04 September 2025
EMADOC-1700519818-2392926

# PRAC List of questions

To be addressed by the marketing authorisation holder(s) for levamisole-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMA/REF/0000293746

INN/active substance: levamisole

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# Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Concerning your levamisole-containing medicinal product(s), please provide:

a) information on the type of marketing authorisation(s), marketing status, prescription status, approved indication(s), pharmaceutical form(s) and strength(s), and dosing regimen, by EU/EEA Member State and non-EU/EEA countries (see Annex). Where applicable, clearly indicate for which EU/EEA member state a specifically dedicated presentation has been granted in a particular indication;

b) figures on sales and patient exposure by medicinal product, approved indication, and age by EU/EEA member states and non-EU/EEA countries (see Annex). If available, estimation of patient exposure in line with established clinical guidelines but outside the approved indication(s) should also be provided, as well as information on patient exposure with single or multiple doses;

c) information included in the summary of product characteristics (SmPC) and package leaflet (PL) regarding the risk of leukoencephalopathy or related central nervous system (CNS) effects, as applicable. Please highlight the main differences between the product information (PI) in the different EU/EEA member states (see Annex);

d) information about the use of the medicinal product(s) in compassionate use programmes or other similar programmes by EU/EEA Member States, as applicable.

Question 2

Please provide a detailed analysis of all available data, including non-clinical data, clinical trials data (both MAH-sponsored and non-sponsored studies, including data from clinical trials sponsored by a partner company, if available), pharmaco-epidemiological studies, literature and post-marketing case reports on leukoencephalopathy and CNS demyelination following levamisole use (where levamisole is the suspected or interacting drug). The search criteria should be clearly stated.

The review of case reports should:

- be performed by using at least the Standardised MedDRA Query (SMQ) *demyelination* (broad) and SMQ *noninfectious encephalopathy/delirium* (broad) as search criteria for retrieving relevant cases from MAHs' databases and EudraVigilance. Causality assessment for these case reports should be performed using the WHO-UMC scoring system;
- include information on patient age and sex, indication (clearly state if the product was used in the approved indication, off-label use, misuse or accidental exposure), duration and dosing regimen (e.g. single or multiple doses, total dose), time to onset, medical history, concomitant medications, relevant investigations performed (e.g. MRI results), seriousness, outcome, dechallenge/rechallenge, along with a short narrative for each identified case.

In addition, provide a discussion on whether any differences in seriousness, outcomes and potential risk factors can be identified between cases involving levamisole used in approved indication(s) and those reported in the context of off label use, misuse or accidental exposure.

Question 3

Based on the review of all available data, please discuss the potential mechanisms underlying levamisole-induced leukoencephalopathy and CNS demyelination. In addition, provide a discussion on whether differences in terms of pathophysiological mechanisms of leukoencephalopathy and demyelinating events may exist across indications or conditions of use, including off label use, misuse or accidental exposure.

Question 4

Please discuss possible risk factors for leukoencephalopathy following levamisole use based on the review of relevant and available data.

Question 5

Please provide evidence of the therapeutic benefit of levamisole-containing medicinal product(s) for each approved indication in the EU/EEA. When applicable, this information should be stratified by age group (children and adults) and dosing regimen.

Question 6

Please provide a critical appraisal of the impact of leukoencephalopathy and CNS demyelination on the benefit-risk balance of your medicinal product(s) in the approved indication(s) in the EU/EEA. This should specifically address aspects relating to age (adults and children), dose and duration of treatment (in case of multiple doses).

Question 7

Please provide details of any specific measures, other than measures included in the SmPC and package leaflet, which have already been taken to minimise the risk(s) of leukoencephalopathy and CNS demyelination of levamisole-containing medicinal product(s) and comment on the impact of such measures.

Question 8

Please provide proposals and justifications together with supportive evidence for further measures to minimise the risk(s) of leukoencephalopathy and CNS demyelination which may improve the benefit-risk balance of levamisole–containing medicinal product(s). Please discuss their feasibility and how their effectiveness should be monitored.

## Annex

Question 1

a)

| EU/EEA member state / non-EU/EEA country | INN | Product name | Type of marketing authorisation | Marketing status | Prescription status (POM/OTC) | Indications | Pharmaceutical forms and strengths | Dosing regimen |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

b)

| EU/EEA member State / non-EU/EEA country | INN | Product name | Indication | Age | Estimated sales | Estimated patient exposure[1] |
|---|---|---|---|---|---|---|
| | | | | | | |

[1] Expressed in patient years and stratified by EU/EEA member state and non-EU/EEA country, by indication and by age (children and adults). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

c)

| **Product Information**[2] | **SmPC** | **PL** | **Main differences in SmPCs/PLs between the different EU/EEA member states** |
|---|---|---|---|
| Therapeutic indication | | | |
| Posology and method of administration | | | |
| Contraindications | | | |
| Special warnings and precautions for use | | | |
| Effects on ability to drive and use machines | | | |
| Undesirable effects | | | |
| Overdose | | | |

[2] Additional row(s) should be added as needed when information on the risks of leukoencephalopathy/CNS events is included in other PI sections.