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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Paracetamol modified and prolonged release

Procedure No.: EMEA/H/A-31/1445

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

On 30 June 2016, the Medical Products Agency (Sweden) triggered a referral under Article 31 of Directive 2001/83/EC based on concerns in relation to the risk of poisonings with paracetamol modified release (MR) tablets as well as on the standard treatment protocol with the antidote N-Acetylcysteine and its adequacy to manage overdoses with paracetamol MR tablets (Salmonson et al. 2016)[1]. The Medical Products Agency asked, in particular, the PRAC to assess the impact of the concerns on the benefit-risk balance of modified-release paracetamol tablets and to issue a recommendation on whether the marketing authorisation for the medicinal product (Alvedon 665 mg MR) should be maintained, varied, suspended or revoked.

The scope of this procedure covers all oral modified release formulations containing paracetamol.

2. Scientific discussion

2.1. Introduction

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.

A MR tablet which contains 665 mg of paracetamol (Alvedon 665 mg MR) is currently authorised in Sweden for the therapeutic indications of headache, toothache, fever associated with common cold, dysmenorrhoea, muscle and joint pain, and as 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.

During recent years, there has been an increase in prescriptions of this product, which is correlated with an increasing number of inquiries to the Swedish Poisons Information Centre concerning suspected poisonings. Experience from published case reports and case reports indicates that the recommended risk assessment of suspected poisonings and the standard treatment protocol with the antidote N-Acetylcysteine (NAC), which is based on experience with overdoses of immediate release (IR) paracetamol, seems to be inadequate to manage overdoses with MR paracetamol. This appears linked to differences in the exposure profile between the Alvedon 665 mg modified released tablets and standard IR paracetamol products.

The standard procedures for assessing and managing overdose and poisoning with paracetamol are designed for the IR paracetamol products. The Swedish Poison Information Centre has undertaken a retrospective pharmacokinetic (PK) and clinical analysis of 53 cases of acute overdose with paracetamol 665 mg modified release tablets, which indicates that the standard procedures may not be suited to treat overdoses with such products. EU Member States (e.g. Denmark) have introduced a protocol for treating the overdoses with paracetamol MR medicinal products. Non-EU countries also have implemented such protocols (e.g. Australia) and these vary in the time-to-treatment and sampling.

Therefore, there is a Union interest to assess how to minimise harm in case of overdosing paracetamol modified or prolonged release tablets, and whether recommendations to manage such cases can be

[1] Salmonson H, Sjöberg G, Brogren J, et al. The standard treatment protocol is inadequate following overdose of extended release paracetamol: A pharmacokinetic and clinical analysis of 53 cases. Clinical Toxicology, 2016:424 (abstract)

further improved, to consider measures to minimise the risk for poisoning with modified or prolonged release tablets, and to evaluate the benefit-risk balance for all indications pertaining to modified or prolonged release tablets.

Consequently, on 30 of June 2016, the Medical Products Agency (Sweden) triggered a referral under Article 31 of Directive 2001/83/EC, and asked the PRAC to assess the impact of the concerns raised on the benefit-risk balance of modified-release (MR) paracetamol tablets and issue a recommendation on whether the marketing authorisation for the medicinal product should be maintained, varied, suspended or revoked.

Alvedon 665mg MR is also authorised in some other EU Member States under different invented names. Other modified- and prolonged-release paracetamol containing products are also available in some EU Member States, and some contain paracetamol in combination with other analgesics. Throughout this Assessment Report the term modified release (MR) is used also when referring to sustained-release, extended-release or modified-release formulations of paracetamol. The scope of this procedure was extended therefore to cover all oral modified release formulations containing paracetamol.

This referral procedure concerns the modified or prolonged release formulation containing paracetamol as single ingredient:

- paracetamol 665 mg modified-release tablet (Alvedon 665 mg MR of GSK Consumer Healthcare). GSK Consumer Healthcare also holds two MAs in Denmark for a 500mg and 1000mg paracetamol modified release tablet, however commercialisation of both of these ceased in 2011.
- paracetamol 500 mg prolonged release tablet (Actavis).

As well as, modified or prolonged-release combinations containing paracetamol with other analgesics (tramadol):

- tramadol/paracetamol 75 mg/650 mg prolonged release tablet (Diliban retard of JABA Recordati & Laboratorios Gebro pharma; and Doreta SR of KRKA).

The exposure to MR paracetamol 665 mg as single exposure during the time period from March 2007 to March 2016 is estimated to be 294 million patients worldwide (the product is marketed also in Australia both as OTC and Rx) and 44 million patients in EEA Member states.

Regarding exposure to tramadol/paracetamol prolonged release tablets:

- Diliban is not marketed yet.
- Doreta SR is authorised in 11 and marketed in 7 EU Member States (MSs). Patient exposure has been estimated taking into account the maximum daily dose of 4 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) for a period covering 14 October 2015 (MA date) to 31 December 2016 at around 1.7 million.

2.2. Quality aspects

The three medicinal products Alvedon 665 mg MR, Diliban retard and Doreta SR are all bilayer prolonged release tablets consisting of an immediate release (IR) layer and a modified release (MR) layer. In all cases, the prolonged release layer contains a hydrophilic polymer that swells in contact

with water to form a gel matrix releasing the active substance by a combination of diffusion through the gel and erosion of the gel.

Dissolution testing was performed with 1, 10 and 20 tablets at different PH's and with different ethanol concentrations. Bezoars were observed *in vitro* for Doreta SR and Alvedon but the dissolution profiles were not significantly affected by bezoar formation. The presented results show reproducible and consistent dissolution characteristics for the three medicinal products in the various experimental conditions, i.e. pH (from 1.2 to 6.8), tablets numbers (up to 20 tablets) and ethanol concentration (from 0% to 20%).

However, the *in vitro* dissolution method used in the investigations has not been demonstrated to have any correlation to the *in vivo* behaviour of the medicinal products. Therefore, no definitive conclusion on the clinical consequences of tablet aggregation *in vivo* can be made based on these in vitro data only, particularly following intake of larger doses.

Additional (literature) investigations indicate that no *in vivo* or *in vitro* model is able to predict bezoar formation in case of paracetamol prolonged release overdose tablets.

Specific to the fixed-dose combination of paracetamol MR and tramadol, a literature review indicates that tramadol does not modify significantly gastric motility, at least not at intended doses and consequently an increased risk of pharmacobezoar formation due to tramadol appears unlikely.

2.3. Clinical aspects

As many data are relevant for both paracetamol MR as a monocomponent or associated with tramadol, unless additional comments are made for the fixed-dose combination of paracetamol MR and tramadol where differences exist with the monocomponent, the following sections are relevant for all paracetamol MR containing medicinal products.

2.3.1. Pharmacokinetics (PK)

Data for Alvedon 665 mg MR provided at the initial marketing authorisation have shown that, at therapeutic dose levels:

The paracetamol 665mg MR tablets and paracetamol 500mg immediate release (IR) tablets had an equivalent extent of absorption, with the MR tablets having a lower maximum concentration (C_{max}) and longer time to peak (T_{max}), as shown in figure 1 below.

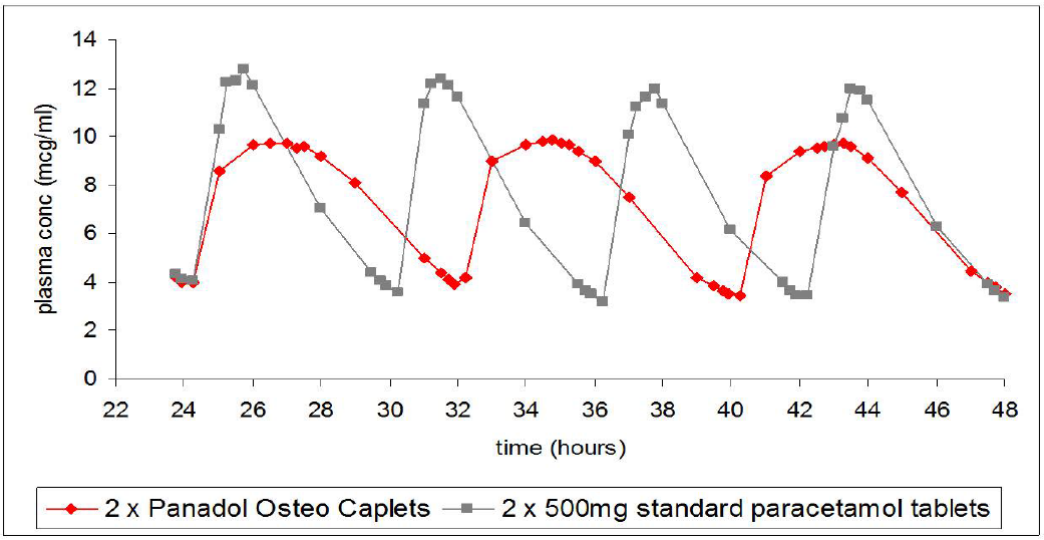

Figure 1. PK profile of paracetamol 665mg MR tablets & paracetamol 500 mg IR tables

The profiles were similar in both fed and fasting states and remained unaffected by food.

There was no evidence of accumulation on repeated dosing.

Post-marketing data demonstrated that the PK profile was significantly modified in poisoned patients. The recent data provided by the Swedish poisoning centre (Salmonson et al. 2017)[2], which are at the trigger of this referral, showed that the PK profile was particularly unpredictable in patients poisoned with the MR formulation (see figure 2 below). During this study unpredictable or erratic PK profiles were observed in the extended release which makes difficult the medical intervention and treatment of the overdose. Fifty-three cases were identified in this study Median age was 26 years (range 13–68), median dose was 20 g (range 10–166) and 74% were females. The pharmacokinetic analysis showed a complex, dose dependent serum versus time profile with prolonged absorption and delayed serum peak concentrations with increasing dose. Ten patients had persistently high serum levels for 24 h or more, six of them had a second peak 8–19 h after ingestion. Seven of 34 patients receiving N-acetylcysteine (NAC) within 8 h had alanine aminotransferase (ALT) above reference range. Three of them developed hepatotoxicity (ALT >1000 IU/l).

[2] 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. Clinical Toxicology, 2017, DOI:10.1080/15563650.2017.1339887

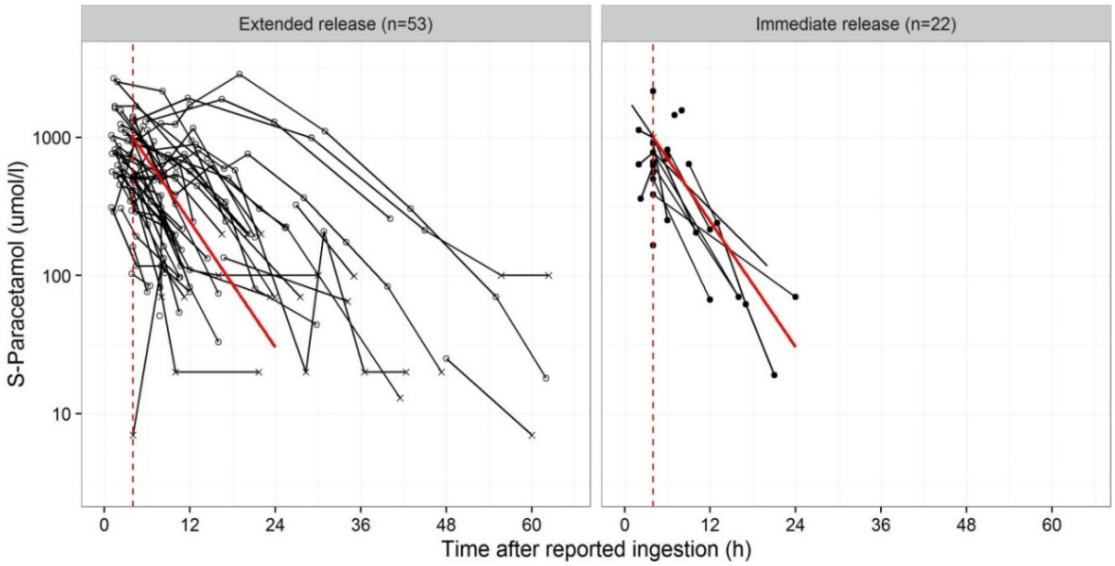

Figure 2. Differences in exposure profile between extended and immediate release paracetamol formulations in a log-linear scale

2.4. Clinical efficacy

The efficacy and safety of standard, IR paracetamol, at a dose ranging from 500 to 1000mg, used up to four times daily, has been established in clinical studies. The benefit-risk balance of paracetamol as a pharmaceutical ingredient is well established in various pain indications, including both acute and chronic pain conditions, as well as an anti-pyretic agent.

Paracetamol 665mg modified release

The paracetamol 665mg MR tablet formulations were developed to provide a more convenient dosing (i.e. 3 times daily) option for patients compared to IR paracetamol 500 mg tablets, which are generally taken up to four times daily (qid).

The paracetamol 665mg MR tablet has a bilayer delivery system composed of an IR layer intended for early release of paracetamol; and a prolonged release layer of paracetamol intended to provide longer lasting analgesia.

In EU Member States where the paracetamol 665mg MR product is approved, the product information (PI) have similar or identical with the ones as IR paracetamol formulations. The MR formulations are suited to longer term use and chronic pain conditions, such as pain of osteoarthritis, where continuous analgesia is needed and where patients might find convenient to take medication less frequently; i.e. 3 times daily instead of 4 times daily.

Four studies were have been submitted to support the benefit/risk balance of Alvedon 665mg MR tablets, two pivotal PK and two pivotal clinical studies.

Efficacy of paracetamol extended release has been demonstrated in 2 pivotal clinical studies: one in chronic pain associated with knee osteoarthritis (OA) (Bacon et al., 2002)[3], and one in acute post-

[3] Bacon TH, Hole JG, North M, Burnett I. Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee. Br J Clin Pharmacol. 2002 Jun;53(6):629-36

surgical dental pain (Coulthard et al., 2001)[4]. These two pain models were selected as representative of other chronic and acute pain indications, such as backache and headache, respectively.

Single dose following third molar extraction (625 patients): the primary objective was to compare the analgesic efficacy of a single dose of paracetamol 665mg MR tablets with that of a standard paracetamol IR tablet against acute pain. Post-operative pain and pain relief assessments were undertaken at time intervals up to 8 hours. This study showed that paracetamol 665mg MR and standard paracetamol IR tablets have similar effect. While paracetamol 665mg MR and paracetamol IR tablets were similar in terms of both onset of analgesia and peak analgesic effect, paracetamol 665mg MR had a longer duration of activity than IR paracetamol. The tolerability profiles were shown to be similar.

Multiple dose study (for 7 days) in patients having mild to moderate osteoarthritis of the knee (403 patients): the primary objective of the knee OA study was to compare the analgesic efficacy of paracetamol 665mg MR tablets against standard IR paracetamol tablets. Paracetamol 665mg MR taken three times daily had similar clinical effect and was therapeutically non-inferior to paracetamol IR taken four times daily in patients with knee pain due to OA. The distribution of adverse events between the treatment groups was similar by body system, severity and relationship to study treatment. Tolerability profiles were similar.

In these two specific indications, paracetamol was considered to have shown efficacy, on a short (7 days) and very short (one intake) treatment duration. Longer duration of treatment was not investigated in the studies supporting the Marketing Authorisation for Alvedon 665mg MR.

Since grant of this marketing authorisation, a new clinical study was performed by the MAH. The study (NCT02311881) evaluated the safety of an investigational prolonged-release 1000mg paracetamol formulation in osteoarthritis of the knee or hip for up to 12 weeks. In this study paracetamol 665mg modified release was used as an active control in 218 patients. The study results did not reach pre-specified criteria of statistical significance for efficacy for either paracetamol formulation against placebo. Both paracetamol formulations were well tolerated.

Published literature.

Williams et al. (2014) [5]: In the clinical study by Williams and colleagues (2014), which was a placebo-controlled study to investigate paracetamol in patients with acute low back pain, patients (n=1652) were randomly allocated to receive either (1) 4 weeks treatment with paracetamol 665 mg MR tablets (tid; equivalent to 3990 mg/day), or (2) as-needed doses of a IR paracetamol (taken when needed for pain relief; maximum 4000 mg/day), or (3) placebo. It is noted that participants did not take the full dose of paracetamol allowed in the study, the overall median daily tablet was 4 of the recommended 6 tablets in the MR paracetamol group and 1.9 of the recommended 8 tablets in the IR paracetamol group. This feature is not easy to explain, but it suggests that the compliance to paracetamol treatment was lower in the IR group than in the MR group, or differences in the need of pain control. There were no significant differences between paracetamol 665 mg MR tablets and either IR paracetamol or placebo with regard to pain relief measures (pain intensity, disability score and global change in pain relief) and other measures (sleep quality, quality of life, use of health services).

[4] Coulthard P, Hill CM, Frame JW, Barry H, Ridge BD, Bacon TH. Pain control with paracetamol from a sustained release formulation and a standard release formulation after third molar surgery: a randomised controlled trial. Br Dent J. 2001 Sep 22;191(6):319-24

[5] Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO, Lin CW. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. Lancet. 2014 Nov 1;384(9954):1586-96

Ortiz et al., (2016) [6]: The MAH refers to an observational study comparing prolonged release (PR) paracetamol with IR paracetamol for treating pain related to osteoarthritis found patients using PR paracetamol more likely to use paracetamol regularly than patients prescribed an IR paracetamol formulation (Ortiz et al., 2016). The study was a retrospective cohort longitudinal analysis on Pharmaceutical Benefit Scheme (PBS) payment claims in a 10% sample of the Australian population, using records from the Department of Human Services, and financially supported by the MAH. Analgesic equivalent days (AED) was calculated for each analgesic, using defined daily doses (DDD): AEDs= (strengths x quantity x number of scripts)/DDD. In total, subjects prescribed extended release (ER) formulations (ERP) took a similar number of AEDs as subjects prescribed IR formulations (IRP). However, the ERP patients took fewer AEDs of opioid analgesics and more AEDs of NSAID/COX-2 inhibitors than the IRP group.

The Australian NBS study by Ortiz and colleagues (2016) did not show all the benefits listed by the MAH, thus not giving a consistent picture in support of MR being more beneficial than IR.

The PRAC noted that the need for additional non-steroidal anti-inflammatory drug (NSAID) use in MR arm vs need for additional codeine containing products and strong opioids may be in favour of a beneficial pain control with MR paracetamol. However, the PRAC also noted that the increase in NSAID use speaks against an overall more beneficial pain control for the MR than the IR formulation. The most interesting finding from this publication was that patients on MR paracetamol, to a lesser extent added opioids. However, due to the limitations of this study, no firm conclusions can be drawn.

Benson et al. 2009[7]: The MAH also refers to an open-label Australian preference study (Benson et al. 2009) that showed a greater preference for the MR formulation among subjects with knee osteoarthritis. This is noted. It is however also noted that this study failed to show any difference in regard to sleep disturbances.

Bacon et al., 2002[8]: The MAH also refers to a randomised double-blind evaluation of pain relief in subjects with knee pain related to osteoarthritis, comparing sustained (slow) release (SR) and IR formulation of paracetamol. There was no difference in pain relief on Day 8 between groups and no difference was shown in regards to number of times woken during night, number of patients woken at least once, minutes of morning stiffness, number of patients with morning stiffness, number of rescue medication tablets taken or number of patients taking rescue medication. These results do not support an advantage of SR formulation over IR formulation.

Yaligod et al. (2014) [9]: A study has been performed by Yaligod and colleagues (2014) in patient with osteoarthritis of the knee. In this randomised, open label, parallel, active controlled clinical study with 250 patients, the efficacy and safety of paracetamol 650 mg dual release tablet twice daily was compared to paracetamol 500 mg IR tablet thrice daily. Duration of the study was 6 weeks. Paracetamol 650 mg dual release was significantly superior to paracetamol 500 mg IR for improvement in all osteoarthritis outcome score (KOOS) subscales at each study visit ($p<0.01$). Adverse effects were significantly less in paracetamol 650 mg dual release group (6% versus 14% in paracetamol IR group; $p<0.05$).

This study is important because the duration of treatment was longer than the study submitted in support of the initial application for the marketing authorisation, i.e. 6 weeks. However, the frequency

[6] Ortiz M, Calcino G, Dunagan F. Prescription usage patterns of two formulations of paracetamol in osteoarthritis: Australia-wide experience 2008-11. Aust Fam Physician. 2016 May;45(5):321-5

[7] Benson M, Marangou A, Russo MA, Durocher J, Collaku A, Starkey YY. Patient preference for sustained-release versus standard paracetamol (acetaminophen): a multicentre, randomized, open-label, two-way crossover study in subjects with knee osteoarthritis. J Int Med Res. 2009 Sep-Oct;37(5):1321-35

[8] Bacon et al 2002, Journ Clin Pharmacol

[9] Yaligod V, Raj DG et al., Dual release paracetamol in osteoarthritis of knee: a randomized controlled clinical trial., J Clin Diagn Res 2014; 8(11): LC11-15

of administration used was different from the normal recommended frequency, i.e. twice a day for the dual release formulation and thrice a day for the IR formulation. Thus the total daily dose was also less than the recommended maximum daily dose for both formulations. The open label design for evaluation of a subjective outcome is a further limitation.

Prior et al. 2014[10] : In the treatment of hip or knee osteoarthritis, Prior and colleagues (2014) have compared paracetamol extended release 1300 mg given three times daily to placebo in 542 outpatient adults (paracetamol: n=267 ; placebo: n= 275). The three primary endpoints measured through week 12 favoured paracetamol extended release (Western Ontario and McMaster Universities Osteoarthritis Index -WOMAC) pain subscale score, WOMAC total index score, patient's global assessment of response.

Altman et al. 2007[11]: Again in the treatment of osteoarthritis of the hip or knee, a randomised, double-blind, parallel group, placebo-controlled study evaluated the efficacy and safety of paracetamol extended-release 650 mg and 1300 mg given three times daily for the treatment of moderate to moderately severe osteoarthritis of the hip or knee. 483 patients were involved in this study. Paracetamol extended release 3900 mg daily was significantly superior to placebo for all three primary endpoints. Paracetamol extended release 1950 mg daily was significantly superior to placebo only with respect to patient assessment of response to therapy.

Finally a randomised study by Schnitzer and colleagues (2009) [12] comparing the efficacy of paracetamol extended release versus rofecoxib in patients with knee osteoarthritis (duration 4 weeks), paracetamol extended release 1300 mg three times daily was non inferior to rofecoxib 12.5 mg.

The above data were submitted by the MAH in support of the efficacy of the paracetamol MR formulations. The MAH considered that the benefits of the paracetamol MR formulation over the IR formulation includes more convenient dosing, potential reduction of end-of dose breakthrough pain, potential prevention of sleep interruption due to pain, reduced pill burden and potentially improved prescription adherence.

Uncertainties remain on the maintenance of the efficacy on the long term, all studies are of a short duration and no information is available on the potential for development of tolerance with time.

The PRAC concluded that of the advantages claimed by the MAH, only increased convenience has been convincingly shown through preference studies. Attempts to show improved sleep have failed. The only study that indicates better pain control is the Ortiz PBS study (2016), showing less use of opioids among MR-treated patients. However, these results come from a retrospective claims study, with substantial limitations and no consistent results in favour of a more beneficial pain control for MR paracetamol than IR.

Tramadol/paracetamol prolonged-release (PR) tablets

Tramadol/paracetamol immediate release (IR) combinations are marketed worldwide with a variety of indications in the treatment of moderate to severe pain. The analgesic efficacy and tolerability of IR tramadol 37.5 mg/paracetamol 325 mg (IR-TP) has been demonstrated in clinical trials evaluating its

[10] Prior MJ, Harrison DD et al., A randomized, double-blind, placebo-controlled 12 week trial of acetaminophen extended release for the treatment of signs and symptoms of osteoarthritis., Curr Med Res Opin 2014; 30(11): 2377-2387

[11] Altman RD, Zinsenheim JR et al. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2007; 15(4): 454-461

[12] Schnitzer TJ, Tesser JR et al., A 4-week randomized study of acetaminophen extended-release versus rofecoxib in knee osteoarthritis, Osteoarthritis Cartilage 2009; 17(1): 1-7

efficacy on several pain-related indications including acute nociceptive pain associated with orthopaedic surgery, osteoarthritis flare, and oral surgery.

The non-inferior analgesic efficacy of PR tramadol HCl 75 mg /paracetamol 650 mg (PR-TP) versus two doses of IR tramadol HCl 37.5 mg /paracetamol 325 mg (IR-TP) was demonstrated in a phase III, double-blind, placebo-controlled, parallel-group study of 320 randomised patients with moderate to severe pain following total knee replacement arthroplasty receiving oral PR-TP (every 12 hours) or IR-TP (every 6 hours) over a period of 48 hours. The study also showed comparable safety profile of both formulations (Park et al., 2015). Similarly, in another randomised non-inferiority trial of PR versus IR paracetamol formulations in patients with fever and pain, the antipyretic and analgesic efficacy of PR paracetamol (1000 mg) tablets taken twice daily was non-inferior to IR paracetamol (500 mg) tablets taken four times daily for three consecutive days (Ghosh et al., 2013).

The tramadol/paracetamol PR tablets are indicated in the symptomatic treatment of moderate to severe pain in adults and adolescents over the age of 12 years.

The MAHs claim the following advantages to the PR combination of tramadol/paracetamol:

- The addition of paracetamol to tramadol has a tramadol-sparing and a paracetamol-sparing effect, with an improvement of efficacy when compared to higher doses of tramadol or paracetamol alone. This allows also a simplification of the therapy (improving patient's compliance), a longer duration of action, and improved pain control during the night, as well as less adverse events.
- The paracetamol/tramadol combination corresponds to a step II treatment from the WHO analgesic ladder. The association of long-acting tramadol/paracetamol provides more consistent pain control, on a "around-the-clock" basis rather than "on demand", which is one of the main recommendations for proper pain control. The use of the tramadol/paracetamol association may allow reducing long-term use of non-steroidal anti-inflammatory drugs. The paracetamol/tramadol association is also free of organ toxicity associated with NSAIDs.

Diliban retard is bioequivalent to the same dose of an IR tramadol/paracetamol product. The efficacy of 75 mg tramadol HCl/650 mg paracetamol PR tablets in moderate to severe pain was demonstrated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical trial (06CCL3-001) performed using acute low back pain as a model.

Diliban retard is bioequivalent to the same dose of IR products. The MAH claimed that in comparison to IR, extended release (ER) analgesics such as Diliban retard offer more consistent and improved treatment of moderate to severe pain during the night, with less need to awaken at night to take another dose and less clock-watching due to a reduced dosing regimen (Nicholson et al. 2009)[13]. Furthermore ER analgesic forms such as Diliban 75 mg/650 mg prolonged release can attenuate of the peaks and troughs in serum concentration in relation to IR forms, which may lead to reduced adverse events (Pergolizzi et al. 2011)[14]. Some authors found that the single components of Diliban administered in an ER dosage form can have an additional benefit in relation to its IR forms. For example Hummel and colleagues[15] (1996) have found tramadol ER can be more effective and safer than IR tramadol in an analgesia study. Another study found prolonged release paracetamol forms

[13] Nicholson B. Benefits of extended-release opioid analgesic formulations in the treatment of chronic pain. Pain Pract. 2009 Jan-Feb;9(1):71-81.

[14] Pergolizzi JV Jr, Taylor R Jr, Raffa RB. Extended-release formulations of tramadol in the treatment of chronic pain. Expert Opin Pharmacother. 2011 Aug;12(11):1757-68.

[15] Hummel T, Roscher S, Pauli E, Frank M, Liefhold J, Fleischer W, Kobal G. Assessment of analgesia in man: tramadol controlled release formula vs. tramadol standard formulation. Eur J Clin Pharmacol. 1996;51(1):31-8.

appear to have an advantage over IR forms in the management of pain associated to osteoarthritis, contributing to a better management (Ortiz et al. 2016)[16].

The approval of Doreta SR rests on bioequivalence data only.

While no clinical studies were concluded with Doreta SR, different MR tramadol / paracetamol containing products have been investigated in a few clinical studies.

Lasko and colleagues (2012) investigated the efficacy and safety in patients with acute low back pain as a pain model. The double-blind phase of the study lasted for 2.5 days and patients who required further analgesia continued into the open-label phase (total trial duration for such patients was 5 days). A single dose of 1-2 of 75 mg/650 mg PR tablets was administered every 10 to 12 hours. The decrease in pain intensity (measured as the sum of pain intensity differences) observed in the tramadol/ paracetamol group was statistically significant in comparison to placebo.

A study by Lee and colleagues (2013) investigated the efficacy and safety of the extended-release tramadol/ paracetamol combination in patients with chronic low back pain. Patients received either the study medication (1-2 75 mg/650 mg tablets twice daily according to pain intensity) or placebo for a period of 4 weeks. Patients in the tramadol/ paracetamol group experienced significant improvements versus placebo in role–physical, general health, and reported health transition domains and significantly higher functional improvements in the personal care score of the used questionnaire.

The adverse effects observed in these studies were in line with the well-known safety profile of the tramadol and paracetamol combination.

Husic and colleagues (2015)[17] conducted a prospective study that showed efficacy of the combination paracetamol/tramadol in 353 patients suffering from cancer pain. Side effects were found in 29.18% of patients, with a predominance of nausea and vomiting.

Mochizuki and colleagues (2016)[18] showed a better efficacy of the tramadol/paracetamol combination than with NSAIDs.

Liu et al. 2012[19]: On the other hand, the importance of human polymorphisms has been emphasized to predict the efficacy of tramadol/paracetamol combination.

Gan et al. 2007[20]: The cytochrome P450 2D6 (CYP2D6) polymorphism may play also a major role in the efficacy and toxicity of tramadol.

In conclusion the MAHs claimed that the addition of paracetamol to tramadol allows a simplification of therapy (improving patient's compliance), a longer duration of action, improved pain control during the night, as well as less adverse events. PRAC concluded that there are some advantages to use of the long-acting tramadol/paracetamol combinations but the benefits are very limited, only a more simplified administration.

[16] Ortiz M, Calcino G, Dunagan F. Prescription usage patterns of two formulations of paracetamol in osteoarthritis: Australia-wide experience 2008-11. Aust Fam Physician. 2016 May;45(5):321-5.

[17] Husic et al., Efficacy and safety of a fixed combination of tramadol and paracetamol as pain therapy within palliative medicine, Mater Sociomed 2015; 27(1): 42-47

[18] Mochizuki et al., Tramadol/paracetamol combination versus NSAID for the treatment of perioperative pain after total knee arthroplasty: a prospective, randomized, open-label clinical trial, J Orthop Sci 2016; 21(5): 625-629

[19] Liu YC et al., Human mu-opioid receptor gene A118G polymorphism predicts the efficacy of tramadol/acetaminophen combination tablets in oxaliplatin-induced painful neuropathy, Cancer 2012; 118(6): 1718-1725

[20] Gan SH et al., Impact of CYP2D6 genetic polymorphism on tramadol pharmacokinetics and pharmacodynamics, Mol Diagn Ther 2007; 11(3): 171-181

2.5. Clinical safety

The tolerability of paracetamol at intended doses is well established. However, paracetamol is the most commonly reported toxic ingestion in the United States, the UK and other EEA countries and is the most common medicinal agent of intentional self-harm.

Under normal dosing the majority of the paracetamol is conjugated with glucuronide and sulphate and eliminated via the kidneys (Prescott et al, 1983)[21]. A small proportion (approximately 15%) is oxidised via cytochrome P450-enzymes to form a reactive metabolite, N–acetyl–p–benzoquinoneimine (NAPQI). NAPQI is normally de-toxified by binding to glutathione within the liver. After an overdose of paracetamol, the conjugation pathway becomes saturated and the metabolism of paracetamol is increasingly diverted towards oxidative metabolism and the production of toxic intermediates. As liver stores of glutathione become depleted, hepatotoxicity results if the rate of formation of NAPQI exceeds the rate of formation of hepatic glutathione.

The risk of hepatotoxicity due to paracetamol depends of the dose but also of the risk factors in the patients. The main other risk factors are age, malnutrition, alcohol intake, intake of co-medications or herbals which stimulate the CYP system or which delay gastric emptying time, chronic liver disease and concomitant renal insufficiency (accompanied by increased phosphate levels). Most episodes of hepatotoxicity occur as a result of late presentation to hospital.

Overdose treatment

The recommendations issued by the national poisons centres vary from a country to another and are based on currently available scientific knowledge.

The paracetamol dosing that may be associated with hepatic injury is subject to wide interindividual variation and depends on the dosing context. The key factors to consider in the risk assessment of an overdose are the dose and concentration (early), clinical and laboratory features suggesting liver damage (late), and any history suggesting susceptibility to toxicity (risk factors).

The basis of the treatment of paracetamol poisoning is constituted essentially by administration of N-acetylcysteine (NAC) intravenously. Different approaches exist regarding the administration of NAC.

A conservative approach is recommended in some EU Member State such as Denmark, where it is recommended to start NAC treatment immediately after hospitalization in case of overdose (in adults in case of paracetamol dose > 6 g; in children < 50 Kg: > 125 mg/Kg), also if paracetamol poisoning is only suspected. The rationale for this recommendation is the potentially unreliable information about the time of ingestion since overdose obtained from poisoned patients. The objective of a systematic treatment is to prevent patients poisoned with paracetamol tablets from not being treated with NAC.

Most countries use 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 of ingestion between ingestion and the blood test.

The Rumack-Matthew nomogram, which plots the independent time in hours vs paracetamol concentration, is generally used to determine if the patient is above of “probable toxicity line” or not (Yoon et al. 2016)[22]. The original nomogram included a paracetamol level of 200 µg/mL at 4 hours and 25 µg/mL at 16 hours after acute ingestion. In the United States, Australia and New Zealand as well as many EU countries, a more conservative recommendation has been established, starting at a 4-hour

[21] Prescott LF. Paracetamol overdosage. Pharmacological considerations and clinical management. Drugs. 1983;25(3):290–314

[22] Yoon E, Babar A, Choudhary M et al., Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update’, Journal of Clinical and Translational Hepatology, 2016, 4, 131–142.

paracetamol concentration of 150 µg/mL and known as the "treatment line" (see figure 3 below) which is intentionally set lower to account for inaccuracies in the history of paracetamol ingestion and inherent laboratory error in paracetamol measurement.

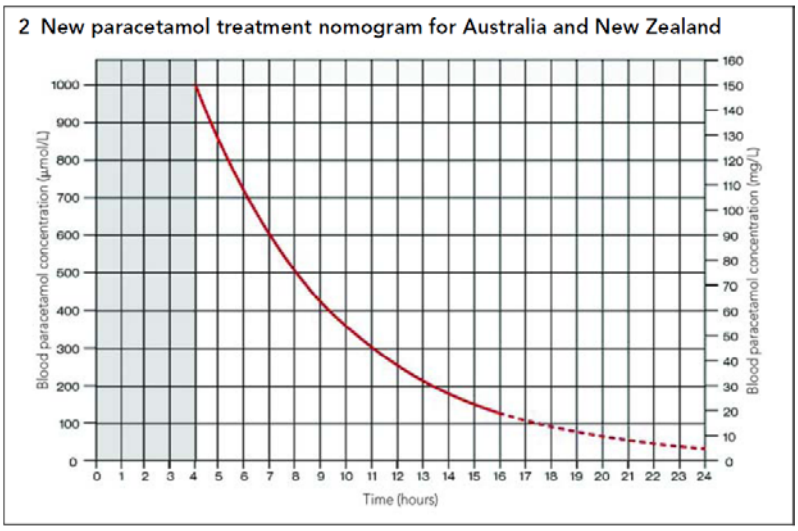

Figure 3. New paracetamol treatment nomogram for Australia and New Zealand

In the UK, the guidelines now recommends a single lower '100mg/L' line on the nomogram for all patients with acute over- dose and to stop assessing risk factors in deciding their need for treatment, on the basis that use of risk factor assessment was poor and inconsistent, and that many of the risk factors were imprecise and difficult to determine with sufficient certainty in clinical practice.

Bateman and colleagues (2014)[23] evaluated the impact of the UK's revised paracetamol poisoning management guidelines. The authors showed that the change has resulted in a highly significant increase in admissions and the proportion of patients treated for paracetamol poisoning (estimated UK effect: 31.1 thousand pre-change; 49.0 thousand post-change).

NAC itself is not devoid of risks and this needs to be considered; it has a non-mast cell-mediated histamine releasing effect. The effect is dose-dependent and, consequently, most systemic reactions to NAC can be seen in connection with the bolus infusion. Side effects occur in up to 50% of patients (Danish Guideline, Bateman et al. 2014). Cutaneous (rash, itching, flushing) and gastrointestinal (nausea, vomiting) effects are most frequently seen. Less frequently, adverse effects affecting respiration (cough, dyspnoea, chest pain, bronchospasm and angioedema) and circulation (hypotension, hypertension, tachycardia, ECG changes) are observed.

These anaphylactoid reactions may result in temporary cessation of therapy, extended treatment and admission duration. Because adverse effects, in particular vomiting and anaphylactoid reactions occur during or soon after infusion of the first 15 min bag, this is given over 60 min in some countries in the hope of reducing adverse effects, although the one clinical trial that assessed this question did not find a difference. This was challenged by Bateman and colleagues (2014) who found that the rates of vomiting requiring anti-emetic therapy and of anaphylactoid reactions were little different with a 60 min infusion as compared with a 15 min infusion, even in patients with low paracetamol concentrations, although they were delayed in patients receiving the 60 min infusion. They also

[23] Bateman D, Carroll R, Pettie J et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment, Br J Clin Pharmacol 2014; 78(3), 610-618.

confirmed a much higher rate of anaphylactoid reactions in those with lower paracetamol concentrations.

Bateman and colleagues (2014) also suggested that changes to paracetamol poisoning management guidelines should take into account the impact in rates of hospital presentation and admission, in use of NAC and in adverse reactions. They further point out that future updates should include better definitions of the amount of paracetamol required to constitute an overdose needing NAC treatment. They also underlined the potential for use of novel biomarkers.

A. Paracetamol in modified release tablets

Cases of overdoses reported

During the procedure the MAH (GSK Consumer Healthcare) performed data base searches and further analyses of the cases reported with paracetamol 665 mg MR. One search was performed on 11 December 2016, and retrieved 308 cases of overdose and medication error, whereof 108 cases were received since the previous assessment. Of these 108 new cases 75 originated from Sweden. The total number of cases probably included duplicates that may be difficult to identify. Of the 308 cases, 83 were considered assessable cases of paracetamol MR intentional overdose.

The MAH presented an overview of the 83 assessable poisoning cases. However, the MAH did not discuss any of the cases more in depth. Two deaths were reported: one in a patient who have not presented to hospital until 48 hours after intoxication, thus the outcome would have been the same had the IR formulation been ingested instead, and another in 79 year old man who received treatment 4-6 hour after intoxication, which normally should prevent liver failure. It is unclear why this case was fatal, and if the outcome would have been another with a different treatment, such as higher NAC doses. Ten cases describe a second peak in paracetamol concentration, with the second peak higher than the value reported after 4 hours or later. This phenomenon reveals the unforeseeable kinetic profile for this product, and although only few of the cases show this pattern, the uncertainty creates a clinical problem every time an individual taking an overdose is to be treated.

From the narratives of 7 cases, it can be seen that paracetamol plasma concentrations may be unpredictable, making individual assessments difficult to undertake.

The MAH noted that the current Australian management guidelines for paracetamol poisoning would have identified 80 out of the 83 cases as needing NAC treatment. The current Swedish protocol would have identified 48 cases on the available data, plus most likely another 11 cases that presented to hospital < 4 hours after intake with high paracetamol concentrations (no 4h measurement was made). Of the remaining 24 cases, no NAC would have been indicated based on the 4h value, but in 3 of these, no more values were presented, which would have been taken according to the Swedish protocol. For another 11 cases, serial measurements were not made at or close to the timepoints stipulated in the Swedish guideline, so the conclusion that they would not receive treatment is not certain. The MAH pointed out that several of these did in fact receive the antidote. It should be kept in mind that many of the cases occurred before the current guidelines were implemented, explaining why they were not followed. From the data presented which show high levels of paracetamol of a longer duration than with paracetamol IR overdoses it is confirmed that a normal NAC treatment scheme is not adequate.

The highly variable PK-profile of an MR overdose presents a risk factor to be taken into account together with all the other possible risk factors (risk factor for hepatotoxicity such as malnutrition, reduced food intake, modulation of CYP 450, chronic alcohol abuse etc.). However, due to a lack of data it is not possible to adopt a definitive decision tree for risk minimization of hepatic injury for paracetamol MR overdoses.

The PRAC requested later in the procedure an analysis which aimed at selecting the cases with hepatotoxicity (IR and MR) and discuss those more in depth. The data suggested that in practice the majority of cases of IR overdose result in the administration of NAC antidote, and that outcome may be favourable even with late presentation. The largest risk factor for hepatotoxicity for IR is time-to-treatment. However, the response did not provide a comparative analysis based on individual cases but rather overview tables, which lacks information on dose, time-to-treatment or the degree of hepatic injury, for example. The overview provided by the MAH did not suggest a different outcome between the MR and the IR overdose and any comparison is limited by the absence of information on the circumstances (e.g. other concomitant medications and clinical history). Furthermore, any comparison built on spontaneously reported cases had high uncertainty, and very limited value. Data with MR paracetamol were too limited to conclude, however, hepatic toxicity can occur even if presentation is <10 hours post-ingestion, although outcomes can be favourable even with late presentation.

As request from the PRAC the MAH assessed more published literature. In case of massive overdoses (>30g) with IR formulations, there are also reports of some PK profile unpredictability and higher rates of hepatotoxicity (Marks et al. 2017[24], Chiew et al. 2017[25]). There are also reports in the literature of more problematic overdoses, in extreme cases, with IR paracetamol; e.g. with delayed or double peaks (Doyon et al. 2009[26], Hendricksen et al. 2010[27]). For the MR formulation, the MAH concluded that delayed peaks of serum paracetamol (s-paracetamol) drug levels can occur following overdose, and that multiple serum samples should be taken to guide management. Treatment with NAC should be maintained as “clinically indicated”.

However, the PRAC concluded that most of these cases referred, particularly reports of double peaks, were in patients with particular characteristics or who had taken a mixture of substances (e.g. opioids); affecting the outcome and that such IR overdoses cannot be compared with the consequence of the inherent characteristics of the MR formulations. Further, the PRAC was not aware of un-confounded cases reporting double peaks following an IR formulation overdose.

The MAH has also contacted Poison Information Centres (PICs) in all countries where MR paracetamol is marketed, and asked for treatment protocol, and hepatotoxicity associated with cases of intoxications with paracetamol. From the Australian PIC, out of the 81 cases where additional data were received, 14 cases were considered ‘late line crossers’ and all had consumed >10 g and therefore would have received treatment with NAC according to Australian treatment guidance. The PRAC noted these data.

Risk associated with overdose with MR formulations

Dart and colleagues (2005)[28] published a review paper looking at the safety of paracetamol MR preparations both at the therapeutic dose level and in overdose. These authors conclude that paracetamol MR tablets would cause the same type of liver damage as paracetamol IR tablets in overdose. Dart and colleagues (2005) concluded that the adverse event and safety profile of MR is similar to the IR formulation of paracetamol.

[24] Marks DJB et al., Outcomes from massive paracetamol overdose: a retrospective observational study, Br J Clin Pharmacol 2017; 83, 1263-1272

[25] Chiew AL, Isbister GK, Kirby KA, Page CB, Chan BSH, Buckley NA. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol. 2017:1-11.

[26] Doyon S, Klein-Schwartz W, Hepatotoxicity Despite Early Administration of Intravenous N-Acetylcysteine for Acute Acetaminophen Overdose. Acad Emerg Med 2009; 16: 34–9

[27] Hendrickson RG, McKeown NJ, West PL, Burke CR., Bactrian (‘double hump’) acetaminophen pharmacokinetics: a case series and review of the literature. J Med Toxicol 2010; 6: 337–44

[28] Dart RC, Green JL, Bogdan GM. The safety profile of sustained release paracetamol during therapeutic use and following overdose. Drug Saf. 2005;28(11):1045-56.

There are three published case studies which identify particularly challenging risk assessment and risk minimisation measures in overdoses with paracetamol MR tablets. Furthermore, an abstract from an additional Australian case series became available 2017 (see further below).

Graudins and colleagues (2010)[29] reported 4 cases of overdose and recommend an additional assay 4 hours after the first blood paracetamol level.

Graudins and colleagues (2014)[30] presented a case series of 42 Australian patients with overdose, and concluded that most patients presenting after paracetamol 665mg MR tablet overdose requiring NAC treatment had an initial serum paracetamol concentration indicating need for treatment. From this cohort review, the authors noted that among patients presenting with paracetamol MR acute single ingestion requiring NAC treatment (27 cases), 85% (23/27) had an initial serum paracetamol concentration indicating the need for treatment. However, 15% (4/27) had an initial non-toxic concentration that later increased above the line. In 14 untreated patients (median ingested dose 7980 mg), one was an unrecognised late line-crosser with initial non-toxic serum paracetamol concentration. It appears that a small number of patients had an initial 'non-toxic' serum paracetamol concentration which subsequently crossed the nomogram line indicating need for treatment with NAC. In the patients with an initial 'non-toxic' serum paracetamol concentration and subsequent line-crossing to a toxic concentration, treatment was indicated based upon the dose ingested as per the current Australasian treatment guideline. A small number of late treatment nomogram line-crossers were seen on repeat paracetamol estimation. Graudins reports that, in general, 'line crossers' tended to have an initial serum paracetamol at 4 h above 500 µmol/L and a reported dose more than 10 g, suggesting that in this group, there should be a high suspicion for a subsequent 'toxic' concentration. Three of the patients who did not receive treatment with NAC should have been treated, based upon their reported dose or later high paracetamol concentration. Graudins concludes that the current Australian nomogram for paracetamol poisoning would have detected all cases requiring NAC treatment. In the cohort hepatotoxicity (a peak ALT more than 1000 IU/L) developed in two patients. One patient had a 'massive' ingestion (945 mg/kg) and the other was a late presenter (9.5 h post-ingestion).

(Salmonson et al, 2017)[2] : Data presented by the Swedish Poisons Centre, (Salmonson et al, 2017) described a series of 53 patients with overdose reported after ingestion paracetamol 665mg MR. The mean age was 30.5 years (range 13–68), median reported dose 23 g (range 10–166) and 76% were females. The number of serum paracetamol concentrations per individual ranged from 1 to 10. Forty-three patients were treated with NAC.

A very high variability has been observed in the PK profiles of MR poisoned patients. Both the absorption duration and the terminal half-live are longer in the poisoned patients as compared to profiles observed at therapeutic dose levels for both the IR and MR formulations. The PK analysis showed saturable absorption as the duration of the absorption was correlated to increasing amounts of ingested drug. A plateau with high serum concentrations for 24 hours or more were observed in 21%, and 5 patients had a second peak approximately 12 hours (range 8–19) after intake.

[29] Graudins A, Chiew A, Chan B. Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol. Intern Med J. 2010, Jan;40(1):72-6

[30] Graudins A. Overdose with modified-release paracetamol (Panadol Osteo®) presenting to a metropolitan emergency medicine network: a case series. Emerg Med Australas. 2014 Aug; 26(4): 398-4

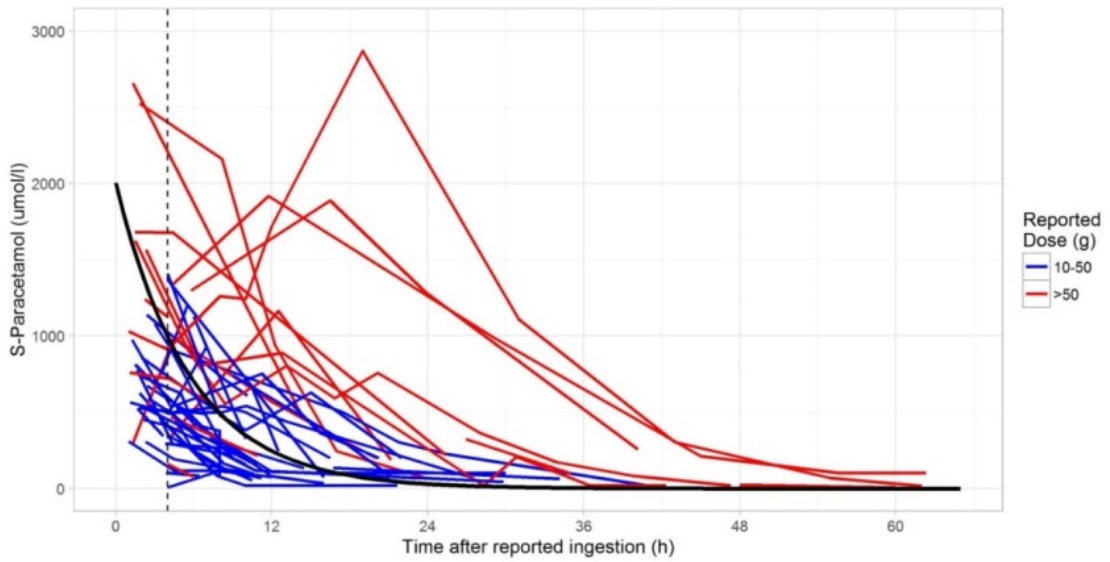

Figure 4. Observed serum paracetamol (s-paracetamol) versus time after ingestion in 53 cases (linear scale). Cases with dose interval 10-50 gram in blue, cases with dose > 50 grams in red.

Late crossing of the standard treatment nomogram (Campbell line) 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.

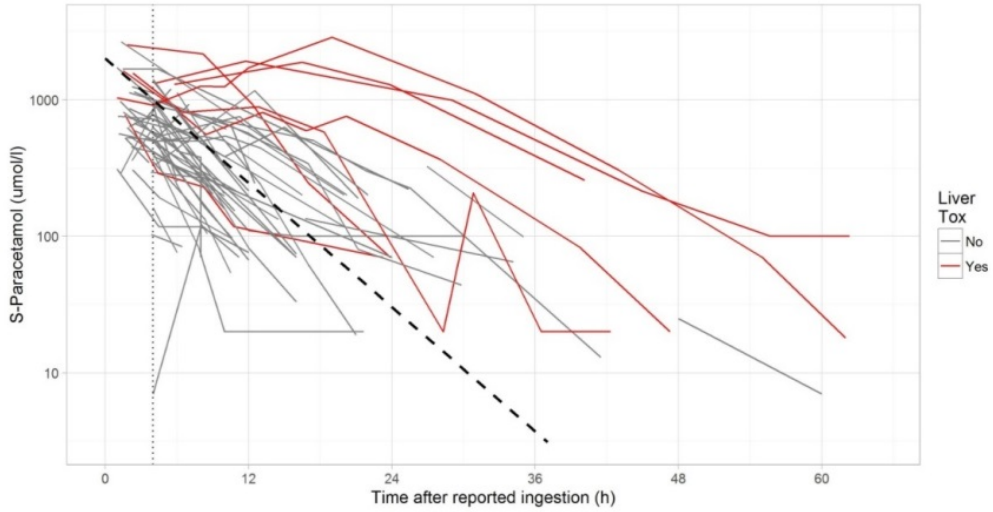

Figure 5. Observed s-paracetamol versus time after ingestion in 53 cases (log-linear scale). Cases with liver impairment despite timely NAC are shown in red.

The authors conclude that the treatment recommendations based on IR formulations are inadequate after intake of toxic doses of this MR preparation. Risk assessment using initial serum samples 4–8 hours after estimated intake cannot be trusted. The authors recommended modifications to the treatment in case of overdose with MR formulation paracetamol. The Swedish Poison Information Centre updated their guidelines in 2016.

In the end of April 2017, an abstract about a prospective observational study in Australia, including 54 patients with acute paracetamol intoxication with MR formulation has been published (Chiew et al, EAPCCT, Basel 2017). Of these, 39 had an initial paracetamol concentration above the nomogram line at 4 hours. Another 7 patients crossed the nomogram after repeat paracetamol concentration measurements, whereof 3 after 2 non-toxic concentration measurements 4 hours apart. Six patients had a double paracetamol peak, whereof 3 >24 hours after ingestion. Thirty patients required prolonged treatment with NAC, in 18 of these due to a paracetamol concentration >150 mg/L 24 hours after intoxication.

Ten patients out of 54 developed hepatotoxicity, defined as ALT >1000 U/L. This seems unexpectedly many based on experience with IR paracetamol. Three of these were treated within 8 hours of ingestion. These data show a similar picture to what has been reported from Sweden, as detailed above.

In conclusion, there were several points of line-crossing across publications i.e. patients for whom it is clear that the current nomogram is not applicable. Moreover, in the different publications, a disconnection between liver function enzymes levels (ALT) and paracetamol levels was consistently reported. This supports the need for better characterisation of the link between paracetamol exposure and liver damage. Single concentration measure seems not to be informative particularly for modified release formulations.

Management of overdoses with paracetamol MR tablets

In some of countries where MR paracetamol is marketed, adaptations of the national guidelines have been made to take into account the specific pharmacokinetics of MR paracetamol containing medicinal products.

The current Danish guidelines recommend NAC to adults who have ingested >6g paracetamol, and 82 of the 83 cases would thus have been treated. The remaining case reported a “handful” of tablets, illustrating the uncertainty that often afflict this kind of information.

In Australia/New Zealand, the guidelines were updated in 2008 and recommend to immediately start NAC if more than 200mg/kg or 10g (whichever is less) has been ingested. If less than this amount has been ingested, serum paracetamol (s-paracetamol) level may be used to determine the need for NAC. In all cases, serum paracetamol levels should be taken at 4 hours post ingestion (as for IR formulations) and repeated 4 hours later. If either level is above the treatment line (nomogram starting at 150 mg/L at 4h) then NAC treatment should be initiated or continued.

The additional testing of s-paracetamol at 4-6h after the first measurement is also recommended by the MAH and has been included in the SmPCs of paracetamol 655mg modified release in several EU Member States. During this procedure, questions were asked to the Australian Therapeutic Goods Administration (TGA) to know if they had gained experience since the publication of the new guidance. However, based on the information available to TGA through spontaneous adverse event reports, it is not possible to know if the new guidance have reduced the risk of hepatic injury in case of overdose with paracetamol MR. In Sweden, the poison centre adopted in 2016 a modified recommendation in case of overdose with MR paracetamol as a consequence of the study by Salmonson et al. (2016). The additional measures include a) performing extra s-paracetamol measurements at 4, 6, 12 and 18 hr in order to determine if starting NAC is necessary and to what extent, b) lowering the action threshold by using the ‘100mg/L’ nomogram in case of overdose with MR paracetamol, and c) bolus dose of NAC followed by the second dose level (12.5 mg/kg/h), used as maintenance dose (≥20 hrs), and this because liver impairment developed in patients treated despite the NAC regime (standard treatment in IR paracetamol overdosed).

The updates proposed to the treatment protocol are based on a limited number of cases from the Swedish poison centre and the cases series published by Graudins and colleagues in 2014[30]. This means that an uncertainty on the effectiveness of the revised treatment protocol remains.

One MAH (GSK Consumer Healthcare) included in the referral procedure developed a population pharmacokinetic model with data from 28 subjects receiving IR paracetamol under therapeutic conditions, 27 subjects receiving MR paracetamol under therapeutic conditions, 52 patients who were exposed to IR paracetamol in the overdose setting, and 219 patients who were exposed to MR paracetamol in the overdose setting were used to build the model. The therapeutic data was obtained from a relative bioavailability study with intensive sampling, the IR overdose data was obtained from the MAH post marketing safety database, and the MR overdose data was obtained through request of poison information centres in Australia and case data from Sweden provided by PRAC. The resulting model proposed was a two compartments model with combined first and zero order absorption and a lag time before absorption. Linear clearance was observed at therapeutic levels and was altered in the overdose setting. Model fitting performances were displayed and were overall acceptable. The MAH claimed that the model was able to describe both the IR and modified release paracetamol pharmacokinetic levels in the overdose setting acceptably well. There was a small amount of deviation from the line of unity at the extrema of the observed concentrations, which the MAH suggested that they were due to limited observations at the very lower and higher ends of the concentrations. However, the proposed model was not able to describe double peaks that are observed in some patients particularly in case of OD with high doses of MR paracetamol. This was considered a substantial shortcoming by the PRAC.

Regarding characterisation of the absorption phase, further model based analysis of the 53 cases from the Swedish Poison Information Centre has been performed by Salmonson and colleagues (2017). This analysis describes the double peak phenomenon occurring at high overdoses. It is shown that the second peak occurs later and later with increasing doses. Essentially, the analysis points to that the standard treatment nomogram used for interpreting serum paracetamol concentration after IR over doses can be misleading for the MR formulation, especially at high overdoses. Projections of half-life based on early concentration measurements are error prone at high over doses since double peaks are expected. Serum paracetamol following MR ingestion needs to be followed over a longer period of time compared to IR to see whether absorption is ongoing or if the terminal phase of the concentration-time profile has been reached. Of note, the model by Salmonson and colleagues (2017) is different compared to the MAH's model as the former can describe the observed double peaks while the latter does not. Since the double peak phenomenon have been observed by others (Chiew et al, (EAPCCT) 2017[31, 32]), it is likely that the model proposed by Salmonson and colleagues (2016, 2017) provided a more realistic description of the data in the absorption phase.

Regarding the disposition model, the model proposed by the MAH is in line with the known mechanisms in case of overdose with paracetamol. The well documented saturation of the absorption and saturation of some of the metabolism pathways are also well captured by the model proposed by the MAH. Line crossers were also observed for IR formulation but their number was relatively more elevated for the MR formulation.

Based on the newly available models, it is acknowledged that a single measurement of s-paracetamol at 4 hours after ingestion as recommended in protocols for IR is not sufficient to adequately estimate the risk for a patient to develop hepatic damage after an overdose of MR paracetamol. However, it is

[31] Chiew et al, 37th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 16–19 May 2017, Basel, Switzerland

[32] Chiew AL, Isbister GK, Kirby KA, Page CB, Chan BSH, Buckley NA. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol. 2017:1-11.

also noted that the MAH did not submit a PK/PD model intended to determine the most optimal way to manage cases of overdose with paracetamol MR.

B. Tramadol/paracetamol prolonged release tablets

The safety profile of paracetamol as well as of tramadol, irrespective of formulation is well established with no significant differences between the slow release and the IR formulations in normal conditions of use. The most common symptoms present at admission were nausea and/or vomiting (66.67% of cases).

Overdose is an already important identified risk for Diliban retard in the risk management plan (RMP) and is monitored in the periodic safety update reports (PSUR) of Diliban retard and Doreta SR.

About one in 12 adults in Nova Scotia filled at least one prescription for paracetamol/opioid combination drugs during a one-year period starting July 2009. Of these individuals, 6% filled prescriptions that supply paracetamol doses greater than the usual recommended daily dose of four gram and one in five exceeded 3.25 grams per day. In case of overdose, paracetamol becomes a dangerous and life-threatening drug due to liver damage and has become the most common cause of acute liver damage in Western countries, as described above.

The effects of tramadol overdose are well known, with the expected characteristics of opioid toxicity; such as vomiting, cardiovascular collapse, consciousness disorders including coma, convulsions and respiratory depression including respiratory arrest. Tramadol in supra therapeutic doses may also reduce GI motility.

At an overdose with these combination products, the effect of tramadol on slowing GI motility, causing convulsions at higher doses, as well vomiting may make the evaluation and risk minimisation of the paracetamol overdose even more unpredictable than after intake of paracetamol only.

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

Based on the data reviewed within this procedure, it is clear that the standard regimen, including use of the nomogram, is inadequate for handling of an overdose with a paracetamol MR formulation. The presence of tramadol further complicates management of these overdoses, e.g. due to reduced GI motility, leading to further delay in paracetamol absorption, and by other effects caused by tramadol such as convulsions and vomiting.

One of the proposals made by the MAHs to minimise the risk was that a prompt communication with the national Poison Centres should be advised as part of the risk minimisation strategy for all overdose cases. However, they have not established that such recommendation will result in adequate risk minimisation throughout the EU, in particular considering the operations of these Centres are substantially different across the EU Member States.

There are also serious doubts on the feasibility of minimising the risk by revising the current overdose protocols in EU due to a lack of evidence on an optimised, proportionate and effective protocol, as well as its feasibility to be implemented across EU Member States. The complexity of managing two specific protocols, a closer monitoring (e.g. frequency of blood sampling) and related to the uncertainty on the ingested formulation are 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.

3. Expert group consultation

An expert group has been consulted (March 2017) to evaluate which modifications to the treatment recommendation would constitute the preferred option to reduce the risk for hepatic injury in case of an overdose with MR paracetamol, taking into account the existence of various guidelines at national level (Poison Centres) and in hospitals.

The experts were asked by the PRAC to comment on the impact of the pharmaceutical characteristics of the products on the risks of hepatotoxicity in the situation of intake of an overdose, and to consider the available *in vitro* dissolution data, the risk of formation of a bezoar (i.e. large aggregates of tablets with an unpredictable disintegration) and the potential of different release profile of the aggregated tablets. The experts considered that *in vitro* data is inadequate to predict PK profile in overdose situations. The conditions under which studies were done do not reflect the clinical situation of patients overdosing. *In vivo* data is essential to clarify the magnitude of the risk. They also considered that the risk that aggregates will form *in vivo* is high and these will influence the risk of hepatotoxicity, which fits with the PK data observed in the Swedish case series. To further complicate the situation, patients may present with altered gastric absorption and poor motility of GI tract. The latter particularly applies to MR combination products with tramadol.

The experts were also requested to comment on data or clinical experience to support that there are patient groups for which the MR paracetamol products have added value. The patients' adherence to treatment of pain is generally good, regardless of formulation. The claimed advantage of administration 3 times a day *vs* 4 times a day was questioned, and the claim that the MR formulation leads to uninterrupted sleep may not be supported by available data. Evidence for efficacy in chronic pain is weak, evidence for acute pain is more robust but the clinical need in this setting could be addressed adequately by the IR formulation. Irrespective of the risk of overdose, the experts could not identify any particular clinical situation or population in which MR shows a clinical advantage over IR.

The experts commenting on harm from overdose, highlighted the complications both in assessment and treatment of poisoning by MR paracetamol, because of the unpredictable release profile of MR, the PK profile and the difficulty in establishing an optimal treatment protocol. The experts noted that, even in some EU Member States where MR products are not currently authorised, cases of poisoning with MR have been observed due to the fact that patients travel across the European Union with their medication, leading to further difficulties in treating patients for overdose. No experience of overdose exists with the combination products, but due to the safety profile of tramadol (e.g. convulsions, vomiting) these products raise even larger concerns.

The current treatment strategies vary between EU Member States. The experts noted that Australia has the largest experience with this MR paracetamol and that the Australian guideline for the management of paracetamol poisoning could be used as a basis for developing EU recommendations, if such guidelines are considered feasible. Currently available data is limited and does not allow robust and detailed recommendations for treatment of overdose with MR formulation to be constructed. However, it was agreed that separate protocols would need to be in place for treating overdose with IR and overdose with MR or unknown formulation. For the latter, the experts noted that at least two s-paracetamol measurements would be needed in order to make a treatment decision, and in case treatment with NAC is initiated, a further sample should be taken before discontinuation. Presence or absence of liver injury needs to be considered in treatment decisions. It is also not possible to recommend a predefined dose threshold for MR paracetamol above which NAC treatment should be systematically initiated.

NAC treatment is associated with relatively frequent vomiting and anaphylactoid reactions (more common at low paracetamol concentrations) which can further complicate the management of

patients. This is a clear drawback for starting systematically NAC treatment before toxic paracetamol concentrations have been established. This was considered to be less of a concern in cases where a higher maintenance dose or of prolonged treatment with NAC would be justified, based on s-paracetamol measurements, and relevant indicators of liver injury.

The experts did not support lowering the nomogram curve, as it is only relevant for the IR formulations. While it is not possible to recommend specific time points for checking s-paracetamol, at least 2 measurements would be necessary in order to make a treatment decision, and another one before discontinuation of NAC. No tests other than checking s-paracetamol and indicators of liver injury would be recommended before discontinuing NAC treatment. A rise in s-paracetamol between two consecutive time points may lead to a treatment decision, but a threshold cannot be defined based on available data, and clinical judgement has to be used.

In overdose, patients are frequently not able to provide information on the exact product/ agent ingested. Not knowing which formulation is involved would potentially imply that patients need to be treated as if they took the MR formulation. However, this in turn would make the results of a single s-paracetamol blood test uninterpretable and the need for repeated s-paracetamol measurements would increase hospital admissions unnecessarily in many instances. It needs to be noted that in poisoning cases the exact formulation is usually not the only unknown variable when deciding on treatment. A somewhat similar problem in paracetamol poisonings is related to repeated overdoses. National poison information centres generally have recommendations for managing these different situations, but the recommendations may vary between member states.

It is plausible that increasing NAC dose and duration could be effective, but data is lacking. It may be feasible to collect data on the tolerability of higher NAC doses, as well as on prolongation of NAC administration, but a system for organized data collection across the EU would be needed.

There were different views among the experts on the effect of reducing pack size. It was noted that larger pack sizes may carry additional risk, but that smaller pack sizes may not be suitable for chronic situations which is where an advantage is claimed.

There was a consensus that bottles may carry additional risk in relation to blister packs and should be reserved for particular setting such as hospital.

Experts considered that educational material for the public are unlikely to be helpful, but that HCPs may benefit from information particularly on the need to avoid prescribing these products to patients at risk of self-harm and on how to treat overdose with these formulations.

In relation to prescription status, experts considered that due to the additional risk of overdose, these products are not suitable for non-prescription status. However it was also noted that the majority of data on overdose originates in Sweden, where the prescription status did not prevent the occurrence of these situations. This may be explained by the higher market penetration of MR formulations in this country.

4. Risk minimisation measure proposals

During the procedure and the oral explanations provided, the MAHs took the opportunity to provide responses and presented a list of risk minimisation measures for the risk of overdoses by MR paracetamol containing medicinal products. These measures included, routine measures, proposed changes to the Product information (section 4.9 of summary of product characteristic, SmPC) to inform the clinicians on the overdose treatment (based on treatment protocol), warning in prescribing the

smallest pack size, and against exceeding the recommended dose (section 4.4 of SmPC). Also in the outer package a proposal for a warning was made. In addition the MAH supported the use of the smaller packaging and only in blister packs.

In terms of the protocol of treatment of the overdose, the MAHs supported that a common treatment protocol can be recommended for all MR paracetamol-containing medicinal products (monocomponent and combination) for simplification of the treatment in all countries. They also suggested that a common DHPC letter could be used to inform the clinicians on the protocol adaptations.

In addition the 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 effectiveness of protocol adaptations.

The PRAC considered all the risk minimisation measures proposed to reduce the risk of overdose e.g. prescription status and reduced pack sizes, 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.

5. Benefit-risk balance

5.1. Initial Benefit-risk assessment

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 - 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 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 (DHCP, 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, DHCP) 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.

5.2. Re-examination procedure

Following the adoption of the PRAC recommendation in September 2017, two MAHs (GSKCH and KRKA d.d., Novo mestro) have requested the re-examination of the recommendation and submitted detailed grounds for the re-examination. These are presented and discussed below.

It is noted that the PRAC is a scientific committee and that, while PRAC operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the PRAC, and therefore the re-examination of the PRAC initial recommendation, adopted in the framework of the referral procedure under Article 31 of Directive 2001/83/EC, focuses only on the scientific grounds for re-examination.

5.2.1. Detailed grounds for re-examination submitted by the MAHs

A. Paracetamol modified release tablets

The MAH of the MR paracetamol only containing product (GSKCH) claimed in their grounds firstly that the benefit-risk balance remains favourable and the available data in acute and chronic pain demonstrate that MR paracetamol offers benefits to patients in its approved indications.

Secondly the MAH argued that the risk related to overdoses can be effectively managed through the proposed N-acetylcysteine (NAC) treatment protocol which is similar to the current Australian and New Zealand treatment guidelines.

Thirdly, the MAH proposed additional risk minimisation measures that would in its view effectively support the appropriate use of the product, and sufficiently prevent the risk of intentional and accidental overdoses.

B. Tramadol/paracetamol prolonged release tablets

For the MR tramadol/paracetamol-containing product, one MAH (KRKA d.d., Novo mestro) presented detailed grounds for Doreta SR.

Firstly, the MAH claimed that their combination of tramadol and paracetamol, intended for treatment of moderate to severe pain, has an important role in the management of pain; its use is reserved for those patients who require a combination of tramadol and paracetamol to adequately manage pain in chronic conditions. The MAH also emphasised that the use of this combination avoids escalation to opioid-containing products and can reduce the intake of NSAIDs.

Secondly, the MAH argued that, the sustained-release tramadol/paracetamol combination should be evaluated independently from single-ingredient paracetamol MR in view its distinct characteristics, namely in terms of indications, target population and prescription status, all these being the factors which impact the patient exposure.

Thirdly, the MAH argued that there is no evidence of increased risk of hepatotoxicity with the combination. Considering all available data, the MAH is of the view that the risk of hepatotoxicity cannot be extrapolated to the tramadol/paracetamol MR combination. Only 3 cases of overdose were identified through the poison centres with the product, none of which was associated with hepatotoxicity. Therefore, the MAH believes there is no evidence of higher risk of hepatotoxicity with the MR combination compared to the IR tramadol/paracetamol combination products.

The MAH also made a comparison of the strength of evidence of increased risk of paracetamol MR formulation with that of paracetamol IR formulation based on the published literature, and presented arguments as to why they considered the strength of evidence not strong.

In addition, the MAH argued that the impact on public health and healthcare systems of the potential increased risk of hepatotoxicity was low with the combination products. The differences in frequency of overdose with MR paracetamol and consecutive risk for liver injury and failure among EU MS were highlighted (Gulmez et al., 2015)[33]. Furthermore, the MAH pointed to the fact that erratic pharmacokinetics of MR paracetamol most likely occur after acute massive overdose, while in its view massive intake of the combination product is less likely to occur. The MAH further considered that the management of overdose of MR paracetamol would be efficient with the revised protocol. The MAH concluded that the impact of the management of the overdose cases on the national healthcare system would to vary between MS and to was expected to be low regarding the combination product, as they consider the potential for overdose with the combination to be low and as revisions in the management protocol are likely to be minimal in MS where it is marketed.

Finally the proposed risk minimisation measures were considered appropriate by the MAH and sufficient to minimise any potential increased risk of hepatotoxicity related with intentional or accidental overdose.

5.2.2. PRAC discussion on grounds for re-examination

The PRAC considered all the elements of the detailed grounds submitted by both MAHs and presented in oral explanations.

A. Paracetamol modified release tablets

Having considered the detailed grounds submitted by GSKCH, 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

[33] Gulmez SE, Larrey D, Pageaux GP, Bernuau J, Bissoli F, Horsmans Y, Thornburn D, McCormick A, Stricker B, Toussi M, Lignot-Maleyran S, Micon S, Hamoud F, Lasalle R, Jove J, Blin P, Moore N. Liver transplant associated with paracetamol overdose: results from the seven-country SALT study. Br J Clin Pharmacol. 2015 Sep;80(3):599-606.

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 (Chiew et al, 2017; Salmonson et al, 2017; Graudins et al, 2014) 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 (Chiew et al, 2015)[34]. 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 N-acetylcysteine dose are administered to patients. The authors also suggest a negligible risk from modest increases in N-acetylcysteine 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[29], 2014[30]) 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 (GSKCH) 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.

[34] Chiew AL, Fountain JS, Graudins A, et al. Summary statement: new guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust 2015; 203 (5): 215-218.

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)[35] 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 (KrKA) 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 et al (2012)[36] investigated the efficacy of MR tramadol/paracetamol formulation for acute low back pain, while Lee et al (2013)[37] 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.

[35] Carroll R, Benger J, Bramley K, Williams S, Griffin L, Potokar J, Gunnell D. (2015). Epidemiology, management and outcome of paracetamol poisoning in an inner city emergency department. Emerg Med J., Feb;32(2):155-60.

[36] Lasko B, Levitt RJ, Rainsford KD, Bouchard S, Rozova A, Robertson S. Extended-release tramadol/paracetamol in moderate-to-severe pain: a randomized, placebo-controlled study in patients with acute low back pain. Curr Med Res Opin. 2012 May;28(5):847-57.

[37] Lee JH, Lee CS; Ultracet ER Study Group. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. Clin Ther. 2013 Nov;35(11):1830-40.

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 (Major et al, 2016[38]; Yoon et al, 2016 [39]).

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.

[38] Major JM, Zhou EH, Wong HL, Trinidad JP, Pham TM, Mehta H, Ding Y, Staffa JA, Iyasu S, Wang C, Willy ME. Trends in rates of acetaminophen-related adverse events in the United States. Pharmacoepidemiol Drug Saf. 2016 May;25(5):590-8.

[39] Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update. J Clin Transl Hepatol. 2016 Jun 28;4(2):131-42

5.2.3. Expert group consultation during the re-examination

A second ad-hoc expert group meeting took place in November 2017, following the request from the MAH (KRKA) of the combination of MR paracetamol/tramadol and a summary of the conclusions is provided below.

The experts considered that, theoretically, the only patient groups that might benefit from the modified release (MR) tramadol/paracetamol combination product are those affected by chronic pain and sleeping interruptions due to pain. However, the experts also considered that there is insufficient evidence to support the added value of tramadol/paracetamol MR formulation over other therapies in such population or any other patient group.

The experts agreed that studies conducted with therapeutic doses of tramadol show only minimal delays in gastric emptying. However, this may be more pronounced at higher overdoses due to the pharmacological properties of tramadol. In the absence of data, it is impossible to conclude on the level of dose at which this effect can be clinically relevant. The delays in gastric emptying are expected to further complicate the clinical management of overdose.

The experts agreed that the management of overdose cases involving MR formulation of paracetamol/tramadol combination, compared to the management of overdose cases involving MR paracetamol alone, would be more complex. Given the tramadol toxicity profile (CNS effects, high risk of seizures and renal failure) there is potential for multi-organ toxicity.

There is evidence indicating that the proposed MR overdose treatment protocol is not optimal; reference was made to the abstract by Chiew and colleagues (2017) which showed a significant toxicity of MR formulation despite NAC treatment and further data and time are needed to gain substantial evidence and define an optimised NAC regimen for the MR overdose management.

The experts conveyed that separate protocols are deemed necessary for treating overdoses of IR or an MR paracetamol formulations, respectively. They also confirmed that in countries where MR paracetamol-containing products are available, cases where the formulation involved in the overdose is unknown should be managed as overdoses due to MR paracetamol.

In principle, a useful model could be developed but the current version as proposed by the MAH (GSKCH) was seen as not sufficient due to sample size limitation and further methodological challenges. The currently proposed PK model was seen to be relevant as a way to describe the data but may not be sufficient as a predictive tool of outcome in individual patients for the purposes of optimising NAC dose. To address uncertainties in the management of overdose cases with the MR formulation of paracetamol, a mechanistic model would be required. This would require collection of rich sampling data from a large number of overdose patients and should also take into account other relevant parameters e.g. solubility of paracetamol, kinetics of the toxic metabolite (NAPQUI), and kinetics of NAC administered as antidote.

The experts noted that it is not possible to extrapolate from a 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.

With regards to the proposal for a PASS study measuring the effectiveness of a new modified model or new guidelines for treatment of paracetamol overdose, this approach was endorsed by the experts. However, a sample size of 100 patients was considered not sufficient. Hypothetically, a good PK model can be used to facilitate the design of a clinical trial which could eventually inform the guidelines for treatment of paracetamol overdose; this will take time to put in place.

In theory, limiting the accessibility by decreasing pack sizes is reasonable. However, from the clinical point of view, this approach may not be suitable for a product intended for chronic treatment.

5.2.4. Conclusion 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.

6. Direct Healthcare Professional Communications

Key elements for a DHPC have been adopted to inform the Healthcare professionals (HCP) of the suspension of the marketing authorisation of the MR paracetamol and MR tramadol/paracetamol-containing medicinal products. A suggested communication plan was also adopted. The documents are enclosed with this report.

The DHPC should be sent to emergency departments, intensive care units, general practitioners in the Member states.

7. Condition(s) for lifting the suspension of the marketing authorisations

To lift the suspension, the MAHs 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.

8. Grounds for Recommendation following the re-examination procedure

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.

Pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisations for paracetamol containing modified-release medicinal products.

The conditions imposed to lift the suspension of the marketing authorisation are set out in the relevant section of this report.

Appendix 1

Divergent position(s)

Procedure No: EMEA/H/A-31/1445

Paracetamol modified and prolonged release products

Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 31 referral for paracetamol containing medicinal products in a modified release (MR) formulation based on the following reasons:

- The benefit/risk balance of the paracetamol containing modified-release formulations in the normal use, within the frame of the marketing authorisation, was positive at the time of marketing authorisation (MA) granting and no new information has been provided to challenge this.
- The issue raised in this referral pertains to off-label uses of the modified release formulation and is mainly associated to intentional overdose (OD) and refers to a pharmacokinetic profile that requires that the protocol to treat overdose should be adapted to avoid undertreating some patients or missing to treat some patients in need.
- When considering the entirety of currently available data, the evidence do not support with reasonable certitude an increase in the risk of severe hepatic injury with the MR formulation as compared to the immediate release (IR) formulation, especially in case of MR formulation containing tramadol and paracetamol due to scarce data. For example some data suggested that increased transaminases, need for liver transplantation and deaths were similar for both formulations at comparable doses. In addition, the evidence does not suggest that there is an increased risk of overdose with the modified release formulation, either intentional or unintentional.
- 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) and were consistent with increased risks of hepatotoxicity observed in massive overdose (> 30g) with IR formulations were similar figures were reported.
- A risk minimization measure to mitigate the risk of hepatotoxicity which has been proposed and agreed by all marketing authorisation holders (MAHs): namely an adapted protocol for paracetamol OD management, based on experience accumulated in Australia with paracetamol MR. Based on Australian experience, there is strong basis indicating that this protocol would have effectively minimized the risk associated with overdose with modified release formulation (delayed serum paracetamol peak, sustained and long lasting plasma concentrations) at a level comparable to that of immediate release formulations at comparable doses.
- The risk minimisations proposed agreed by MAHs included a PASS during which the adapted protocol was planned to be improved based on results of mechanistic PK/PD modelling and simulations that would permit better characterization of the need in N-acetylcysteine (NAC) and determined the best NAC dosing regimen based on stoichiometry of reactions between paracetamol concentrations, metabolites (including *N*–acetyl–*p*–benzoquinone imine; NAPQI)

and NAC. This would have constitute valuable advance as compared to the currently used protocol which based on a nomogram empirically characterized that has shown limitations for management of OD with both IR and MR paracetamol when massive OD are concerned.

- A second PASS was also foreseen to assess the effectiveness of the new protocol and to further mitigate the uncertainties related to the ability of the adapted protocol to achieve similar efficiency in preventing severe outcomes in case of OD with the MR formulation as the one achieved with IR formulation.
- The challenges posed by the implementation of such protocol would have been manageable as in many cases treatment of overdose already need to be tailored to the specifics of each patient (dose ingested, time to presentation at ER, co-ingested drugs or alcohol …).
- Additional measures would have further minimized the risk associated with overdose with MR formulation: updated package leaflet, communication to HCP (DHCP), restriction to the access to bottle packaging and large blister pack size for the patients.

Due to the above mentioned arguments the below mentioned PRAC Members consider the benefit/risk balance of paracetamol MR and sustained release (SR) or prolonged release (PR) tramadol/paracetamol associations positive justifying the maintenance of the marketing authorisations of all paracetamol containing medicinal products in extended-release formulations subject to variation and conditions to the marketing authorisations.

The re-examination procedure did not present any new data to suggest a negative benefit/risk from MR paracetamol containing products.

PRAC Members expressing a divergent opinion:

Ana Sofia Diniz Martins	29 November 2017	Signature: ……
Doris Stenver	29 November 2017	Signature: ……
Eva Jirsová	29 November 2017	Signature: ……
Gabriela Jazbec	29 November 2017	Signature: ……
Jan Neuhauser	29 November 2017	Signature: ……
Julia Pallos	29 November 2017	Signature: ……
Laurence de Fays	29 November 2017	Signature: ……
Lennart Antero Waldenlind	29 November 2017	Signature: ……
Nikica Mirošević Skvrce	29 November 2017	Signature: ……
Roxana Stefania Stroe	29 November 2017	Signature: ……
Sofia Trantza	29 November 2017	Signature: ……
Tatiana Magalova	29 November 2017	Signature: ……
Zane Neikena	29 November 2017	Signature: ……

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

Procedure No: EMEA/H/A-31/1445

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protocol which based on a nomogram empirically characterized that has shown limitations for management of OD with both IR and MR paracetamol when massive OD are concerned.

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The re-examination procedure did not present any new data to suggest a negative benefit/risk from MR paracetamol containing products.

PRAC Member expressing a divergent opinion:

Kirsti Villikka	29 November 2017	Signature: ……

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

Procedure No: EMEA/H/A-31/1445

Paracetamol modified and prolonged release products

Divergent statement

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PRAC Member expressing a divergent opinion:

David Olsen	29 November 2017	Signature: ……