



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 July 2016
EMA/PRAC/451078/2016

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for paracetamol modified or prolonged release tablets.

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

Procedure number: EMEA/H/A-31/1445

INN: paracetamol



1. 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. It is specially intended for chronic pain and other conditions that require continuous dosing. The medicinal product has been authorised in Sweden via a national procedure in 2003 and it is available on prescription only.

The standard procedures for assessing and managing overdose and poisoning with paracetamol are designed for the immediate-release products. The Swedish Poison Information Centre has undertaken a retrospective pharmacokinetic (PK) and clinical analysis of 53 cases of acute overdose with Alvedon 665 mg modified release tablets¹, which indicates that the standard procedures may not be entirely suited to treat overdoses with such products.

This medicinal product is also authorised in some other EU Member States under different names. Other modified- and prolonged-release paracetamol products are also available in some Member States, and some contain paracetamol in combination with other painkillers.

Therefore, there is a Union interest to:

- assess how to minimize the harm in case of overdosing paracetamol modified or prolonged release tablets, and whether recommendations to manage such cases can be further improved;
- consider measures to minimize the risk for poisoning with modified or prolonged release tablets;
- evaluate the benefit/risk balance for all indications pertaining to modified or prolonged release tablets, where the benefit of prolonged exposure and pain relief is weighted against the increased risk of serious harm following overdose;

The review will be carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), following a request from the Swedish medicines regulator, the Medical Products Agency

2. Questions

The marketing authorisation holders (MAHs) for paracetamol modified or prolonged release tablets as set out in Annex I are requested to provide the following:

Question 1

Please provide:

- a) Information on your currently authorised paracetamol modified or prolonged release tablet in the different Member States. This should include information about the current marketing and legal (i.e. prescription vs. non-prescription) status; the approved indication(s), doses, (including treatment duration and the maximum daily dose), strengths and the advice in relation to overdose included in the Product information (PI). Please tabulate the above

¹ *Salmonson H, et al.: The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol 2016;54:424 (Abstract 124)*

requested information including main differences between the PI in the different EU Member States (see tabulation attached), if applicable.

- b) Information on sales figures and estimated patient exposure for your paracetamol modified or prolonged release tablet, presented as follows:
- The exposure data should include a yearly breakdown of sales and exposure over the last 10 years for each Member State where the product is approved.
 - If possible, the exposure data should also be stratified by type and size for different packages such as blister packs or bottles.

Question 2

Please provide all cases where, following intake of modified or prolonged release paracetamol tablets, the standard assessment and treatment of paracetamol poisoning has been insufficient to prevent serious outcomes of an overdose, or were additional measures on top of the standard treatment have been taken to avoid serious outcomes.

Cases should be summarised in a tabulated format and narratives should be provided.

The tabulation should include but may not be limited to the following: patient age, sex, dose ingested (gram), packages (e.g. blister or bottle), time from intake to first paracetamol concentration measurement (h), time from intake to treatment start (h), treatments, use of N-acetylcysteine (yes/no), duration of NAC treatment (h), dose of NAC treatment, hepatic injury (e.g. max SGPT, SGOT and bilirubin (these should be expressed as ULN), INR), outcome (e.g. liver transplantation, fatality).

A background summary on epidemiological data on expected outcome from treatment of paracetamol poisoning with immediate release formulations should be provided for reference.

Question 3

- a. Please describe the composition of your product including the mechanism for modified /prolonged release properties of your product.
- b. Please present pharmacokinetic profiles of your product following overdose if data are available.
- c. Following overdoses with one modified release paracetamol tablet (Salmonson H. et al. 2016¹), unpredictable pharmacokinetic profiles, compared with immediate release formulations of paracetamol, have been observed. Please discuss possible explanations for such differences, if considered relevant for you product and in relation to any pharmacokinetic data available. This should include a discussion of the possibility for tablet aggregation following intake of many tablets, which may be due to the gel matrix which is formed when the tablet depot layer is in contact with water or other possible mechanisms. Any additional data, published or unpublished, on the above mentioned risks that can give further support for a possible explanation should also be provided (including non-clinical data if available).

Question 4

The benefit of paracetamol for the symptomatic treatment of pain, and fever is undisputed. The additional benefit of the modified or prolonged release tablets under discussion is related to prolonged effect duration and thereby need for less frequent dosing during the day. The MAH should provide a benefit/risk discussion for all approved indications separately, where the benefit of prolonged exposure

and pain relief / fever reduction is weighted against the risk of overdose (accidental or intentional) and subsequent serious consequences of poisoning due to unpredictable pharmacokinetic profile observed with one modified release product (Salmonson H. et al. 2016 ¹)

Question 5

Please provide proposals and justifications for any additional risk minimisation measures which may improve the benefit-risk balance of your product and prevent the occurrence of overdoses and subsequent harm. These measures should be discussed separately for the situations of intentional versus unintentional overdose.

- Please discuss means for further harm reduction in case of poisoning with your product, and whether the recommendations for handling overdoses with paracetamol modified or prolonged release formulations can be refined, taking into account available literature sources.
- Please discuss further measures for minimizing the risk for overdose including the following. Additional aspects should also be considered, as appropriate:
 - to restrict the use to only patient groups where prolonged pain relief /fever reduction in comparison with immediate release formulations, is of particular benefit.
 - Legal status
 - Size and type of packages.
 - Communication activities
- Please discuss how the effectiveness of the harm reduction and risk minimisation measures should be monitored.

Question 6

- Please address how assessment and management of poisoning with the modified or prolonged release formulation can be further studied.

TABULATION

Question 1

a)

INN	Product name	Marketing status	Legal Status	Indications	Packaging	Strength	Package size

Dosing (SmPC)	Maximum daily dose (SmPC)	Treatment duration (SmPC)	Warnings and precautions on overdose (SmPC)	Overdose (SmPC)	Warnings and precautions on overdose (PL)	Overdose (PL)	Main differences between the SmPC/PIL in the different EU Member States

b)

INNs	Product name	Country	Sales figures	Indication	Sales figures	Packaging	Sales figures