LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

NOTIFICATION TO THE PRAC OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is an official referral under Article 31 of Directive 2001/83/EC to the PRAC made by Sweden-Medical Products Agency (MPA)

Product Name (s) in the referring Member State if applicable	Alvedon, 665 mg, modified release tablet
Active substance(s) *Please clarify name(s) and total number(s) of active substance(s)*	Paracetamol
Pharmaceutical form(s) *If all pharmaceutical forms are included, state 'All'.* *If not all pharmaceutical forms are included, please specify the ones included.*	Modified release tablet
Strength(s) *If all strengths are included, state 'All'.* *If not all strengths are included, please specify the ones included.*	*665 mg*
Route of administration(s)	*Oral use*
Applicants/Marketing Authorisation Holder(s) In the referring Member State	GlaxoSmithKline Consumer Healthcare AB

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Background

A modified release (MR) tablet which contains 665 mg of paracetamol is currently authorised in Sweden and marketed as Alvedon 665mg modified release tablet for the therapeutic indications *Headache, toothache, cold-related fever, menstrual cramps, muscle and joint pain, as an analgesic for rheumatic pain, hyperpyrexia. Specially intended for chronic pain and other conditions that require continuous dosing*. The medicinal product was approved in Sweden via a national procedure in 2003 and it is available on prescription only. This medicinal product is also authorised in some other EU Member States.

The Alvedon 665 mg modified release tablet contains two layers. Thirty (30) % of the paracetamol content is immediately released from the outer layer. The remaining 70% is part of an inner depot-layer; which consists of a hydroxy propyl methyl cellulose (HPMC) - polymer. Following uptake of water, the polymer forms a gel around the tablet matrix. Paracetamol is released from the gel matrix depot layer through a combination of diffusion and erosion of the gel layer, giving a prolonged release of paracetamol.

During recent years, there has been an increase in prescriptions of this medicinal product. In parallel, an increasing number of inquiries to the Swedish Poisons Information Centre concerning suspected poisonings have been received.

Experience from published case reports and case reports identified by the Swedish Poisons Information Centre, indicate that the recommended risk assessment of suspected poisonings and the standard treatment protocol with the antidote N-Acetylcysteine, which is based on experience with overdoses of immediate release (IR) paracetamol, seem to be insufficient to manage overdoses with this modified release paracetamol tablet.

The Swedish Poison Information Centre has undertaken a retrospective pharmacokinetic (PK) and clinical analysis (Salmonson H, et al. Clin Toxicol 2016;54:424 (Abstract 124)) of 53 cases of acute overdose with Alvedon 665 mg modified release tablets which have been reported to them between 2009-2015. From this analysis, the following was concluded:

- In comparisons with what would be expected with IR formulations, the exposure profile following an overdose and the subsequent clinical course are unpredictable. Namely, absorption was prolonged and maximal plasma concentrations of paracetamol were observed later than what would be expected from overdoses with paracetamol in IR formulations. The unpredictability was more apparent with increasing dose.
- The standard assessment and treatment protocol, based on overdoses with paracetamol in IR formulations, was insufficient in the majority of cases.
- Cases of overdose with Alvedon 665 mg modified release tablets causing hepatic injuries, despite timely treatment, have been identified.

Issues to be considered

Based on the above-mentioned safety concerns, having considered that this medicinal product is authorised in several Member States, Sweden considers that there is a Union interest to:

- assess how to minimize the harm in case of overdosing the Alvedon 665 mg modified release tablet, and whether recommendations to manage such cases can be further improved;

- consider measures to minimize the risk for poisoning with the Alvedon 665 mg modified release tablet;
- evaluate the benefit/risk balance for all indications pertaining to the Alvedon 665 mg modified release tablet, where the benefit of prolonged exposure and pain relief is weighted against the increased risk of serious harm following overdose;

In view of the above and the necessity to take an action at EU level, Sweden considers it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether the 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.

[redacted]
Marie Gårdmark
Director Licensing
The Medical Products Agency

30 June 2016