Annex II

Scientific conclusions

Scientific conclusions

On 30 June 2016, Sweden triggered a procedure under Article 31 of Directive 2001/83/EC, and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of products with modified or prolonged release properties containing paracetamol and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 30 November 2017 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Paracetamol is one of the most commonly utilised compounds worldwide; its use as an anti-pyretic or analgesic drug has been predominant since 1955. Paracetamol is used in various pain types such as headache, migraine, dysmenorrhoea, sore throat, musculoskeletal pain, pain after dental procedures/tooth extraction, toothache and the pain of osteoarthritis and for fever. Under normal conditions of use, it has an established favourable benefit/risk profile.

Products with modified or prolonged release properties containing paracetamol, which are intended to have a longer action, are available in several EU Member States. These include products with paracetamol as a single ingredient; namely modified release (MR) tablets containing 500 mg, 665 mg or 1000 mg paracetamol, and paracetamol 500 mg prolonged release tablet. Furthermore, there are prolonged-release combination products containing tramadol/paracetamol 75 mg/650 mg.

The claimed specific benefits of the MR formulations relate to a reduction of daily tablet intake (from 4 to 3 times daily dosing for the single ingredient products, and the simplified regimen of 2 from 4 tablets for the combination products) do not outweigh the risks of hepatic toxicity in case of overdose.

The main safety concern with paracetamol is hepatic toxicity following intake of high, supra-therapeutic doses, which can be fatal unless adequately treated. Paracetamol is the most commonly reported toxic ingestion of a medical substance in the UK and some other EEA countries (e.g. Sweden) and is the most common medicinal agent of intentional self-harm. If the patient presents to emergency medical care in time following an overdose, there is an effective antidote available – N-acetylcysteine (NAC). Most countries have adopted guidelines which rely on a nomogram to establish whether the patient should be treated with NAC or not, relating the serum paracetamol concentration to the number of hours between ingestion and the blood test. Most episodes of hepatotoxicity occur as a result of late presentation to hospital.

For paracetamol MR tablets 319 spontaneous adverse event reports of overdose (OD) were identified since marketing authorisation. Of these 319 cases, almost all (98%) are from Sweden (67%) and Australia (31%). The majority of patients recovered or improved while 2 patients needed liver transplants. There were 5 fatal cases reported out of the 319 cases. Seven cases were reported to be unintentional but none of them were fatal.

Three overdose cases (none of which was fatal) have been identified involving tramadol/paracetamol fixed dose combination product following an inquiry to national Poison centres during this procedure, as only Doreta SR is marketed. Diliban retard is not yet placed in the EU market.

Data published by the Swedish Poison Centre described a series of 53 patients with reported overdose with paracetamol 665mg MR (range 10-166 g). A very high variability has been observed in the PK profiles of patients poisoned with MR formulations. Both the absorption duration and the terminal half-live were prolonged in the poisoned patients, sometimes resulting in double peaks. Late crossing of the standard treatment nomogram were seen in 19% of the cases. Eleven patients (21%) had a serum

alanine aminotransferase (ALT), above the reference range (ALT >50 IU/L) at 24 h or later. Out of these, six patients developed hepatotoxicity (ALT >1000 IU/L). Seven of the eleven patients with an ALT above the reference range were treated with NAC within 8 h of ingestion, of which three developed hepatotoxicity. The PRAC concluded that the treatment recommendations of overdoses based on standard paracetamol formulations, including use of the nomogram, are inadequate after intake of toxic doses of MR formulations. Dose is an important factor when interpreting poisoning data with paracetamol. It is agreed in the scientific community that massive overdoses are particularly challenging to handle. Inherent PK characteristics of these MR products; with one part of the paracetamol content being released immediately, and one (larger) part with a delayed release, differ from the immediate release (IR) formulations. This translates into different PK profiles also at overdoses which is supported by available data including published case series. This includes unexpectedly prolonged paracetamol exposure and double peaks. This unpredictability was not sufficiently mitigated by the modelling and simulation measures submitted by the MAH GSK Consumer Healthcare. Furthermore, the role of risk factors such as co-medications or underlying diseases on the PK profile, in particular the delayed and double peak formation is not sufficiently understood to anticipate the population at risks and better manage the cases of overdose with paracetamol MR containing medicinal products.

An ad-hoc expert group meeting was held within this procedure with scientific and clinical experts in the management of poisoning. The experts were of the same views as the PRAC regarding the complications both in assessment and treatment of poisoning by paracetamol MR and the subsequent related potential for severe harm and this is due to the unpredictable release profile of MR paracetamol, the PK profile and the difficulty in establishing and implementing an optimal treatment protocol MR paracetamol poisoning is associated with additional complications. The experts also noted that separate protocols would need to be in place for treating overdose with IR paracetamol and overdose with MR paracetamol or unknown formulation; and that the current nomograms are relevant only for IR paracetamol formulations.

In addition to the concerns expressed in relation to MR formulations containing paracetamol as a single ingredient, the experts concluded that the treatment of overdose with paracetamol/tramadol combination products raises further concerns. This was due to the safety profile of tramadol (e.g. convulsions, vomiting), which the group considered very likely to present additional challenges for handling an overdose with a prolonged release combination product of paracetamol and tramadol.

During the procedure, all MAHs have recommended as part of the risk minimisation strategy that in case of poisoning the emergency medical services should promptly contact the national Poison Centres. However, it is unclear if such a recommendation is feasible and will result in effective risk minimisation throughout the EU, since the operations of these Centres are different in the EU Member States. In addition all MAHs proposed to conduct a Post-authorisation safety study (PASS) to collect details of cases of overdose with paracetamol and to optimize the management of overdose assess. The PRAC also considered, notwithstanding the feasibility and effectiveness concerns, that the shortcomings of such measures would not be proportionate, notably considering the modest benefits of these medicinal products.

The high variability in PK-profile of an overdose with a MR paracetamol containing product, and the continuously present uncertainties related to what formulation (IR or MR paracetamol) and the dose the patient has ingested, leads to serious safety concern in managing paracetamol overdoses. For the individual patient who has taken an MR overdose this means a longer and more complex encounter with health care services, and an uncertainty if adequate treatment can be provided. This uncertainty is not acceptable by the PRAC in view of the severity of liver toxicity associated with paracetamol overdose. Protocol based on a systematic treatment with NAC would also lead to a number of patients unnecessarily being treated or over-treated with NAC which is not proportionate and acceptable in view

of the adverse reactions cutaneous like rash, itching, flushing and gastrointestinal like nausea, vomiting) associated with treatment with NAC. All these uncertainties and the identified disadvantages for patients having taken a paracetamol overdose, seriously question the feasibility and reliability in the recommendations proposed by the MAHs.

The PRAC concluded that the standard regimen for treatment of paracetamol poisoning, including use of the nomogram, which has been successful in preventing hepatotoxicity following IR overdoses, is inadequate for handling of an overdose with a paracetamol MR formulation. Although it was recognised that repeated, and patient-tailored plasma sampling for determination of paracetamol levels and liver enzymes together with tailored administration of NAC may be sufficient to avoid serious hepatic damage, if the patient presents to the medical emergency unit in time, it is currently not possible to determine an effective and proportionate overdose protocol for such overdose due to lack of evidence.

Further, the feasibility of determining and implementing effective measures across EU Member States is questioned, due to the complexity of managing two specific protocols, a close monitoring (increased blood sampling) and the complexity due to the uncertainty on the ingested formulation that is prejudicial to the patient in view of the risk of not using an effective protocol and the safety concern related to the unnecessary administration of NAC.

Notwithstanding the feasibility of a revised overdose protocol, it is not acceptable for the PRAC to expose the patients to such revised protocol without sufficient evidence on its effectiveness. In this regard, the MAHs proposal to gain further experience on this proposed revised protocol by the means of a post-authorisation safety study was not endorsed.

All MAHs proposed additional measures that would further minimise the risks associated with overdose with MR formulation for example updated package leaflet, communication to HCP (DHPC, education materials), prescription status, restriction of access to bottle packaging and large blister pack size for the patients. These risk minimisation measures intended to reduce the risk for hepatic injury following an overdose with an MR formulation of paracetamol or the combination of paracetamol and tramadol were not considered by the PRAC to be sufficiently effective and reliable. In particular with regards to the intentional overdose. Indeed, the product is already under prescription in the EU concerned Member States except in Portugal – this measure would have an effect limited to PT and would not further minimise the risk in other EU Member States. The restriction of pack size, whilst not deprive of any effect, would not sufficiently restrict the access to these medicinal products and is unlikely to prevent overdose, in particular intentional ones. The measures to improve the awareness on the risk of overdose (educational material, product information, labelling, DHPC) was not considered effective to prevent case of overdose, especially when intentional, as information to the patients and healthcare professionals is already extensive.

In conclusion, the complex PK profile after an overdose of paracetamol MR containing medicinal products, and the fact that the standard treatment protocol for paracetamol poisoning is inadequate for these products and the severe risk of hepatotoxicity related to overdose with paracetamol raises a serious risk to public health at Union level.

The absence of effective measures to sufficiently prevent the cases of overdoses and the uncertainties regarding feasibility and effectiveness of revised treatment protocols for MR overdoses across the EU, and the disadvantages they would cause for patients are serious concerns. It is not considered that this safety concern of serious and potentially fatal hepatic injury in case of overdose with paracetamol MR formulations is sufficiently minimised by effective risk minimisation measures to prevent this risk and to manage it once it occurs. The proposed risks minimisations by the MAHs are not considered feasible, effective and proportionate by the PRAC. In view of the above, the safety concern identified is not outweighed by the benefits of these products for the treatment of the approved indications.

The PRAC as a consequence considers that the benefit-risk balance of with modified release paracetamol containing products is no longer favourable.

Re-examination procedure

Following the adoption of the PRAC recommendation in September 2017, two MAHs (GSKCH and KRKA d.d., Novo mesto) have requested the re-examination of the recommendation and submitted detailed grounds for the re-examination. A second expert group meeting was convened.

PRAC discussion on the detailed grounds for re-examination

A. Paracetamol modified release tablets

Having considered the detailed grounds submitted by the MAH, the PRAC confirmed its previous position that the evidence of clinical advantage of monocomponent MR paracetamol in chronic pain is very weak. The evidence of the efficacy in acute pain is more robust but the clinical need of a mofidied-release formulation is less important and the claimed benefits of the medicinal product are not substantial for this clinical setting. Based on available data, the PRAC did not identify in the authorised indications any substantial clinical benefit which would be only specific to the MR formulation.

The PRAC discussed the available clinical studies during the re-examination phase in view of the grounds submitted by the MAH. The PRAC acknowledged the limitations of the existing studies as they were not designed to compare influence of dose versus formulation on unpredictable PK or outcome. Available data indicates that patients considered at high risk of hepatotoxicity are those with high initial paracetamol concentrations. The vast majority of the serious cases reported with paracetamol MR formulation happened in overdoses with more than 30 g of paracetamol (considered a massive overdose by Marks et al, 2017). Data from the study by Chiew and colleagues (2017) indicates that rate of hepatotoxicity declines when either activated charcoal or increased NAC dose are administered to patients. The authors also suggest a negligible risk from modest increases in NAC dose in those with a high paracetamol ratio.

The Rumack-Matthew nomogram was developed for single overdose with precise time of ingestion and cannot accurately assess risk after repeated overdoses, acute overdose of a sustained-release product, or when the time of ingestion is unknown or patients present beyond 24 hours. Delayed absorption or double peaks observed both with IR and MR paracetamol formulation depending on the dose ingested have been described up to date. The shortcomings of Rumack-Matthew nomogram have already been identified thus leading to different treatment protocols in case of co-ingestion of other products (particularly those who affect gastric motility) or in cases when no information can be obtained from the patients (e.g. time of ingestion is unknown).

In addition, publications describing case series of overdose with modified-release paracetamol from Australia, such as Graudins and colleagues (2010, 2014) have been assessed as providing experience on the treatment protocol with NAC and supportive information regarding PK of paracetamol in cases of overdose with MR formulation.

The PRAC acknowledged the need for a better characterisation of the risk (relationship with the dose, the concentrations and the toxicity) as well as the need to address uncertainties on the handling of patients with MR paracetamol products overdose (e.g. the appropriate threshold to start NAC administration, the dose and duration of NAC treatment as well as the optimal number of paracetamol concentration that need to be determined). In this sense, the second expert group meeting expressed the view that the model currently proposed by the MAH was not sufficient due to sample size limitation and further methodological challenges. To address uncertainties in the management of overdose cases

with the MR formulation of paracetamol, a mechanistic model would be required taking into account other relevant parameters (e.g. solubility of paracetamol, kinetics of the toxic metabolite (NAPQUI) and of NAC administered as antidote). Therefore PRAC considers that in view of the sample size needed for the model to be sufficiently powered to address the current uncertainties, such mechanistic model could not be developed in a reasonable timeframe and patients would still be exposed to the risk of overdose with paracetamol MR.

It is acknowledged that the rate of overdose is not the same in all EU MSs depending on different factors (e.g. legal status, pattern of use of pain relief medicines). The overdose treatment guidelines also differ among MSs depending on the healthcare systems. Available data clearly suggest that treatment with NAC should not be discontinued before additional paracetamol concentration and ALT value have been determined. In cases where ingested dose is unknown or time of ingestion is unknown or different substances were taken, treatment with NAC is usually promptly started.

In the literature only few studies investigate whether treatment guidelines are followed and these are mostly done with IR formulation and mainly in Australia. However, study by Carroll and colleagues (2015) that investigated the influence of the change to UK overdose treatment guidelines showed that a proportion of patients is already being treated on a case by case basis, independently of existing UK treatment guidelines.

During the re-examination a comparison of the effectiveness of revised treatment protocol to that of standard established treatment protocol used for the management of overdose with IR paracetamol in the prevention of paracetamol-related hepatotoxicity was made. The measurement of the effectiveness of a modified model or new guidelines for treatment of MR paracetamol overdose was discussed by the second ad-hoc expert group, however the sample size (100 patients) was not considered sufficient. The PRAC was in agreement with the ad-hoc expert group views.

Whilst adaptation of the existing guidelines on treatment of overdose could be done, PRAC considered that the development of a common protocol would result in overexposing certain patients to NAC and the subsequent risks related to the use of NAC (e.g. hypersensitivity including anaphylactic shock).

As part of their risk minimisation strategy, the MAH have recommended that in case of poisoning the emergency medical services should promptly contact the national Poison Centres. However, the feasibility such a recommendation questioned and PRAC considered that it would not result in effective risk minimisation throughout the EU, since the operations of these Centres are different in the EU Member States.

In addition, the MAH proposed to conduct a Post-authorisation safety study (PASS) to collect details of cases of overdose with MR paracetamol and to optimise the management of overdose.

The PRAC also considered that the above proposals would have a questionable feasibility and effectiveness and would not effectively address the risk of hepatotoxicity following intentional or accidental overdose. The PRAC considered the other risk minimisation measures proposed within the re-examination procedure (e.g. school programmes, restriction to pack type and size, educational materials and direct communication to HCPs) but concluded that these would neither be sufficient nor appropriate to adequately minimise the risk of intentional and unintentional overdose and consequential risk of hepatotoxicity.

B. Tramadol/paracetamol prolonged release tablets

The MAH submitted a literature review to justify the clinical benefit of the tramadol/paracetamol MR combination in pain management. Tramadol/paracetamol MR tablets are indicated for treatment of moderate and severe pain conditions. From the literature review two publications were the most

relevant where Lasko and colleagues (2012) investigated the efficacy of MR tramadol/paracetamol formulation for acute low back pain, while Lee and colleagues (2013) for chronic low back pain. It is acknowledged by PRAC that MR formulation may provide adequate control of pain and fewer dosing decreases the possibility for medication errors and improves patients' compliance. However, in view of the risk related to these products, PRAC could not identify an indication with substantial clinical benefit which would be only specific to the tramadol/paracetamol MR formulation.

At the ad-hoc expert group meeting convened during the re-examination, experts concluded that the only patient groups that might benefit from the MR tramadol/paracetamol combination product are those affected by chronic pain and sleeping interruptions due to pain. On the other hand, the experts also considered that there is insufficient evidence in this clinical setting to support the added value of tramadol/paracetamol MR formulation over other therapies in such population or any other patient group. PRAC was in agreement with the experts views.

Due to the difference in the severity of conditions, there is a possibility of difference in the risk of suicidality between these two populations of patients using this fixed-dose combination with tramadol versus the MR paracetamol as monocomponent. It has to also be taken into account that there could be a subgroup of tramadol abusers in which risk of suicidality is different. In addition, due to the presence of opioid component, there is risk of unintentional overdose. It was also noted that the FDA has recognised the dangers of the prescription combination of paracetamol and opioids and, in January 2014 implemented a fixed amount of paracetamol approved per dosage unit of combination.

The MAH referred to the limited number of overdoses reported with the fixed-dose combination are limited. However, this has to be put in perspective of the limited exposure.

Furthermore, the PRAC confirmed that despite the difference in the target population and the clinical settings, the fixed-dose combination of MR paracetamol/tramadol can result in overdoses that are severe in view of the risk of hepatotoxicity of paracetamol and the toxicity of tramadol (e.g. CNS effects including high risk of seizures, and renal failure). These overdoses are even more unpredictable and more complex to manage than MR paracetamol alone due to the combination with tramadol.

The PRAC agreed with the outcome of an ad-hoc expert group meeting convened during the re-examination, where the experts concluded that it is not possible to extrapolate from a PK model developed for paracetamol as a single ingredient to the combination of paracetamol/tramadol. Separate model for the combination, based on appropriate data would be necessary to address uncertainties in the management of a combination overdose.

Other risk minimisation measures proposed by the MAH to address the risk associated with overdose of the combination were considered by PRAC such as update of the product information to include stronger warnings related to at-risk patients and concomitant use with other paracetamol-containing products, DHPC and restriction of availability of certain type of packaging (i.e. bottles) and restriction of available pack size (max. 48 tablets). While no cases of overdose were reported in children below 12 years of age, the PRAC noted that the risk of unintentional overdose with Doreta SR is minimal in the patient population due to e.g. the restricted use in children, the child resistant package. Overall, the measures proposed were considered neither sufficient nor appropriate to adequately minimise the risk of intentional and unintentional overdose. With regards to the small pack sizes, whilst these could have been an efficient measure to restrict availability, this would not be adequate for medicinal products mainly relevant in a chronic pain setting.

Conclusions on the benefit-risk balance following the re-examination procedure

Further to the review of all data submitted related to the paracetamol MR and paracetamol/ tramadol MR products, in particular the risk of intentional and accidental overdoses related to their use, PRAC considered that the severe risk of hepatotoxicity related to overdoses, the complex PK profile of these products after an overdose, which makes the standard treatment protocol for paracetamol poisoning inadequate raises a serious risk to public health at Union level. Arguments presented by the MAHs and views expressed by the experts during the re-examination phase did not alleviate any of the concerns by PRAC on the complex PK observed with overdose and the options for their management.

PRAC confirmed its position that in order to better characterise the risks and address uncertainties about management of overdoses, a larger sample size was needed for the model to be sufficiently powered and that such mechanistic model could not be developed in a reasonable timeframe.

The PRAC assessed the proposed risk minimisation measures during the re-examination phase, and concluded that there are uncertainties regarding their feasibility and their effectiveness, in particular with regards to revised treatment protocols for MR overdoses across the EU, and the potential harms to patients who would be unnecessarily overexposed to NAC.

It is considered that the serious and potentially fatal hepatic injury in case of overdose with paracetamol MR and paracetamol/tramadol MR formulations cannot be sufficiently minimised by effective risk minimisation measures to prevent this risk and to manage it once it occurs. In view of the above, it is considered that this risk is not outweighed by their benefits in the approved indications.

Therefore, in view of all the above, including the consultation with the second ad-hoc expert group, and the argumentation presented by the MAHs in the detailed grounds as well as in the oral explanations, the PRAC concluded that the benefit-risk balance of with modified release paracetamol and paracetamol/tramadol containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for modified release paracetamol containing medicinal products (see Annex I).
- The PRAC noted that the efficacy of MR paracetamol, as a single ingredient or in combination with tramadol, has been documented in representative acute and chronic pain models, and that the benefits of paracetamol as well as tramadol in general, are well established. The PRAC noted the claimed specific benefits of the MR formulations related to a reduction of daily tablet intake; from 4 to 3 times daily dosing for the single ingredient products, and the simplified regimen of 2 from 4 tablets for the combination products.
- The PRAC reviewed all the available data submitted with regard to overdose of the paracetamol containing MR products, including intentional and accidental overdose. This included the responses submitted by the marketing authorisation holders (MAHs) in writing and during oral explanations, the grounds for the re-examination as submitted by the two concerned MAHs, as well as the advice from the two groups of experts in the management of poisoning, pain management and pharmacokinetics, published studies and spontaneous reports of overdose. The PRAC also considered risk management of overdoses with paracetamol in general, both in the EU and world-wide.
- The PRAC considered the highly variable PK-profile of overdoses with MR paracetamol formulations, and the uncertainties related to the quantity and the formulation of the product that the patient has ingested, increase the challenges in effectively minimising the risk for paracetamol toxicity.
- The PRAC also noted that in addition to the uncertainties on how to minimise the risk for paracetamol toxicity, the safety profile of tramadol was considered to present additional challenges for minimising the risks for toxicity (e.g. CNS effects, high-risk of seizures and renal failure) following an overdose with a prolonged release combination product of paracetamol and tramadol.
- The PRAC also considered the proposed risk minimisation measures to reduce the risk of overdose through education, communication and restricting availability and concluded that these measures would not be sufficient to minimise the risk of intentional and accidental overdoses to an acceptable level. Furthermore, the risk minimisation measures intended to reduce the risk for hepatic injury following an overdose with an MR formulation of paracetamol or the combination of paracetamol and tramadol were not considered to be sufficiently effective and reliable.
- The Committee concluded, in view of the available data including the detailed grounds submitted by MAHs during the re-examination phase, that the risk for serious hepatic injury following an overdose with MR paracetamol containing products, could not be adequately minimised such as this risk could be outweighed by the benefits of these products in the treatment of pain and fever.

Therefore, in view of the above, the PRAC concluded that the benefit-risk balance of with modified release paracetamol containing products is no longer favourable and recommended that the marketing authorisations of these products should be suspended.

To lift the suspension, the PRAC recommended that the MAHs should provide evidence of proportionate, feasible and effective measures to minimise the risk for hepatic injury following intentional or accidental overdoses with modified release paracetamol containing products.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agree with the PRAC overall conclusions and grounds for recommendation.

The CMDh considered the documentation submitted by one MAH (KRKA d.d., Novo mesto) in support of their product and concluded that it did not affect the conclusions of the PRAC.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of products containing paracetamol, modified and prolonged release is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the suspension of the marketing authorisations for products containing paracetamol, modified and prolonged release.

For the suspension of products containing paracetamol, modified and prolonged release to be lifted, the marketing authorisation holders shall provide evidence in support of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk of hepatic injury following intentional or accidental overdoses with modified release paracetamol containing products.