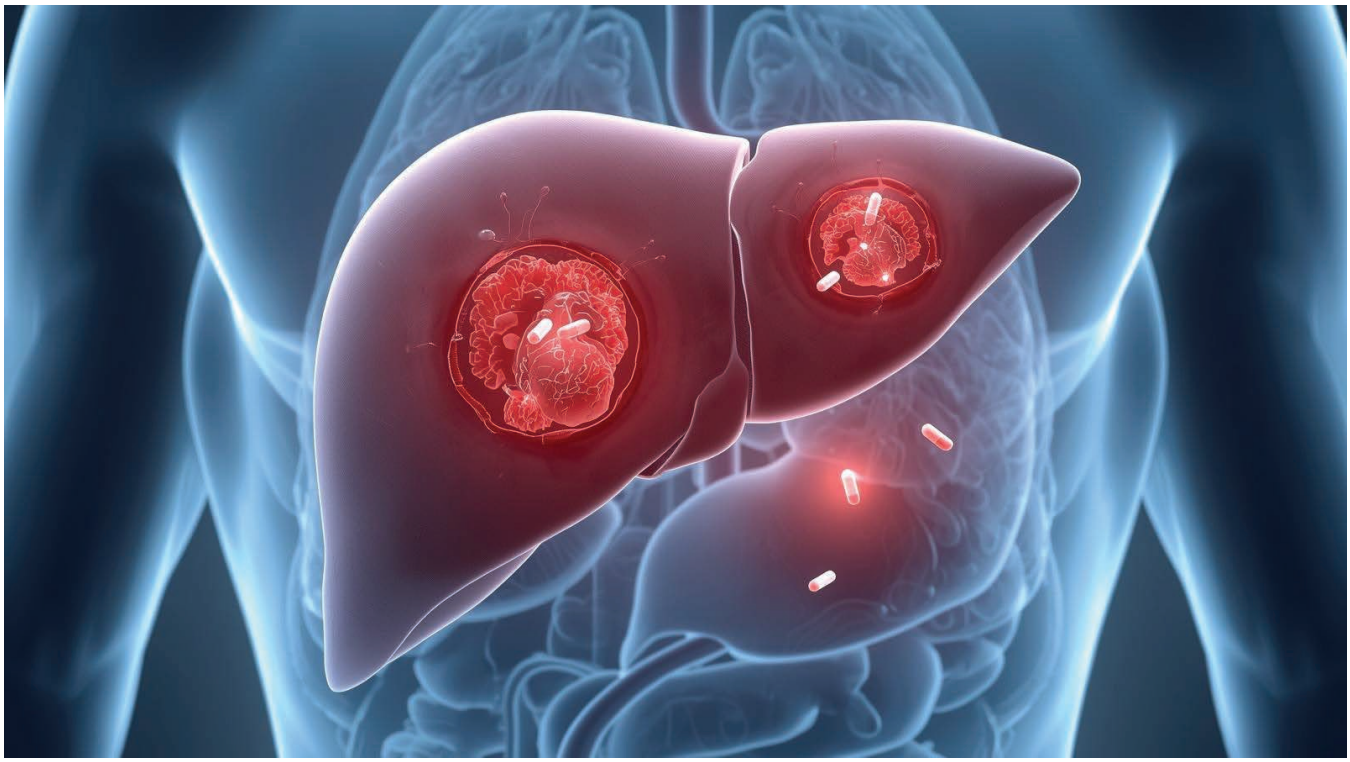
The concomitant use of lorlatinib and strong CYP3A inducers is contraindicated due to the risk of serious hepatotoxicity. When used in the absence of strong CYP3A4 inducers, an association with hepatotoxicity can neither be confirmed nor excluded. Healthcare professionals are encouraged to provide detailed clinical narratives when reporting adverse events. This will improve the characterisation of lorlatinib-associated hepatotoxicity, both with and without concomitant use of strong CYP3A inducers.

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

References:

1. National Pharmaceutical Regulatory Agency (NPRA). The Malaysian National ADR Database (QUEST3+) [Internet]. 2025 [cited 2025 Aug 26]. Available from: https://www.npra.gov.my (access restricted).
2. Uppsala Monitoring Centre (UMC). The WHO Global ICSR Database (VigiBase) [Internet]. 2025 [cited 2025 Aug 26]. Available from: https://www.vigilyze.who-umc.org (access restricted)
3. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, Mazieres J, Kim DW, Mok T, Polli A, Thurm H. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. New England Journal of Medicine. 2020 Nov 19;383(21):2018-29. Available from: https://doi.org/10.1056/NEJMoa2027187
4. National Pharmaceutical Regulatory Agency (NPRA). Lorviqua Film-Coated Tablets (lorlatinib) [Package Insert]. QUEST3+ Product Search. 2024 Dec 30 [cited 2025 Sep 26]. Available from: http://www.npra.gov.my
5. Hu W, Lettiere D, Tse S, Johnson TR, Biddle KE, Thibault S, Palazzi X, Chen J, Pithavala YK, Finkelstein M. Liver toxicity observed with lorlatinib when combined with strong CYP3A inducers: evaluation of cynomolgus monkey as a nonclinical model for assessing the mechanism of combinational toxicity. Toxicological Sciences. 2021 Aug 1;182(2):183-94. Available from: https://doi.org/10.1093/toxsci/kfab056
6. Food and Drug Administration (FDA), United States. Lobrena - lorlatinib tablets, for oral use [prescribing information]. Drugs@FDA: FDA-Approved Drugs. 2024 Feb [cited 2025 Aug 26]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm



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What's New

List of Safety Alerts and Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Sulfamethoxazole, Trimethoprim (Cotrimoxazole)	Risk of Circulatory Shock	14-Nov-2025	NPRA.600-1/9/13(76) Jld.1 [15 Jan 2026]
2	Clindamycin	Risk of Oesophagitis and Oesophageal Ulcer		NPRA.600-1/9/13(75) Jld.1 [15 Jan 2026]
3	Prescription Opioid	Risk of Oesophageal Dysfunction	22-Jan-2026	-
4	Garcinia Cambogia and Hydroxycitric Acid	Risk of Hepatotoxicity	27-Jan-2026	-
5	Vitamin B6 (Pyridoxine)	Risk of Peripheral Neuropathy	27-Jan-2026	-
6	Linezolid	Risk of Rhabdomyolysis	10-Feb-2026	NPRA.600-1/9/13(74) Jld.1 [15 Jan 2026]
7	Palbociclib	Risk of Venous Thromboembolism	10-Feb-2026	NPRA.600-1/9/13(73) Jld.1 [15 Jan 2026]

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit **www.npra.gov.my**
2. Report ADR **as Healthcare Professional**

   Download the **ADR manual form** and submit the completed form via email or post:

   fv@npra.gov.my

   Pharmacovigilance Section,
   National Pharmaceutical Regulatory Agency (NPRA),
   Ministry of Health, Malaysia.
   Lot 36, Jalan Prof Diraja Ungku Aziz (Jalan Universiti),
   46200 Petaling Jaya, Selangor, Malaysia.

NPRA Safety Information Mailing List

To join the mailing list:

a) scan the QR code to complete the **subscription form** available on the NPRA website, or

b) send an email with your details to **fv@npra.gov.my**