**NOTIFICATION TO THE CHMP/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 CHMP made by Ireland:

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| Product Name(s) in the Referring Member State, if applicable | Ipidacrine containing medicinal products |
| Active substance(s) | Ipidacrine |
| Pharmaceutical form(s) | All |
| Strength(s) | All |
| Route(s) of Administration | All |
| Applicant in the referring Member State | AS Grindeks |

**Background**

Ipidacrine is a reversible acetylcholinesterase inhibitor (ACHI). Although its mechanism of action is not fully understood, in addition to enhancing acetylcholine-mediated neurotransmission, it is thought to stimulate impulse transmission in the CNS and neuromuscular synapses by blocking membrane potassium channels. It is also thought to have adrenaline, serotonin, histamine and oxytocin-like effects on smooth muscle. Ipidacrine was first synthesised in 1976 in the USSR.

In 1997, Latvia granted a national marketing authorisation (MA) for the originator product Neiromidin (MAH Olainfarm AS). In 2008, following the accession of Latvia to the European Union (EU), a MA was granted for this product in this Member State in accordance with Article 10a of Directive 2001/83/EC on the basis of well-established use. Neiromidin is currently authorised in Latvia as 20 mg tablets and 5mg/ml and 15mg/ml solution for injections in the treatment of adults with:

- Peripheral nervous system diseases (neuritis, polyneuritis, polyneuropathy, polyradiculoneuropathy, myasthenia gravis and myasthenic syndrome of various aetiology);
- Bulbar palsy and paresis;
- Organic CNS lesions with movement disorders during the recovery period;
- Demyelinating diseases as part of complex therapy;
- Memory disorders of various origins (Alzheimer's disease and other types of senile dementia)*;
- Intestinal atony*.

(* tablets only)

Generic marketing authorisations with Neiromidin designated as the reference medicinal product, have been granted by the following EU/EEA Member States: Bulgaria, Croatia, Hungary, Lithuania, Latvia, Poland, Romania, Slovenia, and Slovakia. In 2023, applications for generic marketing authorisations were submitted under the decentralised procedure (DCP) in Austria, Finland, Norway and Ireland. In the context of the latter procedure, Ireland

expressed its concerns in relation to the authorisation of a generic version of Neiromidin (AT/H/1381/001-003/DC).

**Issues to be considered**

Efficacy

Certain key documentation concerning the marketing authorisation of the reference medicinal product is not available to the HPRA.

The authorised indications represent a heterogeneous group of diseases with a wide range of different underlying pathophysiologies and symptoms that require different treatment modalities. They are vague, poorly defined, and not aligned to regulatory[1], therapeutic or scientific guidelines, e.g. "complex therapy of demyelinating disease", including multiple sclerosis[2,3], "memory disorders of various origins", including Alzheimer's disease[4,5].

During the course of the above DCP, it came to light that the available data pertaining to efficacy of ipidacrine in all the authorised indications appear to stem mainly from open label, uncontrolled, and observational studies. The studies are focussed on narrow conditions with small numbers of subjects, have limited general applicability, and do not lend themselves to meta-analysis because of missing data, widely divergent methodologies and differing patient characteristics.

These data are limited in their substantiation of the efficacy of the authorised indications (and associated posologies). In particular, for the indications in "peripheral nervous system diseases (neuritis, polyneuritis, polyneuropathy, polyradiculoneuropathy, myasthenia gravis and myasthenic syndrome of various aetiology)" and "memory disorders of various origins (Alzheimer's disease and other types of senile dementia)", no data have been identified to substantiate the authorised posology in the higher dose range and at the maximum daily dose of 200 mg.

Peripheral nervous system diseases such as neuritis, polyneuritis and polyradiculoneuropathy, are associated with complex underlying pathogeneses, not limited to reduced cholinergic transmission. The use of ipidacrine for the treatment of such conditions as a single agent or in combination with other therapeutics is not provided in any established therapeutic guidelines (e.g. 2010 European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain, 2021 European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy). Against this background, a double-blind, randomised, placebo-controlled trial of Neiromidin 20 mg tablets in the treatment of patients with lumbosacral radiculopathy sponsored by the MAH of Neiromidin was identified by HPRA as a clinical trial of interest (EudraCT2019-002632-90). The results of this failed study contribute to the uncertainty surrounding the efficacy of ipidacrine in the treatment of conditions with similar underlying pathogeneses, i.e. neuritis, polyneuritis, polyradiculoneuropathy.

Hepatic safety concerns

In 2018, results from a "repeated dose 90-day oral toxicity study with recovery period in rats" demonstrated an ipidacrine-related decrease in serum glucose levels at all doses tested in female rats (irreversible at the highest tested dose). Therefore, a no-observed-adverse-effect level (NOAEL) for toxicity in female rats was not identified, and the safety margins in

comparison to expected clinical exposure cannot be determined. Whilst the clinical significance of these findings is unknown, as reflected since in the SmPC, the irreversible effect on glucose levels contributes to uncertainty with respect to ipidacrine's hepatic safety profile.[6]

Ipidacrine and tacrine are highly structurally similar aminopyridines. Tacrine was authorised in 1993 for Alzheimer's disease and marketed globally for 20 years before it was withdrawn mainly due to its hepatotoxicity. Therapy with tacrine was associated with serum aminotransferase (ALT) elevations. Routine monitoring of serum ALT levels for the first six months of therapy was recommended, nevertheless fatal cases of liver injury attributed to tacrine were reported.[7] Tacrine-induced hepatotoxicity was thought to be mediated through the 7-OH-tacrine molecule, however the exact mechanism has never been fully elucidated. For ipidacrine, it was postulated that a similar metabolite to 7-OH-tacrine was unlikely to form. In 2023, *in vitro* results suggested that 7-OH-tacrine is the least hepatotoxic metabolite of tacrine in non-clinical modelling and that tacrine's hepatotoxic mechanism should be revisited (Novak, 2023).[8] Whilst the metabolism of ipidacrine is still generally not well understood, these results raise serious concerns that the mechanism of liver toxicity of tacrine could also be relevant for ipidacrine.

In addition, in support of the generic applications, a single-dose (ipidacrine 20 mg), two period, two-treatment, crossover bioequivalence study performed in 2015 reported elevations from baseline in hepatic clinical chemistry. Notwithstanding the limitations of interpreting safety data from such a study, these data contribute to the concern that exposure to ipidacrine may well cause detrimental hepatic load, resulting in a potential hepatic safety risk.

Conclusion

The HPRA considers that there are serious concerns regarding the benefit/risk balance of ipidacrine-containing medicinal products as a result of the paucity of the data supporting the efficacy in its ill-defined authorised indications and of the emergence of new data casting doubt on the efficacy in neuritis, polyneuritis, polyradiculoneuropathy, as well as raising concerns around its hepatotoxicity potential. Treatment of vulnerable patient populations when therapeutic efficacy is lacking is of utmost concern, particularly when there are established efficacious alternatives available. Therefore, taking also into account the expected increase in exposure of patients across the Union to ipidacrine (due to the recent approvals of generic medicinal products in over a third of EU/EEA Member States) and the related potential risk to human health, HPRA is of the view that there is a need to reevaluate the benefit/risk profile of ipidacrine in the authorised indications.

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

Signed Finnuala Lonsdale

Date Digitally signed by Finnuala Lonsdale
DN: cn=Finnuala Lonsdale, o=HPRA, ou=Director HPAR, email=finnuala.lonsdale@hpra.ie, c=IE
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1. EC Guideline on Summary of Product Characteristics (2009)
2. EMA Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis, 2015, EMA/CHMP/771815/2011, Rev. 2
3. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP et al. Eur J Neurol. 2018 Feb;25(2):215-237. doi: 10.1111/ene.13536. Epub 2018 Jan 19. Erratum in: Eur J Neurol. 2018 Mar;25(3):605. doi: 10.1111/ene.13590. PMID: 29352526
4. EMA Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease, CPMP/EWP/553/95 Rev.2
5. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia 2012
6. EMA Reflection paper on non-clinical evaluation of drug-induced liver injury (EMEA/CHMP/SWP/150115/2006)
7. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Tacrine. [Updated 2020 Jan 15].
8. Tacrine First-Phase Biotransformation and Associated Hepatotoxicity: A Possible Way to Avoid Quinone Methide Formation. Martin Novak, Marie Vajrychova, Stefania Koutsilieri, Despoina-Christina Sismanoglou, Tereza Kobrlova et al. ACS Chemical Biology 2023 18 (9), 1993-2002. DOI: 10.1021/acschembio.3c00219