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SCIENCE MEDICINES HEALTH

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Modified-release paracetamol-containing products to be suspended from EU market

Recommendation endorsed due to the difficulty in managing overdose

On 13 December 2017 the CMDh¹ endorsed by majority a European Medicines Agency recommendation to suspend marketing of modified- or prolonged-release products containing paracetamol (designed to release paracetamol slowly over a longer period than the usual immediate-release products). The recommendation was made by the Agency's experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC).

CMDh agreed with the Agency's advice that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine, since the treatment procedures for immediate-release products are not appropriate for modified-release paracetamol. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified-release products, making it difficult to decide how the overdose should be managed.

CMDh noted the PRAC conclusion that practical measures to sufficiently reduce the risk to patients had not been identified. Furthermore, it had not proved possible to agree a feasible and standardised way to adapt the management of overdose across the EU to cover both immediate- and modified-release paracetamol products. The CMDh therefore endorsed the PRAC recommendation that the marketing authorisations for medicines containing modified-release paracetamol, alone or combined with the opioid medicine tramadol, should be suspended.

The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks.

Immediate-release paracetamol products, which are not affected by this review, will continue to be available as before.

Because the CMDh decision was agreed by majority vote it was sent to the European Commission which issued a final legally binding decision valid throughout the EU on 19/02/2018.

¹ The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.



Information for patients

- Paracetamol medicines designed to release the active ingredient over a long period (modified-release medicines) are being taken off the market.
- These modified-release medicines are being removed from the market because of the difficulty in managing overdoses.
- Some modified-release medicines are available in combination with another painkiller, tramadol. These combination products are also being removed.
- If you are taking modified-release medicines, you can continue to do so. However, you will need to speak to your doctor or pharmacist about the best replacement if you need further treatment once your supply runs out.
- Ordinary 'immediate-release' paracetamol medicines are not affected by this review and will continue to be available as before.
- When used correctly and at the recommended doses, paracetamol is an effective and safe treatment for pain and fever.
- Patients should continue using paracetamol medicines in line with instructions in the package leaflets, particularly instructions on how much to take.
- You should seek medical advice quickly if you have taken, or think you may have taken, more than the recommended amount of any paracetamol-containing product.

Information for healthcare professionals

- Modified-release paracetamol (alone or combined with tramadol) is being removed from the EU market since overdoses with modified-release paracetamol products can be unpredictable in their pharmacokinetics, and complex to manage.
- The established treatment guidelines for paracetamol overdose are based on the immediate-release products and may not be effective for treatment of overdoses with modified-release paracetamol.
- There are no issues with modified-release paracetamol preparations when used in accordance with their product information. Patients can safely continue treatment in the approved indication and doses with any remaining supply. Prescribers should discuss switching to an appropriate alternative if necessary once patients' supply runs out.
- Until modified-release products have been removed from the market, adaptations of the standard protocol for paracetamol overdose should be considered. Although this should be determined at local level in consultation with local Poison Information Centres, the following general guidance may be helpful unless local guidelines have already been adapted or already recommend a more conservative approach:
 - where overdose with ≥ 10 g of paracetamol (or ≥ 150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine, NAC) should be started immediately regardless of the initial serum paracetamol level, since serum paracetamol level after acute overdose with modified-release products may peak up to 24 hours after ingestion;

- where <10 g of paracetamol has been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low levels. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated;
- if time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available;
- if NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L;
- antidote should be dosed as recommended by the local Poison Information Centre.

The Agency's recommendations are based on a review of available data including a retrospective pharmacokinetic and clinical analysis of 53 cases of acute overdose with modified-release paracetamol by the Swedish Poison Information Centre,¹ which found that the standard treatment protocol utilising solely the Rumack-Matthew nomogram (or variations thereof) based on conventional paracetamol formulations may not be effective for overdoses with modified-release paracetamol formulations. The maximum plasma concentration may occur later, and high concentrations, in particular after large doses, may persist for several days. The usual protocols of sampling and treatment regimens used in the management of overdose with immediate-release formulations are therefore not adequate. The dose of NAC may have to be increased and the optimal dosing has not been determined. These results confirm a similar Australian case series.^{2,3}

A letter providing further information and advice in case of known or suspected overdoses with paracetamol modified-release containing products will be circulated to healthcare professionals who deal with paracetamol overdosage in the affected Member States.

References

1. Salmonson H, Sjöberg G, Brogren J The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified release formulation: a pharmacokinetic and clinical analysis of 53 cases. *Clin Toxicol (Phila)* 2017 Jun 23:1-6. doi: 10.1080/15563650.2017.1339887
2. Graudins A, Chiew A, Chan B. Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol. *Intern Med J* 2010; **40**(1):72-6.
3. Graudins A. Overdose with modified-release paracetamol (Panadol Osteo®) presenting to a metropolitan emergency medicine network: a case series. *Emerg Med Australas* 2014; **26**(4): 398-402.

More about the medicine

Paracetamol has been widely used for many years to relieve pain and fever in adults and children. Paracetamol-containing immediate-release products have been authorised in all EU Member States but are not included in EMA's review.

Products covered by this review contain paracetamol for modified-release and are intended to be taken by mouth and have a longer action. They are available in Belgium, Denmark, Finland, Greece, Iceland, Luxembourg, the Netherlands, Portugal, Romania, and Sweden under various names including Alvedon 665 mg, Panadol Arthro, Panadol Extend, Panadol Retard 8 hours, Panodil 665 mg, Paratabs Retard and Pinex Retard.

Modified-release medicines containing paracetamol with the opioid painkiller tramadol are available under the names Diliban Retard or Doreta SR in Bulgaria, Czech Republic, Estonia, Hungary, Iceland, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia and Spain, and these medicines are also covered by this review.

More about the procedure

The review of modified-release paracetamol was initiated on 30 June 2016 at the request of Sweden, under [Article 31 of Directive 2001/83/EC](#).

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety of human medicines, which made recommendations in September 2017. Following a request from companies involved in the review, the PRAC re-examined and confirmed its previous recommendation in December 2017. The PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority vote, the CMDh position was sent to the European Commission, which issued an EU-wide legally binding decision.