



Medicines & Healthcare products  
Regulatory Agency

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Our Ref: **FOI2024/00668**

28 November 2024

Dear [REDACTED]

Thank you for your Freedom of Information (Fol) request received on 31 October. You wrote:

*We are currently writing a new protocol for front line stop smoking advisers to improve the support they give to people who smoke and use certain medications, namely -*

- Clozapine
- Olanzapine
- Fluphenazine
- Haloperidol

*We are interested to know of any adverse events related to these medications that are known or suspected of being associated with smoking or change of smoking status (cessation).*

*Ideally - knowing how many deaths, and any adverse events requiring hospitalization, plus adverse events overall over the past 1/ 5 / 10 years + would be very helpful please.*

*Please could you advise if this is something that you can provide, and if any other level of verification or authorisation is required for this request.*

*Many thanks for your support on this. Please do let me know if you know of anything else that would be helpful to support staff working with clients on these medications.*

## MHRA Response

We confirm that we hold the information you have requested and provide it below.

As per your request, we have searched for all spontaneous suspected UK Adverse Drug Reaction (ADR) reports up to and including 27<sup>th</sup> November 2024 for the substances clozapine, olanzapine, fluphenazine, and haloperidol, where the patient's reported past medical history contained a smoking related term.

The MHRA code all reported reactions and past medical history terms within suspected ADR reports using the Medical Dictionary for Regulatory Activities (MedDRA). There are five levels to the MedDRA hierarchy, arranged from very specific to very general. MedDRA maps the most specific Lower-Level Terms (LLTs) to Preferred Terms (PTs), to Higher Level Terms

(HLTs), to Higher Level Group Terms (HLGTs) and finally to a System Organ Class (SOC). A list of PTs were chosen to conduct the search you requested concerning smoking, which included: Tobacco user, Ex-tobacco user, Smoking cessation therapy, Amblyopia tobacco, and Nicotinic stomatitis.

Please note that past medical history is an optional field and as such is not always provided. Therefore, there may be additional cases where the patient had a past medical history related to smoking, but this is not possible to determine. In addition, where a past medical history term is provided in the patient's past medical history this does not necessarily mean it is related to the adverse events. The time frame in which these reported history events occurred in relation to the adverse reactions or whether the reported history event is still ongoing is also rarely reported.

Please find attached Annex A containing Tables 1-4 for clozapine, olanzapine, fluphenazine and haloperidol, respectively with a past patient medical history of smoking, which contain the total number of spontaneous suspected UK Adverse Drug Reaction (ADR) reports received in the last 10 years including those with a fatal outcome and where the patient was hospitalised.

Please note, Yellow Card data for clozapine is subject to reporting bias which results in an unusually high number of reports compared to other medicines. This is because people treated with clozapine in the UK are required to undergo weekly, 2- weekly or monthly blood monitoring and are monitored more closely in clinical practice than patients receiving most other medicines. This in turn increases the likelihood that adverse reactions, as well as co-incident medical events, are detected and reported to us.

When considering the provided spontaneous ADR data, it is also important to be aware of the following points:

- A reported reaction does not necessarily mean it has been caused by the drug, only that the reporter had a suspicion it may have. The fact that symptoms occur after use of a drug, and are reported via the Yellow Card scheme, does not in itself mean that they are proven to have been caused by the drug. Underlying or concurrent illnesses may be responsible and such events can also be coincidental.
- It is also important to note that the number of reports received via the Yellow Card scheme does not directly equate to the number of people who suffer adverse reactions and therefore cannot be used to determine the incidence of a reaction. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, the extent of use of a particular drug, and may be stimulated by promotion and publicity about a drug. Reporting tends to be highest for newly introduced medicines during the first one to two years on the market and then falls over time. Please also note that the patient medical history field is not always filled out by the reporter. For these reasons the data should not be used as a basis for determining incidence of side effects.

If you have any queries about this letter, please contact us quoting the reference number above.

Yours sincerely,

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If you are not happy with this response you may request an internal review by e-mailing [foi.request@mhra.gov.uk](mailto:foi.request@mhra.gov.uk) or by writing to: MHRA Central Freedom of Information Team, 10 South, Colonnade, Canary Wharf, London, E14 4PU

Any request for an internal review must be received by us within 40 working days of the date of this letter. Please note we are not obliged to provide a review if it is requested after more than 40 working days.

If you are not content with the outcome of the internal review, you may apply directly to the Information Commissioner's Office for a decision. Generally, the Commissioner cannot make a decision unless you have exhausted our own complaints procedure. The Information Commissioner can be contacted at: The Information Commissioner's Office, Wycliffe House, Water Lane, Wilmslow, Cheshire SK9 5AF.

Website: [ICO FOI and EIR complaints](#) or telephone 0303 123 1113.

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