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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

INN/active substance: levamisole

Procedure number: EMA/REF/0000293746

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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.

2. Scientific discussion

2.1. Introduction

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 *Ancylostoma 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.

Beyond its authorised use as anthelminthic, due to its anti-inflammatory and immunomodulatory properties, levamisole has also been used off-label to treat recurrent aphthous ulcer (Cortes et al., 2022), paediatric nephrotic syndrome (KDIGO 2025) and as an adjuvant for chemotherapy in combination with 5-fluorouracil for adenocarcinoma of the colon (Zakharova et al., 2022). No levamisole containing medicines are currently authorised in these indications in the EU. Growing evidence indicates that levamisole is also misused as cocaine adulterant worldwide (Cortes et al.,2022).

As of 31 August 2025, the estimated cumulative exposure to levamisole worldwide was 355,212.37 patient-years, which corresponds to 129,652,513.33 patient treatment courses. However, exposure in the European Economic Area (EEA) only accounts for 10% of the total worldwide exposure. Sales data from 2014 to 2024 indicate a trend of decreasing sales, and consequently a reduction in patient exposure to levamisole across EU countries over this period.

Leukoencephalopathy with demyelinating lesions at central nervous system (CNS) level has been reported following levamisole administration, whether used in its authorised indication, off label, misused or following accidental exposure, and PRAC has previously concluded that a causal relationship between levamisole and leukoencephalopathy was at least a reasonable possibility.

Leukoencephalopathy can be long-lasting, debilitating, and potentially life-threatening, and must be promptly diagnosed and treated. This disease affects the white matter of the brain, resulting in signs and symptoms related to disruption of fibre tracts within the nervous system, depending on the localisation of the lesions.

To further assess this risk and its impact on the benefit-risk balance of levamisole-containing medicinal products, PRAC requested the marketing authorisation holders (MAHs) to provide a detailed analysis of all available data, including clinical trials data, data from the literature and post-marketing case reports on leukoencephalopathy and CNS demyelination following levamisole use, and non-clinical data. The PRAC also consulted a group of independent experts. A summary of the most relevant information is included below.

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

2.2. Data on the risk of leukoencephalopathy

2.2.1. Clinical trials data

One of the concerned MAHs provided data from company-sponsored studies that were conducted since the clinical development of the medicinal product was initiated. From the 13 clinical studies where anthelmintic indication was studied, a total of 6,799 subjects were exposed to levamisole. No serious adverse events were reported in the anthelmintic indication. The serious adverse events occurred in the indications of colon cancer (20/21) and nephrotic syndrome (1/21) and are possibly related to leukoencephalopathy/demyelination. In most cases, limited information was provided, including the exact dosing, and time-to-onset (TTO). In 19 out of 21 reports, the patients were also taking fluorouracil as a part of the protocol. It should be noted that fluorouracil is a confounding factor since leukoencephalopathy is a listed event in section 4.8 of EU SmPC for fluorouracil. The same MAH provided a summary of 14 clinical studies performed by a licence partner in which leukoencephalopathy or demyelination were not reported.

2.2.2. Post marketing safety data

Post-marketing safety cases with preferred terms under Standardised MedDRA Query (SMQ) Demyelination and SMQ non-infectious encephalopathy/delirium reported for levamisole-containing products were provided by one MAH in the context of this procedure. Causality assessment was performed based on the WHO-UMC system for standardised case causality assessment.

The MAH provided an analysis including 177 worldwide cases retrieved from EudraVigilance and from the MAH's safety database through 8 September 2025, reported with preferred terms under the two SMQs mentioned above. Eighty (80) out of the 177 cases originated from literature sources.

The most relevant preferred terms reported included leukoencephalopathy (52), toxic leukoencephalopathy (2), posterior reversible encephalopathy syndrome (2), encephalopathy (10), toxic encephalopathy (2), hypoxic-ischaemic encephalopathy (1), encephalomyelitis (6), acute disseminated encephalomyelitis (3), demyelination (4), progressive multifocal leukoencephalopathy (PML) (5), multiple sclerosis (1), relapsing-remitting multiple sclerosis (1), and delirium (2). Additionally, the following preferred terms were identified and considered relevant: coma (17), confusional state (13), agitation (11), somnolence (9) and muscular weakness (8).

The vast majority of cases (81%, 143/177) were reported by healthcare professionals (HCPs). With respect to geographical distribution, 40% of cases (70/177) occurred in Europe, the same percentage in Commonwealth of Independent States (CIS) & Asia-Pacific, and the remaining 37 cases occurred in rest of the world. A predominance of cases from France (41), Russia (31), and USA (28) was noted. The vast majority of cases (39/41) reported in France were in the context of misuse/accidental exposure (i.e., illicit drug use, cocaine being co-suspect/interacting drug). Cases reported from Russia should be interpreted in the context of the country's higher exposure levels. Finally, cases from the USA were mostly related to off-label use or misuse of levamisole.

Based on indication of use, 19 cases were reported with on-label use, 72 cases with off-label use, 61 cases with misuse/accidental exposure (including cases of illicit drug use), and for 25 cases the indication was unknown/not reported.

Cases reported with off-label use and cases with misuse/accidental exposure at levamisole were considered out of scope for this procedure as levamisole was not used in the approved indication. However, cases that reported use of levamisole in the approved indication and dose (on-label cases) and cases for which the indication was unknown/not reported but in a cumulative dose of maximum 300 mg were considered relevant and analysed in depth in an aggregated manner.

Out of the 177 cases, 159 cases (89,83%) were serious, while 18 cases (10,17%) were non-serious. In a significant number of cases, levamisole was reported as a single suspect product and patients did not have any relevant medical history reported except one case where patient had recent diagnosis of meningism.

Moreover, 9 cases were fatal and 13 cases were considered as life-threatening. Among these reports, 7 fatal and 6 life-threatening cases were indicative of illicit use of levamisole as a cocaine adulterant. The remaining 2 fatal cases referred to off-label use, in doses that exceed the approved ones, both cases being reviewed and assessed as possible cases. However, as levamisole was administered off label, these two cases were considered as being out of scope for this procedure. Regarding the remaining 7 life-threatening cases, 1 was reported in the approved indication, although with limited relevance due to gastrointestinal source of neurological impairment, 3 in off-label use and 3 in unknown indication. Causality for the latter 3 life-threatening cases with levamisole administered in unknown indication was assessed as probable in 1 case and possible in 2 cases. These 3 life-threatening cases include 2 well-described cases reported encephalomyelitis or levamisole-associated/induced acute disseminated

encephalomyelitis (ADEM) with the use of levamisole in a single dose administration (100 and 150 mg, respectively) for an unknown indication (one assessed as probable and the other as possible). Although the indication of levamisole use was not specified in these two cases, the dose regimens were within the recommended dose in the approved indication. No confounder factors were identified in these cases (no co-suspected medication or relevant medical history). For the third case, the life-threatening criteria is questionable as the patient had a quick recovery without any relevant medical intervention, as per case information.

Out of the 177 cases, following the review of cases where levamisole was used in the approved indication and dose, 10 serious cases (1 possible, 9 probable causality) were identified. After the review of cases when levamisole was used in unknown indication but in a cumulative dose of maximum 300 mg, 12 cases (6 possible causality, 4 probable causality, 2 with causality unassessable) were identified. Nine (9) of the 12 cases were serious.

Among the cases where the dosing regimen was provided (99 cases), levamisole was administered in a single dose in 39 cases and in multiple doses in 60 cases. Additionally, from the reports with available information, the overall female-male distribution was comparable (83 vs. 81 cases). However, when reviewing cases with more specific terms close to leukoencephalopathy, the number of cases involving female patients was nearly twice that of male patients (57 vs. 31). Moreover, the incidence of leukoencephalopathy appears to be lower in children than in adults, as only 13 out of 177 reported cases involved infants, children, or adolescents. Age was not specified in 10 cases. Finally, where reported, time-to-onset was within 1 month for the majority of cases (45 cases), followed by onset between 1 and 6 months (9 cases).

With regards to seriousness across age groups, disproportionality in paediatric cases (12) vs. adult cases (141) was noted, with serious cases occurring mostly in adults. Focusing on seriousness by dosing regimen (single vs. multiple), the number of serious cases was higher when levamisole was administered in multiple doses (59) compared with single dose (37). However, dose regimen was not reported for a significant proportion of serious cases (40%). When analysing data regarding seriousness by duration of treatment, it should be noted that a significant proportion (30%) of serious cases were observed when levamisole was administered for 1-2 days, although no information on duration of treatment was available in 36% of cases.

The review identified positive dechallenge in 7 cases and positive rechallenge in 6 cases. Positive rechallenge cases were reported with levamisole administration for colon cancer (2), paediatric nephrosis syndrome (1), prophylaxis (2), and unknown indication (1). Of note, the latter concerns a case (adult male patient) described in the literature (El Kallab et al., 2003) in which the dose regimen was in line with levamisole administration in its approved indication (a first single dose of 150 mg, followed by the same dose two weeks later). This case describes a levamisole-induced encephalopathy supported by clinical, laboratory and imaging data. Time-to-onset was of hours after the second dose and the patient had sequelae on long term, recovering after 4 years. Levamisole was the only suspected drug, and no relevant medical history was reported.

2.2.3. Published literature

The scientific literature was reviewed to identify available evidence related to levamisole-containing medicinal products and the risk of leukoencephalopathy. Of note, different names are used in the medical literature for levamisole-associated leukoencephalopathy, including multifocal inflammatory leukoencephalopathy induced by levamisole, levamisole-induced demyelinating encephalopathy, levamisole-induced multiple inflammatory leukoencephalopathy, levamisole-associated multifocal inflammatory encephalopathy (LAMIE), and levamisole-induced leukoencephalopathy (LILE).

Fominykh V. et al. (2022) conducted a prospective, observational study with the ambulatory service for neurological disorders of two hospitals in Russia. Patients diagnosed with levamisole-associated multifocal inflammatory encephalopathy during the period 2016-2021 were included in the study according to the inclusion and exclusion criteria. Patients included in the study had taken levamisole within 6 months before the onset of neurological symptoms, were 18 years old or older and presented with acute neurological symptoms and magnetic resonance imaging (MRI) consistent with any demyelinating disorder. Patients were excluded if they had positive results of infection or other neurological diagnoses. Levamisole dosage reported varied between 50 mg and 300 mg. Forty-four patients were included in the study with a mean age 41±12.44 years, male:female ratio of 12:31, and follow-up time from 1 year to 5 years. Time-to-onset was 1 day to 17 weeks. The authors noted a high variability of LAMIE. Importantly, this study included 2 cases of positive rechallenge, after repeated levamisole exposure within 3 and 5 years. Additionally, 3 patients converted to multiple sclerosis, which had been described in earlier studies (Lin et al., 2007, Lin et al., 2010). The authors hypothesized that in susceptible patients, levamisole-associated multiple inflammatory encephalopathy can trigger a chronic immune-mediated process at the CNS level. Regarding the two cases with positive rechallenge, in both cases, levamisole was taken the first time for an unknown indication and the second time for prophylaxis. The total dose was not specified, but according to the study authors, it was between 50 and 300 mg (within recommended dose). Both patients had recurrent LAMIE, confirmed by MRI findings. Time-to-onset after the second administration was 3 weeks for one patient and 4 months for the other. No relevant medical history or co-suspected medication were reported. Both cases were assessed with probable causality. According to the information on recovery presented in the article, one patient was discharged after the second LAMIE episode with clinical improvement, but general weakness remained. One year later, neither new MRI lesion nor new symptoms were found. For the other patient, over the next year after the first LAMIE episode, gradual clinical improvement was noted, and a follow-up MRI showed a reduction in the number and size of lesions. After one year the patient recovered completely. The second LAMIE episode occurred 5 years later and needed hospitalisation and intensive treatment with corticosteroids and plasmapheresis. The patient was subsequently discharged with the improvement of symptoms. This is in line with several literature reports describing prolonged treatment and hospitalisation, with patients recovering after several months or up to a year.

The supplementary material of the literature article Fominykh et al. (2022) describes a fatal case of LAMIE with post-mortem autopsy. The case refers to a 31 years-old-man who was hospitalised with a 3-weeks history of behavioural changes and signs of catatonia. The patient had taken levamisole in unknown dose and unknown date in the past. Brain MRI demonstrated multiple cortical and subcortical, white matter and corpus callosum lesions. The patient received corticosteroid therapy and plasmapheresis, but the patient's condition worsened and he became comatose. He was transferred to another hospital and the computed tomography scan (CT) and MRI scan showed cerebral oedema with enlargement and spreading of lesions. The treatment with corticoids and plasmapheresis continued. Three weeks after hospitalisation, recurrent bleeding from a duodenal ulcer developed. Thirty-three (33) days after admission, the patient passed away due to serious somatic pathology and no improvement in coma state.

Another single-centre retrospective study from Russia (Zakharova et al., 2022) included 30 patients diagnosed with levamisole-induced multiple inflammatory leukoencephalopathy, followed between June 2012 and December 2019. In all cases, patients used levamisole as an anthelmintic medication and doses of levamisole did not exceed therapeutic ones (i.e., total dose of 50 to 150 mg). All patients had levamisole exposure from 2 to 8 weeks before symptoms onset, acute or subacute polysymptomatic onset of neurological disturbances, and MRI-confirmed lesions. Of the 30 patients included in the analysis, 19 were females (63,3%) and the mean age of diagnosis was 46,9 years (age range from 23

to 56 years). Time-to-onset was from 2 to 8 weeks from levamisole administration. Constitutional symptoms were observed in 17 patients (57%), including fever, headache, general weakness, and dizziness. Additionally, 14 patients (47%) presented with motor impairment, 13 patients (43%) had dysarthria and 9 patients (30%) showed cognitive impairment. The follow-up was performed at 3 years (10 patients), 5 years (5 patients), 7-9 years (15 patients). According to the information on recovery presented in the article, 18 patients showed mild neurological deficit on the last available follow-up, and 12 patients showed total recovery. Of note, the majority of patients were initially misdiagnosed, 10 with ADEM, 4 with multiple sclerosis, 8 with stroke on admission, 1 with CNS lymphoma, and 1 with a suspect of having a psychiatric disorder. With regards to the differential diagnosis, since no specific marker exists, the authors noted that the most challenging aspect was to differ amongst various immune mediated disorders with brain demyelination process. Importantly, for most patients, the link between neurological demyelinating condition presenting as leukoencephalopathy and levamisole use was revealed after several months after treatment, during the follow-up assessment. The authors concluded that growing evidence suggested that a single administration of levamisole, even in low dose, could potentially lead to severe neurological deficit and the differential diagnosis remained difficult for suspected cases of levamisole-induced multiple inflammatory leukoencephalopathy, which could lead to delayed therapy initiation, and consequently, incomplete recovery.

Cortes et al. (2022) conducted a systematic review of 62 reported cases of CNS demyelination associated with levamisole use in patients without a prior history of demyelinating disorders, based on literature published up to February 2021. Patients mean age was 45.1 ± 13.3 years, and two thirds of them were women. Patients were exposed to variable total doses of levamisole (50 to 13,500 mg) mainly for the treatment of recurrent aphthous ulcers and intestinal parasitic infections. In all patients, brain MRI showed multiple, hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery images characteristic of demyelination in the white matter. Only 4 out of 62 patients underwent brain biopsy, with findings compatible with active demyelination, consistent with an inflammatory leukoencephalopathy and overall similar to those seen in other demyelinating disorders such as multiple sclerosis. The authors of the article concluded that the importance of levamisole discontinuation and avoidance was underscored by one report of recurrence of symptoms and worsening MRI lesions after a drug re-exposure. In addition, the authors stated that failure to promptly diagnose CNS demyelination following levamisole use could lead to an unfavourable outcome, with long-term neurological sequelae.

Two publications describing individual case reports were also identified. Belova et al. (2020) described the case of a 43-year-old female patient who took one dose of levamisole (150 mg) for prevention of helminthiasis. After a few days (not specified) the patient repeated the dose and suddenly developed weakness in her legs and slurred speech. The patient was finally diagnosed with multifocal inflammatory levamisole-induced leukoencephalopathy after more than three years of disease progression, incorrect diagnosis and inadequate treatment. The authors highlighted the importance of awareness among physicians of these risks and the consequences of diagnostic errors and inadequate treatment. Long et al. (2015) described the case of a 42-years-old man with subacute onset of right hemiparesis and mild cognitive impairment after 600 mg levamisole administration, with 30 days prior to the onset of symptoms. The patient was diagnosed with levamisole-induced leukoencephalopathy based on MRI findings, and the treatment consisted of high-dose intravenous corticosteroid therapy. The patient's condition improved within 3 months, with the follow-up MRI showing a decreased size of lesions.

Yan et al. (2013) published a retrospective analysis of the clinical features and MRI findings of 15 patients (5 males and 10 females) with levamisole-induced demyelinating leukoencephalopathy. Time-to-onset was two weeks to two months, with a dose range of 50 to 150 mg. As MRI pattern, all patients demonstrated abnormal brain MRI, with scattered multiple cerebral foci observed in all

patients. Moreover, a retrospective analysis from Xu N. et al. (2009) describes 16 cases of LILE between January 2002 and December 2008 in a Chinese hospital. Two patients used levamisole for recurrent aphthous ulcer with doses and duration of treatment exceeding the recommendation for anthelminthic treatment, and were, therefore, considered not relevant in the context of this review. The remaining 14 cases (5 males and 9 females mean age 36±12 years) refer to patients treated for Ascaris infection with one or two doses of levamisole. Among these, there were 2 cases of paediatric patients, of 14 and 7 years-old and both male, who took 50 mg of levamisole in a single administration. Time-to-onset was 1 to 90 days, with a mean of 26 days. Two patients showed neurological symptoms on the day after initial dose, including one paediatric patient (14 years-old). With respect to clinical features, motor weakness was the most common manifestation (10 patients). Dysphasia or aphasia and cognitive changes (including apathy and memory impairment) were reported in 8 patients (57%), facial palsy, blurred vision in 6 patients (43%), hyperreflexia, urinary incontinence, paraesthesia were reported in 3 patients (21%), and conscious disturbance and seizure in 2 patients (14%). Moreover, the authors noted that based on the MRI findings, LILE could not be distinguished from multiple sclerosis and ADEM and the diagnosis was both dependent on the clinical features and imaging appearances. In relation to recovery, all patients achieved a total or partial clinical remission after high-dose corticosteroid therapy and hyperbaric oxygen therapy. The authors concluded that a single dose of levamisole can induce demyelinating encephalopathy and the early diagnosis depends on clinical features and radiological appearance.

Finally, in a conference paper (Zheng Rong-yuan et al., 1994) consisting of several pharmacoepidemiological studies in China, cases of encephalitis syndrome after levamisole treatment were highlighted, with the onset of symptoms after 1 to 2 months after taking levamisole. Levamisole treatment was identified as a pathogenic risk factor, statistically significant, for the encephalitis syndrome, as well as the female gender, with the difference between genders being statistically significant (p=0,02776).

In addition to the safety data reported in the literature described above, the possible mechanisms to explain leukoencephalopathy following levamisole use have also been discussed in the literature. Although not fully elucidated, the most plausible mechanism for leukoencephalopathy following levamisole use is considered to be immune-mediated, as observed in vivo and in vitro studies (Stevenson et al., 1991; Vandevelde et al., 1978; Spreafico et al., 1975). The hypothesis on immune-mediated mechanism is supported by clinical features and MRI findings, as well as by the documented improvement observed in patients treated with corticosteroids and plasma exchange. Additionally, no dose-response relationship has been demonstrated, and lesions may develop days to weeks after exposure (Férrer et. al., 2025; Fominykh et al., 2022; Vandevelde et al., 1978). Finally, the use of levamisole has been associated with several clinical syndromes, including agranulocytosis, purpuric cutaneous vasculitis, leukoencephalopathy and hypersensitivity reactions. These findings suggest that levamisole can trigger type I and type III hypersensitivity reactions and seems to have a common mechanism in generating the above-mentioned adverse reactions known to be associated with levamisole use (Larocque & Hoffman, 2012).

In conclusion, levamisole does not seem to induce direct neurotoxic effects, and the above-mentioned findings support the possibility of an immune-mediated mechanism of toxicity for CNS demyelination presenting as leukoencephalopathy.

2.3. Discussion on the risk of leukoencephalopathy

Levamisole-associated leukoencephalopathy is described in the literature as a serious neurological complication that affects predominantly the white matter of the brain and to a lesser extent the grey matter of the brain. Damage to the fibre tracts at the CNS level leads to a range of clinical

manifestations, which vary depending on the location of the lesions. Leukoencephalopathy may present with constitutional symptoms (e.g. hyperthermia, malaise, general weakness, nausea, vomiting, headache, dizziness) and neurologic signs and symptoms (most often muscular weakness, language impairment, cognitive dysfunction, and ataxia).

According to the literature reviewed, the most plausible mechanism for levamisole-associated leukoencephalopathy is considered to be an immune-mediated mechanism. 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.

Although the review of the available clinical trial data did not identify any new safety concerns related to the risk of leukoencephalopathy, the analysis of post-marketing safety data identified 159 serious cases associated with the use of levamisole. Further, in a significant number of post-marketing and literature safety cases, levamisole was reported as a single suspect product and patients did not have any relevant medical history reported, except one case where the patient had recent diagnosis of meningism.

The review identified 9 fatal cases of leukoencephalopathy, of which 7 were indicative of illicit use of levamisole as a cocaine adulterant and 2 involved use at doses exceeding those recommended. These cases were therefore considered of limited significance for the evaluation as they refer to off-label use of levamisole. An additional fatal case with leukoencephalopathy following levamisole use was reported in literature, with dose and indication unknown (Fominykh et al., 2022, Supplementary material). In addition to the fatal cases, 13 life-threatening cases were reported, of which 2 relevant cases were identified, reporting encephalomyelitis/ADEM with the use of levamisole in a single dose administration (100 and 150 mg, respectively) for an unknown indication (one assessed as probable and the other as possible). No case reported co-suspected medication, nor any relevant medical history. Although the fatal and life-threatening cases reported post-marketing were not in the authorised indications, the 2 life-threatening cases both reporting encephalomyelitis/ADEM provide support that severe, life-threatening CNS reactions, may occur after a single dose administration of levamisole.

Following the review of cases where levamisole was used in the approved indication and dose, out of the 177 cases, 10 serious cases (1 possible, 9 probable causality) were identified. After the review of cases in which levamisole was used in unknown indication but in a cumulative dose of maximum 300 mg, from the total of 177 cases, 12 cases (6 possible causality, 4 probable causality, 2 with causality unassessable) were identified. Nine (9) of the 12 cases were serious. These cases confirm the serious risk of leukoencephalopathy associated with the administration of levamisole in a cumulative dose of maximum 300 mg.

Furthermore, the cases with positive dechallenge (7 cases) together with the cases with positive rechallenge (6 cases) identified from post-marketing and literature data provide further support a causal association between leukoencephalopathy and levamisole use.

In the majority of the cases reviewed, time-to-onset was within one month, while a smaller number of cases had a time to onset between 1 and 6 months. In the literature, the time to onset varied between 1 day to 3 months in most studies (Côrtes et al., 2022; Zakharova et al., 2021; Xu et al., 2009). Nonetheless, latency was reported as sometimes longer, up to 17 weeks and in very rare cases even a year after exposure (Fominykh et al. 2022).

Possible risk factors were investigated from literature and post-marketing data. A predominance of female patients was noted in some publications (Fominykh et al. 2022, Zakharova et al. 2022, Xu et al 2009, L. Cortes et al. 2022). However, this observation alone does not allow for reliable risk stratification. When considering the totality of post-marketing cases, no imbalance between female/male distribution was observed. However, when reviewing cases with more specific terms close

to leukoencephalopathy, the number of cases in female patients was almost double of those reported in male patients. Furthermore, the incidence of leukoencephalopathy appears to be lower in children than in the adult population, as only 13 out of 177 reported cases involved infants, children, or adolescents. However, context regarding patient exposure in this population is missing and these observations alone do not allow for reliable risk stratification.

Upon analysis of dosing regimen (single vs. multiple), the number of serious post-marketing cases reported was higher when levamisole was administered in multiple doses compared with single dose. However, dose regimen was not reported for a significant proportion of serious cases (40%), and no conclusions can be draw based on this observation. Furthermore, a significant proportion of serious cases were observed when levamisole was administered for 1-2 days, suggesting that the seriousness of the risk of leukoencephalopathy is not proportional with treatment duration with levamisole. Similarly, the seriousness of the risk of leukoencephalopathy does not appear to be dependent on the total dose administered. This is also supported by literature data, where cases of leukoencephlopathy were observed both after one single dose, as well with multiple dosing (Fominykh V. et al. 2022, Luan Cortes et al. 2022, Zakharova et al., 2022, Belova et al. 2020, Yan et al. 2013). In summary, levamisole can induce leukoencephalopathy even after a single low dose of 50 mg in the approved indication, demonstrating that the risk of leukoencephalopathy is not dose dependent (Zakharova et al. 2022; Xu et al. 2009; Fominykh et al. 2022).

According to literature data, levamisole-induced leukoencephalopathy is associated with challenging diagnosis, including clinical symptoms, MRI findings, biological markers, history of levamisole use and excluding other conditions associated with CNS demyelination. Different authors highlighted the potential for misdiagnosis, since cases have been presented where patients were initially misdiagnosed with other conditions such as ADEM, multiple sclerosis and stroke. This lengthy and complex differential diagnosis can postpone the start of adequate treatment and lead to delayed patient recovery or recovery with long term/permanent sequelae. In addition to the foregoing, information about levamisole intake is often missed in the medical history of patients, and the link between neurological symptoms and levamisole intake is often only detected during follow-up assessments, sometimes after several months (Zakharova et al, 2022). This further contributes to misdiagnosis or delayed diagnosis of levamisole-induced leukoencephalopathy.

The prognosis for patients with levamisole-associated leukoencephalopathy was favourable in most cases if adequate treatment is administered, with full or partial recovery (Fominykh et al., 2022; Cortes et al., 2022; Zakharova et al 2022). Nonetheless, recovery was often prolonged, involving long hospitalisations and treatment with corticosteroid therapy (Zakharova et al 2022; Xu et al. 2009). Some patients additionally underwent plasma exchange in cases where steroid therapy alone was ineffective (Zakharova et al., 2022, Fominykh et al., 2022). Moreover, hyperbaric oxygen therapy was noted in the analysis of Xu et al. (2009), and cytostatic therapy was used in patients with severe course of the disease (Fominykh et al., 2022). This is in line with post-marketing experience, where several reports described prolonged treatment and hospitalisation, with patients recovering after several months or up to a year.

To minimise the risk of levamisole-induced leukoencephalopathy, a number of risk minimisation measures were proposed by the MAHs of levamisole-containing products. This included an update of the product information, to restrict the use of levamisole to cases in which no other anthelmintics are available or suitable, and the development of educational material for patients to further inform of the neurological symptoms as well the need to monitor the risk for a period of 8 weeks after drug administration.

The proposal to restrict the indication to diagnostically confirmed cases of helminth infection and to cases when no other anthelminthics are available or suitable was not considered adequate to reduce

the risk of levamisole-induced leukoencephalopathy as this risk is considered unpredictable. In addition, it would only lead to a reduced patient exposure without minimising the risk of leukoencephalopathy occurrence in patients who receive levamisole. This is also the reason why the proposal to contraindicate levamisole in patients with a medical or family history of demyelinating disease, in addition to the fact that this is not supported by any relevant data assessed within the referral procedure. For the cases with a previous episode of levamisole-induced leukoencephalopathy, the proposal is considered reasonable and supported by observed cases of positive rechallenge. However, it would only be effective for a limited number of patients, and it is considered to have a limited impact. For the majority of cases reported, no history of levamisole-induced leukoencephalopathy was observed. Moreover, while the proposal to update the product information to include leukoencephalopathy as an adverse drug reaction and a warning on the risk of leukoencephalopathy, or the proposal to introduce educational material for the patients, could increase awareness of the risk of leukoencephalopathy and reduce the number of the patients exposed to levamisole, it would not reduce the risk in patients exposed to levamisole. Considering that no risk factors have been identified in the current review, no measures could be identified to reduce the risk of leukoencephalopathy. Finally, a proposal was made by the MAH(s) to add some wording in the product information to inform on the increased risk of leukoencephalopathy associated with high doses of levamisole. This proposal was not supported as not in accordance with the data reviewed and the above conclusion that the risk of leukoencephalopathy is not dose dependent.

Overall, the proposed RMMs would not effectively reduce the risk of leukoencephalopathy and are expected to solely decrease exposure due to safety concerns. Based on the information retrieved from literature and spontaneous cases, no patients at increased risk of developing leukoencephalopathy associated with levamisole use can be identified. The risk appears in an idiosyncratic manner and is reported even after a single approved dose.

In conclusion, no risk minimisation measures were found to be appropriate and effective to reduce the risk to an acceptable level, due to complexity of the condition, no clear risk factors and unpredictable nature of the event.

To better characterise the risk, both MAHs proposed to implement a follow-up questionnaire for relevant neurological individual case safety reports (ICSRs) to collect further data on latency, MRI, steroid response and cumulative dose. However, this proposal was considered inadequate in view of the limited levamisole exposure in the EU and low frequency of adverse event reporting.

3. Expert consultation

The PRAC consulted the Scientific Advisory Group (SAG) on vaccines and therapies for infectious diseases with additional experts in neurology to provide their view on levamisole's place in therapy and its medical need for the treatment of helminthic species in the EU/EEA, as well as whether a patient population could be identified for whom levamisole would represent the only therapeutic option.

According to the experts, levamisole plays a very limited and declining role in the treatment of human helminth infections in the EU/EEA. For the helminth species targeted by this drug, there are effective therapeutic alternatives, including benzimidazoles (albendazole, mebendazole), pyrantel, and ivermectin, which are widely used in current clinical practice and recognized as standard treatments, particularly by the WHO. The experts noted that these standard treatments are available in European countries where levamisole is currently marketed. Several experts emphasised that in addition to its neurological side effects, levamisole is associated with significant safety concerns, particularly haematological ones. The experts also noted that there are no specific medical conditions (such as

pregnancy, renal or hepatic insufficiency) in which levamisole could constitute the only therapeutic option. The possibility of intolerance/allergy to all other treatments, which could represent a specific indication for levamisole, was raised but seems highly unlikely. The possibility of using levamisole in the context of helminth resistance to other anthelmintic treatments was also discussed. However, the experts considered this scenario to be very unlikely in humans. Indeed, although reduced efficacy and emerging resistance signals have been reported for some first-line anthelmintics, particularly benzimidazoles, in mass drug administration settings, no widespread, clinically validated resistance has been demonstrated in humans, and effective therapeutic alternatives remain available for all relevant helminth infections in the EU/EEA.

In view of these factors, the SAG concluded that levamisole currently has no place in the treatment of helminth infections in the EU/EEA.

Additionally, the PRAC consulted the SAG on the possibility to identify patients at risk for levamisole-induced leukoencephalopathy and how this risk could be minimised in clinical practice, considering that it has an idiosyncratic nature and it may appear after a single dose.

Given the risk of leukoencephalopathy, the mechanism of which suggests an immune-mediated nature, the experts first pointed out that a history of leukoencephalopathy or acute or chronic demyelination (e.g., multiple sclerosis, optic neuromyelitis) should be considered a contraindication to taking levamisole. The group noted that, in most of the cases identified in this review, there was no relevant medical history, particularly no neurological history such as those mentioned above, in subjects who developed levamisole-induced leukoencephalopathy. The group noted that, although some data suggest a slightly higher frequency of reports in women, this observation does not allow for reliable risk stratification. Age does not appear to be a significant factor either, as cases have been reported in both children and adults. Furthermore, analysis of the cases showed no link between the occurrence of leukoencephalopathy and the dosage or duration of treatment. Finally, given the rarity of the event, the group considered that studying genetic markers of predisposition would be complex to carry out, not to mention that it would be of little relevance given the limited role of levamisole in the treatment of these infections.

Overall, the SAG considers that it is currently impossible to predict which patients are at risk of levamisole-induced leukoencephalopathy, as the experts were unable to identify any risk factors, dose relationship, or clinical pattern. Given this finding, the idiosyncratic nature, and the rarity of levamisole-induced leukoencephalopathy, the SAG has been unable to identify any measures that would effectively minimise the risk of such an event occurring in clinical practice.

4. Benefit-risk balance

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 (SAG on vaccines and therapies for infectious diseases with additional experts in neurology).

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, Fominykh et al. 2022). 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 (Cortes L. et al 2022).

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 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.

5. Risk management

The Committee, having considered the data submitted in the procedure, was of the opinion that no feasible and proportionate risk minimisation measure would reduce the risk to an acceptable level (see section 2.3. for details on the measures reviewed).

5.1. Direct Healthcare Professional Communications and Communication plan (DHPC)

The Committee adopted the wording of a DHPC, to inform healthcare professionals of the conclusions of the review and upcoming unavailability of levamisole-containing medicinal products in the EU due to the risk of leukoencephalopathy. The Committee also agreed on a communication plan.

6. Grounds for 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.

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