**NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC**

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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Romania:

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| Product Name(s) in the Referring Member State, if applicable | Levamisol Arena |
| Active substance(s) | Levamisole |
| Pharmaceutical form(s) | All |
| Strength(s) | All |
| Route(s) of Administration | All |
| Marketing Authorisation Holder in the referring Member State | Arena Group S.A. |

**Background**

Levamisole is an imidazothiazole derivative, authorised as a fast-acting anthelminthic agent. The International Birth Date of levamisole hydrochloride is April 1966 based on first approval in Brazil. The first European authorisation date is considered to be 14 June 1966. Currently, at the EU level, levamisole-containing medicinal products are authorised in Hungary, Lithuania, Latvia and Romania.

Levamisole is indicated in the above Member States for the treatment of infections with some or all of the following worm species: *Ascaris lumbricoides*, *Necator americanus*, *Ancylostoma duodenale, Strongyloides stercoralis, Trichostrongylus colubriformis*. It acts by paralyzing the worm's musculature within seconds of contact by acting on nematode nerve ganglia. Unable to maintain their position, the worms are expelled by normal peristaltic movement, usually within 24 hours of levamisole administration. Although it is certain that levamisole primarily influences the neuromuscular system of nematodes, it is possible that in some helminths the

inhibition of the fumarate reductase system also contributes to the anthelmintic efficacy of levamisole.

Levamisole-containing medicinal products are available as tablets for oral use with strengths of 50 mg and 150 mg and are recommended for use in a single dose, for adults and children. A second standard dose should be given in cases of severe hookworm infection or if the infection is still present three weeks after the treatment.

Levamisole is included in the World Health Organisation (WHO) model list of essential medicines (2023) under the category of intestinal anthelmintics as 150 mg and 50 mg tablets[1] and in the 2023 WHO model list of essential medicines for children as 50 mg tablets[2].

Beyond its authorised use as anthelminthic, due to its immunomodulatory properties, levamisole has also been used to treat recurrent aphthous ulcer[3], paediatric nephrotic syndrome[4] and as adjuvant for chemotherapy in combination with 5-fluorouracil for adenocarcinoma of the colon[5]. Growing evidence indicates that levamisole is misused as cocaine adulterant worldwide[3].

In terms of safety concerns, levamisole use is known to be associated with haematologic abnormalities (agranulocytosis, leukopenia and neutropenia), leukocytoclastic vasculitis and encephalopathy.

As regards haematologic abnormalities (agranulocytosis, leukopenia, neutropenia) and leukocytoclastic vasculitis, no new safety data was identified. Therefore, haematologic abnormalities (agranulocytosis, leukopenia, neutropenia) and leukocytoclastic vasculitis are not further discussed in the next section titled, "Issues to be considered".

In the PSUR submission assessed as part of the first periodic safety update report single assessment (PSUSA) procedure for levamisole (PSUSA/00001845/202501)[6], leukoencephalopathy is listed as a potential risk. Recent data from post-marketing sources and literature added more weight to the risk of leukoencephalopathy, which is discussed in further detail in the next section.

In 1990 FDA approved levamisole as an adjuvant treatment for colon cancer with 5-fluorouracil. Later, in the early 2000s, it was withdrawn from the US market due to safety concerns (serious, long-term complications such as neutropenia, agranulocytosis, vasculitis and demyelinating leukoencephalopathy)[3].

Levamisole was also withdrawn from Canada in 2003 because of side effects including agranulocytosis, vasculitis and leukoencephalopathy[7].

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1 https://iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf

2 https://iris.who.int/bitstream/handle/10665/371091/WHO-MHP-HPS-EML-2023.03-eng.pdf

3 Luan Côrtes, Silas Santana, Thiago Gonçalves Fukuda, Aroldo Bacellar, Central nervous system demyelination following isolated levamisole use: Case report and systematic review. Neuroimmunology Reports, 2022

4 Executive summary of the KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children, Floege Jürgen et al. Kidney International, Volume 107, Issue 5, 806 - 808; https://doi.org/10.1016/j.kint.2024.11.006

5 Zakharova M. et al., 2022 Levamisole-Induced Leukoencephalopathy in Russia: Analysis of 30 Cases. Current Drug Safety. 2022;17(4):319-326

6 IRIS case number: EMA/PSUR/0000268962, data lock point (DLP): 14 January 2025, 10 year-submission frequency

7 Dartevel A. et al., Levamisole-induced vasculopathy: A systematic review, Seminars in Arthritis and Rheumatism, Volume 48, Issue 5, 2019, Pages 921-926, ISSN 0049-0172, https://doi.org/10.1016/j.semarthrit.2018.07.010

In France, the occurrence of serious adverse reactions like agranulocytosis and leukoencephalitis led to the withdrawal of levamisole-based products as anthelmintic from the market in 1998[8].

**Issues to be considered**

*Leukoencephalopathy following levamisole use*

Leukoencephalopathy and CNS demyelination have been reported following levamisole use, either in its authorised indication or off-label use or misuse/accidental exposure[9] [3].

Leukoencephalopathy is a demyelinating disease, which can be long-lasting and debilitating, life threatening or fatal, and must be promptly recognised and treated.

Several possible mechanisms have been discussed in the literature to explain leukoencephalopathy following levamisole use, including an immune-mediated response, a direct toxic action of levamisole, as well as biochemical alterations induced by levamisole. Still, the most plausible mechanism[5] is considered an immune-mediated mechanism of levamisole-induced leukoencephalopathy, based on clinical and magnetic resonance imaging (MRI) improvement observed in patients following treatment with steroids and plasma exchange.

*New safety data*

In the context of the first PSUSA procedure for levamisole (PSUSA/00001845/202501), recent data from post-marketing sources and literature added more weight to the risk of leukoencephalopathy as detailed below.

In the EudraVigilance data analysis system (EVDAS), the Lead Member State (LMS) Romania identified 52 spontaneous cases of leukoencephalopathy reported with levamisole, all serious, of which 2 cases are considered life-threatening and one fatal. In 18 out of the 52 cases, levamisole was administered in the authorised indication.

Of the remaining cases, levamisole was administered for an unapproved indication in 30 cases, misused as cocaine adulterant in 2 cases, and used for an unknown indication in 2 cases.

From the 18 cases reported with levamisole in the authorised indication, further to causality assessment (according to the WHO-UMC system), Romania considers all cases as possibly related to levamisole treatment. In 10 of those cases, it was the only drug administered, in a single dose. Regarding time to onset (TTO), it was reported within 3 months in the majority of cases.

Relevant additional literature articles regarding leukoencephalopathy and CNS demyelination were also identified by Romania, describing leukoencephalopathy cases after levamisole use.

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8 https://pubmed.ncbi.nlm.nih.gov/33180273/

9 Drug-related demyelinating syndromes: understanding risk factors, pathophysiological mechanisms and magnetic resonance imaging findings; Carolina M Rimkus et. al, 2211-0348/© 2021 Elsevier B.V. https://doi.org/10.1016/j.msard.2021.103146

In view of the data assessed from the literature and spontaneous reports on the risk of leukoencephalopathy, Romania considers that a causal relationship between levamisole and leukoencephalopathy is at least a reasonable possibility.

Romania considers at this stage that no risk factors were identified in the literature and spontaneous reports and no risk minimisations measures could be identified in order to reduce the risk of occurrence of severe leukoencephalopathy in patients in the authorised indication.

Romania further considers that due to the severity of leukoencephalopathy, its long-lasting, debilitating and life-threatening potential, the fact that no risk factors for leukoencephalopathy have been identified from the spontaneous reported cases or literature sources reviewed within the recent PSUSA, serious concerns are raised on the benefit risk-balance of levamisole-containing medicinal products in the authorised indication.

*Need for benefit/risk balance review*

Romania considers that the above-mentioned serious concern should be further investigated in an appropriate regulatory procedure.

An EU review of these products would allow for further assessment of the evidence of leukoencephalopathy and CNS demyelination following the use of levamisole, including a potential consultation with relevant experts, and of its impact on the benefit-risk balance of levamisole-containing medicinal products in their authorised indication.

In view of the above and of the necessity to take an action at EU level, Romania considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed Date 28.08.2025

p. p. PRESIDENT

Elena Valeria BRODEA [redacted]

VICE-PRESIDENT