Annex II

Scientific conclusions

Scientific conclusions

Levamisole is a synthetic imidazothiazole derivative that acts as a fast-acting anthelminthic. Levamisole acts by paralysing the helminth's musculature within seconds of contact by acting on nematode nerve ganglia. Unable to maintain their position, the helminths are expelled by normal peristaltic movement, usually within 24 hours of levamisole administration.

Levamisole-containing medicinal products are currently authorised as prescription-only medicines in four EU Member States, Hungary, Latvia, Lithuania, and Romania, for the treatment of infections caused by the following gastro-intestinal helminth species: *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis, Trichostrongylus colubriformis* and *Ancylo stoma duodenale* (with the listed helminthic species varying between EU Member States). Helminth infections are among the most common infections worldwide, affecting the poorest and more deprived communities with poor access to clean water, sanitation and hygiene in tropical and subtropical areas, with the highest prevalence reported from sub-Saharan Africa, China, South America and Asia. These infections are usually of mild nature and not life-threatening, with clinical presentation depending on the number of worms harboured. People with infections of light intensity (few worms) are usually asymptomatic. Heavier infections can cause a range of symptoms, from intestinal manifestations (diarrhoea and abdominal pain), malnutrition, general malaise and weakness to impaired growth and physical development.

In the EU, levamisole-containing medicinal products are available as tablets for oral use with strengths of 50 mg and 150 mg. In adults, the recommended posology is usually a single tablet of 150 mg. In EU Member States where levamisole is approved for paediatric use, a single dose of 2.5 mg/kg of body mass is recommended. A second standard dose should be given in cases of severe hookworm (*Necator americanus* and *Ancylostoma duodenale*) infection or if the infection is not resolved after a single administration.

As part of the first periodic safety update report (PSUR) single-assessment (PSUSA) procedure (PSUSA/00001845/202501) for the active substance levamisole, serious cases of leukoencephalopathy following levamisole use, one of which resulted in death were assessed. Leukoencephalopathy had already been identified as a potential risk with levamisole, and the general term 'encephalopathy' is reflected in the product information of levamisole-containing medicinal products. Nonetheless, based on further data from the literature on the risk of leukoencephalopathy and spontaneous reports assessed in the PSUSA procedure, PRAC concluded that a causal relationship between levamisole and leukoencephalopathy was at least a reasonable possibility and that in view of the severity of the risk, its long-lasting, debilitating and potentially life-threatening nature, and the absence of identified risk factors, a thorough review of all available data, which may include consultation with relevant experts, was warranted.

On 28 August 2025, the National Authority of Medicines and Medical Devices of Romania (NAMMDR) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of levamisole-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

The PRAC considered all available data in relation to the safety concern of leukoencephalopathy associated with the use of levamisole-containing products. This included the responses submitted by the marketing authorisation holders in writing, data from clinical trials, from spontaneous reporting and from the literature, non-clinical data, as well as the views expressed by a group of independent experts.

The efficacy of levamisole-containing medicinal products in the authorised indications is considered well-established and was not questioned in this procedure. Efficacy was previously demonstrated and no new efficacy data were identified during this review.

Levamisole-associated leukoencephalopathy is recognised in the medical literature as a severe and impairing disease, that often requires lengthy and difficult differential diagnostics, which may delay the initiation of appropriate treatment and may lead to prolonged recovery or lasting complications.

Available data shows that levamisole-induced leukoencephalopathy has an idiosyncratic nature, i.e., it is not dose-dependent and can occur even after a single low dose. The time-to-onset is usually within 2 and 8 weeks, but longer latency of up to several months has been reported, which also presents a challenge in monitoring of the risk. In a significant number of reports, levamisole was reported as the single suspect product and patients did not have any relevant medical history reported.

Although the event of leukoencephalopathy was resolved in most cases, in several reports, a serious clinical picture was described, treatment and hospitalisation were prolonged, and patients only recovered after several months up to a year. The PRAC noted that life-threatening cases have been reported in post-marketing setting following levamisole use (unknown indication) in a single administration of levamisole at a dose of maximum 150 mg.

The most plausible mechanism for levamisole-induced leukoencephalopathy is considered to be an immune-mediated process. This hypothesis is supported by clinical features and MRI findings, as well as by the documented improvement observed in patients treated with corticosteroids and plasma exchange. This is further supported by the fact that no dose-response relationship has been demonstrated, and lesions may develop days to weeks after exposure (Férrer et. al, 2025[1], Fominykh et al. 2022[2]). According to the literature, evidence from animal models of levamisole neurotoxicity also suggests that the drug induces a harmful immune response to an unknown antigen that culminates in demyelination in predisposed subjects, rather than directly damaging oligodendrocytes (Cortês L. et al 2022[3]).

In conclusion, based on all data reviewed and analysed from post-marketing experience and literature, the PRAC considers that a causal association between levamisole use and leukoencephalopathy is established. This is supported by multiple cases with a plausible temporal relationship (including two well described cases with positive rechallenge), several cases with no alternative aetiologies for leukoencephalopathy and a plausible mechanism implicating an immune-mediated reaction (Fominykh et al, 2022). The PRAC considers that leukoencephalopathy following levamisole use has been well characterised and described, including possible mechanism of occurrence.

Since no risk factors, dose relationship, or clinical pattern could be identified, the PRAC could not identify any measures that would allow healthcare professionals to identify which patients treated with levamisole could be at risk of develop leukoencephalopathy. This aligns with the position of the SAG experts, who concluded that it is not possible to predict which patients are at risk of levamisole-induced leukoencephalopathy. PRAC therefore concluded that any measure aiming at restricting the use of levamisole would not be adequate, as if it would lead to a reduced exposure, patients exposed to levamisole would still be at risk of leukoencephalopathy, which is regarded as serious, unpredictable, and potentially life-threatening, particularly if left untreated. Similarly, given the idiosyncratic nature and rarity of levamisole-induced leukoencephalopathy, PRAC considered that

[1] Férrer JVCC, Machado LS, Júnior LJMGF, Andrade LA, Moraes MPM, Pedroso JL, Barsottini OGP. Chronic levamisole-induced leukoencephalopathy: Uncommon presentation of two cases with adult-onset progressive symptoms. Neuroimmunology Reports 2025; 7.
[2] Férrer JVCC, Machado LS, Júnior LJMGF, Andrade LA, Moraes MPM, Pedroso JL, Barsottini OGP. Chronic levamisole-induced leukoencephalopathy: Uncommon presentation of two cases with adult-onset progressive symptoms. Neuroimmunology Reports 2025; 7.
[3] Côrtes L, Santana S, Fukuda TG, Bacellar A. Central nervous system demyelination following isolated levamisole use: Case report and systematic review, Neuroimmunology Reports 2022; 2.

any measure aiming at increasing awareness of healthcare professionals or patients about this risk would not be effective to reduce the risk of such an event occurring in clinical practice. These conclusions were shared by the SAG experts.

In view of the above, the PRAC concluded that the risk of leukoencephalopathy, a serious and potentially life-threatening neurological disease, outweighs the benefits of levamisole-containing medicinal products in treatment of helminth infections.

Furthermore, the PRAC could not identify conditions which, if fulfilled, would demonstrate a positive benefit-risk balance for levamisole-containing medicinal products in a defined patient population.

Consequently, the PRAC recommended the revocation of the marketing authorisations for levamisole-containing medicinal products.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on levamisole-containing medicinal products.
- The PRAC reviewed the available data in relation to the risk of leukoencephalopathy and CNS demyelination associated with the use of levamisole-containing medicinal products. This included the responses submitted by the marketing authorisation holders in writing, data from clinical trials, spontaneous reporting and literature, non-clinical data, as well as the views expressed by a group of independent experts.
- Based on the data assessed, the PRAC confirmed a causal association between levamisole and leukoencephalopathy, a serious, long-lasting, debilitating, and potentially life-threatening neurologic disease.
- PRAC could not identify risk factors for levamisole-induced leukoencephalopathy and noted that the risk was unpredictable, occurring even after a single dose. The PRAC therefore could not identify any risk minimisation measures that would effectively reduce the risk of leukoencephalopathy.
- The PRAC concluded that the risks of leukoencephalopathy outweigh the benefit of levamisole in the treatment of intestinal helminth infections, which are in most cases of mild nature.
- Further, the PRAC could not identify conditions which, if fulfilled, would demonstrate a positive benefit-risk balance for levamisole-containing medicinal products in a defined patient population.

The Committee, as a consequence, considers that the benefit-risk balance of levamisole-containing products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for levamisole-containing products.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of levamisole-containing medicinal products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the revocation of the marketing authorisations for levamisole-containing medicinal products.