IPAR

Type II
Final Variation Assessment Report

Palladone SR 4, 8, 16 & 24 mg Prolonged Release Capsules (Hydromorphone Hydrochloride)
IE/H/131/01-04/II/30

Palladone 1.3, 2.6 mg Capsules
IE/H/131/05-06/II/30

Marketing Authorisation Holder: Mundipharma Pharmaceuticals Ltd

Date: 7th May 2013

Deadline for Comments by CMS – Day 85	1st June, 2013

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ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Palladone 1.3, 2.6 mg Capsules & Palladone SR 4, 8, 16 & 24 Prolonged Release Capsules
Name of the active substance (INN, common name):	Hydromorphone Hydrochloride
Pharmaco-therapeutic group (ATC code)	N02A A03
Pharmaceutical form(s) and strength(s)	1.3 & 2.6 mg Capsules & 4, 8, 16 & 24 SR Prolonged Release Capsules

Procedure number	IE/H/131/01-06/II/30
Member States concerned	IE/H/131/01-04/II/30 – NO IE/H/131/05-06/II/30 – DE &NO

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Nature of change/s requested	B.II.d.1.E Change in the specification parameters and/or limits of the finished product

Active Substance Master File (ASMF) Assessment Report/s	N/A

I INTRODUCTION

I RECOMMENDATION

Based on the review of the data on quality and safety, the RMS considers that the variation for Palladone 1.3, 2.6 mg Capsules & Palladone SR 4, 8, 16 & 24 Prolonged Release Capsules (Hydromorphone Hydrochloride) to change the limits for related substances in the finished product specifications is approvable.

II. EXECUTIVE SUMMARY

II.I Scope of Variation

During the renewal applications for the Palladone range, commitments were made to submit variations to change the limits for related substances in the finished product specifications. These commitments were requested by the RMS as the levels of some degradation products exceeded the registered specification limits when tested at the recommended long-term ICH conditions (25° C/60%RH) but the same batches were within specification following storage at a lower relative humidity (25°C/35%RH).

Taking into account the mean derived storage conditions for Zone I countries based on prevailing annual climatic conditions (21°C/45%RH), it was accepted at the time of the renewal that there was no immediate concern regarding the quality of product on the market in Member States involved in these procedures.
However, it was also recognised that the standard ICH long-term storage conditions for stability studies in both zone I and II countries is 25°C/60%RH and shelf-lives for medicinal products are set based on the stability demonstrated under ICH conditions. Therefore the MAH agreed to initiate a project to carry out toxicological studies to justify a widening of the impurity limits in the finished product specifications and thus conclusively address the OOS results for impurities obtained during the registered shelf-life of the product.
The present and proposed specifications for related substances which reflect the findings of the toxicological studies and a review of available batch data and stability data are included as Annex 1 to this report. Changes (including both widening and tightening) are proposed to the release and shelf-life limits for a number of related substances.
As part of this variation it is also proposed to amend the specifications for microbiological contamination to include a cross-reference to the acceptance criteria for non-aqueous preparations for oral use in Ph. Eur. 5.1.4.

II QUALITY ASPECTS

III.1.1 Potential serious risks to public health

N/A

III.1.2 Points for clarification

Query raised in the PVAR

1. No pharmaceutical data (batch analysis or stability data) has been provided as part of this variation to support the proposed changes in the specification limits and in particular the proposed widening of the shelf-life total impurity limits for the prolonged-release capsules. The MAH should provide a summary of the available batch analysis and stability data (with particular emphasis on data from more recent batches) to support the proposed changes in the finished product specifications.
   Summary of MAH response:
   Prolonged-release capsules
   To support the change of shelf-life limits for total impurities, stability data up to 24 months is provided for the following batches of prolonged-release capsules, where the maximum total impurity amounts were seen during stability testing at 25°C/60% RH:
   Table 1 Batches for which the maximum total impurity amounts were seen during stability testing at 25°C/60% RH

Table 1 Batches for which the maximum total impurity amounts were seen during stability testing at 25°C/60% RH		
Strength	**Batch number**	**Total Impurity Amount**
4 mg	117756	4.9%
8 mg	146250	4.5%
16 mg	112531	4.7%
24 mg	135118	3.5%

A summary of batch analysis and stability data from studies conducted since 2007 are also provided for five batches of each strength of prolonged-release capsules. The MAH believes that the data support the changes to the shelf-life specification limits of the single named impurities and the total impurity limits, as all results at 25°C/60% RH are within the new impurity limits at release and during shelf life.
The MAH believes that the data show that the tightened release limit of 0.2% for all impurities is sufficient to ensure compliance with the shelf-life limits for the duration of the registered shelf-life.
Immediate-release capsules
Batch analysis and stability data from studies conducted since 2007 are provided for five batches of each strength of immediate-release capsules.
The MAH believes that the data support the changes to the shelf-life specification limits of the single named impurities and the total impurity limits, as all results at 25°C/60% RH are within the new impurity limits at release and during shelf life.
The data show that the tightened release limit of 0.2% for all impurities is sufficient to ensure compliance with the shelf-life limits for the duration of the registered shelf-life.
Assessor comment:
The additional batch analysis and stability data provided by the MAH support the proposed total impurity limits for the prolonged-release capsule. The data also provide assurance for both immediate-release and prolonged-release capsules that the proposed release limits should ensure compliance with the shelf-life limits at the end of the registered shelf-life. Issue resolved.

Query raised in the PVAR

2. The MAH should provide assurance (based on a review of the historical batch release and stability data) that the release limits for all impurities are sufficiently tight to ensure compliance with the proposed shelf-life limits for the duration of the registered shelf-life.
Summary of MAH response:
Batch analysis and stability data are provided, as summarised in the response to Question 1.
The data presented are all within the proposed release and shelf life impurity limits and show that the tightened release limit of 0.2% for all impurities is sufficient to ensure compliance with the proposed shelf-life limits for the duration of the registered shelf-life.
Assessor comment:
See the assessment of the response to Question 1 – issue resolved.

Query raised in the PVAR

3. The MAH should provide assurance that appropriate method validation studies have been performed to establish that the approved method for related substances is suitable to control Dihydroxyhydromorphone and 7α–(6β–dihydromorphinyl) Hydromorphone at the proposed specification limits (the range of previous method validation studies may need to be extended).
Summary of MAH response:

The MAH states that the approved methods (HYDM-054 & HYDM-056) for related substances are suitable to control Dihydroxyhydromorphone at the updated specification limit of 2.2%, as the new limit for this impurity is within the range of previous method validation studies conducted (the linearity of response for hydromorphone hydrochloride over the concentration range 0 to 150.3% of nominal hydromorphone content was investigated).
In the absence of a suitable standard for Dihydroxyhydromorphone, this impurity has been quantified with respect to the Hydromorphone standard using HYDM-054 & HYDM-056.
For the qualification studies a limited sample of Dihydroxyhydromorphone was synthesised. Based on this, the

Relative Response Factor (RRF) with respect to Hydromorphone was calculated to be approximately 1.8. As the RRF of 1.8 is an approximate value the MAH decided not to alter the approved methods HYDM-054 & HYDM-056. The MAH believes that this decision is supported by the fact that the determination of Dihydroxyhydromorphone content with respect to Hydromorphone, in the absence of an RRF, produces an over estimation of the Dihydroxyhydromorphone content in Palladone immediate-release and prolonged-release capsules. Therefore the MAH concludes that there will be no impact on product quality or patient safety.
Approved methods HYDM-055 & HYDM-057 (for late eluting impurities) were validated for linearity, accuracy and precision for related substances over the range 0 to 1.3% related substance with respect to the nominal hydromorphone content (using pseudohydromorphone to represent all late eluting impurities). The new specification limit of 2.0% for 7α-(6β-dihydromorphinyl) Hydromorphone is outside the original validated range for the method. Additional method validation was performed and is provided to support the increased limit, by conducting repeating linearity over an extended range of 0 to 2.6%. The MAH states that results show that the method is suitable to control the specified limit of 2.0% of 7α-(6β-dihydromorphinyl) Hydromorphone.
Assessor comment:
The MAH has provided sufficient assurance that the method has been adequately validated to control dihydroxymorphone at the proposed specification limit. Even though the MAH has not taken into account the relative response factor with respect to hydromorphone in the calculation of the dihydroxymorphone content, the practical implication of this is an overestimation of the dihydroxymorphone content which does not represent a safety concern.
The additional linearity data provided to demonstrate that the method is capable of controlling for 7α-(6β-dihydromorphinyl) Hydromorphone at the proposed 2.0% limit has been provided and is acceptable.
Issue resolved.

III NON-CLINICAL ASPECTS

N/A

V OVERALL CONCLUSIONS

The MAH has satisfactorily addressed all of the points for clarification that were raised by the RMS in the PVAR and the proposed changes to the limits for related substances in the finished product specifications can be approved.