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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Jascha Johann Hörnisch	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Katelijne Van Keymeulen	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Jitka Vokrouhlická	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 modified-release formulation of paracetamol is widely used in the clinical practice as an effective analgesic, especially in chronically ill patients suffering from pain due to both benign and malignant diseases, e.g. multiple myeloma. The formulation is also used for its antipyretic activity, especially in patients who suffers from fever due to e.g. malignant haematological diseases (leukemias or lymphomas). In the refractory and palliative setting of these diseases, fever is a common symptom. The modified release paracetamol is effective with an acceptable safety profile in these groups of patients, enabling them to have a better overall living and a coherent night's sleep.

- 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Katrine Damkjaer Madsen	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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. 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Johanna Ruotsalainen	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Sabina Uzeirbegović	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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.
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Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Judit Pandi	13 December 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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Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Orn Gudmundsson	13 December 2017	Signature: ……

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

Paracetamol modified and prolonged release products

Divergent statement

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- 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Monta Emersone	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Cheryl Aquilina	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Inger Heggebø	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Marta Marcelino	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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 CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Marina Popescu	13 December 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

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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.
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Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Nevenka Prpar	13 December 2017	Signature: ……

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

Paracetamol modified and prolonged release products

Divergent statement

The following member of CMDh did not agree with the PRAC's Recommendation on the Article 31 referral for products containing paracetamol, modified and prolonged release, 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 where 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.
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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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Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDh Member expressing a divergent opinion:

Maria Polaková	13 December 2017	Signature: ……