**PUBLIC SUMMARY DOCUMENT**
**Product:** Hydromorphone hydrochloride, prolonged release tablets, 8 mg, 16 mg, 32 mg, 64 mg, Jurnista®
**Sponsor:** Janssen-Cilag Pty Ltd.
**Date of PBAC Consideration:** November 2008

## 1. Purpose of Application

To seek a Restricted Benefit listing in the General and Dental Schedules for chronic severe disabling pain not responding to non-narcotic analgesics.

An Authority Required listing in the Palliative Care Schedule was also requested for palliative care patients with chronic severe disabling pain not responding to non-narcotic analgesics.

## 2. Background

This was the first submission requesting listing of this hydromorphone hydrochloride prolonged release tablet formulation.

At the July 2005 meeting the PBAC recommended the listing of hydromorphone hydrochloride extended release capsules (Palladone® XL) as a restricted benefit for the treatment of chronic severe disabling pain not responding to non-narcotic analgesics, noting the benefits of having a range of different opioids available to allow physicians to tailor treatment to individual requirements. The product was withdrawn later in 2005 due to a potential dose-dumping effect if used concomitantly with alcohol.

## 3. Registration Status

Hydromorphone hydrochloride prolonged release tablets were registered by the Therapeutic Goods Administration on 29 July 2008 for the treatment of moderate to severe pain, to be used in patients requiring continuous analgesia.

## 4. Listing Requested and PBAC's View

General Schedule:
Caution:
The risk of drug dependence is high.

Restricted Benefit
Chronic severe disabling pain not responding to non-narcotic analgesics.

Note:
Authorities for increased maximum quantities and/or repeats will be granted only for:
(i) chronic severe disabling pain associated with proven malignant neoplasia; or
(ii) chronic severe disabling pain not responding to non-narcotic analgesics where the total duration of narcotic analgesic treatment is less than 12 months; or
(iii) first application for treatment beyond 12 months of chronic severe disabling pain not responding to non-narcotic analgesics where the patient's pain management has been reviewed through consultation by the patient with another medical practitioner, and the clinical need for continuing narcotic analgesic treatment has been confirmed. The date of the consultation must be no more than 3 months prior to the application for a PBS authority. The

full name of the medical practitioner consulted and the date of consultation are to be provided at the time of application; or
(iv) subsequent application for treatment of chronic severe disabling pain not responding to non-narcotic analgesics where a PBS authority prescription for treatment beyond 12 months has previously been issued for this patient.

Dental Schedule:
Caution:
The risk of drug dependence is high.

Restricted Benefit:
Chronic severe disabling pain not responding to non-narcotic analgesics.

Note:
Prescribing of drugs of addiction by dentists is not permitted in some States/Territories.

The PBAC deemed that a listing in the Palliative Care Schedule would be inappropriate

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

Hydromorphone prolonged release tablets offer an additional treatment option in the management of chronic pain.

## 6. Comparator

The submission nominated oxycodone controlled release (CR) tablets as the comparator. The PBAC accepted this as appropriate.

## 7. Clinical Trials

The submission presented one direct randomised comparative trial (unpublished) and one supplementary randomised comparative trial (Hale 07) comparing OROS hydromorphone and oxycodone CR in patients with chronic pain due to non-cancer causes.

The submission also presented an indirect comparison of one direct randomised trial of OROS hydromorphone (unpublished) and three direct randomised trials of oxycodone CR with morphine sustained release (SR) (Mucci 98, Heisk 97 and Brue 98) as the common comparator in the treatment of chronic pain due to cancer.

Details of the studies published at the time of the submission are presented in the table below.

| Trial ID | Protocol title/Publication title | Publication citation |
|---|---|---|
| Hale 07 | Efficacy and tolerability of once-daily OROS (registered trademark) hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: Results of a 6-week, randomized, open-label, noninferiority analysis. | Hale M, et al. *Clinical Therapeutics* 2007; 29(5):874-888. |
| Mucci 98 | Controlled-release oxycodone compared with controlled-release | Mucci-LoRusso P, et al. *European Journal of Pain* 1998; 2(3): 239-249 |

| Trial ID | Protocol title/Publication title | Publication citation |
|---|---|---|
| | morphine in the treatment of cancer pain: a randomised, double-blind, parallel-group study. | |
| Brue 98 | Randomised, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. | Bruerea E, et al. *Journal of Clinical Oncology* 1998; 16(10): 3222-3229 |
| Heisk 97 | Controlled-release oxycodone and morphine in cancer related pain.<br><br>Morphine or oxycodone in cancer pain? | Heiskanen T et al. *Pain* 1997; 73: 37-45<br><br>Heiskanen T et al. *Acta Oncologica* 2000; 39(8): 941-47 |

## 8. Results of Trials

The submission presented two efficacy analyses: in non-cancer pain (direct) and in cancer pain (indirect).

In the non-cancer pain trial ANA3001, OROS hydromorphone and oxycodone CR were considered to be equivalent in terms of change from baseline to endpoint in mean brief pain inventory (BPI) pain severity sub-score 'pain right now' for both ITT and PP analyses. This was based on the pre-specified equivalence criterion where the upper boundary of the confidence interval is below the non-inferiority margin of 1.0.

From the cancer pain trials, OROS hydromorphone and morphine SR were considered equivalent (95% two-sided CI for the difference between the adjusted means lies within -1.5 to 1.5), in terms of change from baseline to endpoint in the mean of the last two recorded scores for "worst pain" both in the ITT and PP analysis during the immediate release phase.

It was noted that overall, the primary outcomes in the trials for treatment of non-cancer and cancer pain vary between the trials.

The results of two indirect comparisons based on standardised mean difference and normalisation of the rating scale to a common scale of 11 points were provided. Based on the standardised mean difference methodology, OROS hydromorphone and oxycodone CR are considered equivalent. Based on the normalised score methodology, however, OROS hydromorphone was considered superior to oxycodone CR (95 % two-sided CI for the difference between the adjusted means lies within -1.5 to 1.5).

In the direct non-cancer pain trial, the most common adverse events were nausea, constipation, vomiting, fatigue and hyperhidrosis, in both treatment groups. In Hale 07, the most common adverse events were nausea, constipation, vomiting and somnolence. The incidence of constipation was higher in patients taking OROS hydromorphone compared to oxycodone CR in both trials, however the differences were not statistically significant.

In the unpublished cancer pain trial, the event rate of constipation and headache was higher in OROS hydromorphone than in morphine SR patients. The rate of nausea, vomiting and dizziness was higher in morphine SR patients. In Mucci 98, more patients in the oxycodone

CR group reported adverse events compared to the morphine SR group. In Heisk 97, constipation was significantly more common with oxycodone CR, while vomiting occurred significantly more with morphine SR.

*For PBAC's comments on these results, see Recommendation and Reasons.*

## 9. Clinical Claim

The submission claimed OROS hydromorphone was non-inferior in terms of comparative effectiveness and comparative safety to oxycodone CR.

*For PBAC's view, see Recommendation and Reasons.*

## 10. Economic Analysis

The submission presented a cost-minimisation analysis claiming the equi-effective doses to be OROS hydromorphone 26.4 mg and oxycodone CR 74 mg, giving a ratio of 1 : 2.80. This was accepted by the PBAC.

The submission calculated the weighted average dose used for OROS hydromorphone and oxycodone CR in chronic pain (due to cancer and non-cancer causes) based on the trial data.

## 11. Estimated PBS Usage and Financial Implications

The submission estimated the number of prescriptions per year to be greater than 200,000 in Year 5 with net savings to the PBS of less than $10 million per year over the first 5 years of listing.

## 12. Recommendation and Reasons

The PBAC recommended the listing of hydromorphone hydrochloride prolonged release tablets on the PBS in the General and Dental schedules for the treatment of chronic severe disabling pain not responding to non-narcotic analgesics on a cost minimisation basis to oxycodone controlled release (CR) tablets. The equi-effective doses are 26.4 mg hydromorphone hydrochloride prolonged release to 74 mg oxycodone hydrochloride controlled release, giving a ratio of 1: 2.8.

The PBAC considered the evidence presented supported the claim of non-inferior clinical efficacy of hydromorphone PR compared to oxycodone CR for both non-cancer and cancer related chronic pain, with results possibly favouring hydromorphone in the treatment of cancer related pain.

The comparative safety data presented supported the claim of non-inferior safety of hydromorphone PR tablets compared to oxycodone CR tablets, however the Committee was very concerned with likelihood of serious toxicity if the product is crushed and injected intravenously. The PBAC requested its DUSC employ their relationship with the National Drug and Alcohol Research Centre (NDARC) to be alerted if NDARC becomes aware of issues with illicit use of hydromorphone PR tablets. The PBAC also requested that the National Prescribing Service (NPS) educate prescribers of the potential serious toxicity of the hydromorphone PR tablet product and remind prescribers of the potential for diversion of opioids from the PBS. The Committee also requested that the ADRAC alert it if it becomes aware of reports of toxicity related to hydromorphone PR tablets.

The PBAC did not recommend the application for listing in the Palliative Care Schedule as the Committee deemed the listing would be inappropriate considering the use of hydromorphone PR tablets in the treatment of chronic pain is not specific to the palliative care setting. The PBAC noted that prescribers would be able to access hydromorphone PR tablets through the General Schedule for their palliative care patients, consistent with the listing of other opioids on the PBS for the treatment of chronic pain.

***Recommendation***

HYDROMORPHONE HYDROCHLORIDE, prolonged release tablets, 8 mg, 16 mg, 32 mg, and 64 mg, Jurnista®

Restriction:

General Schedule:

Caution:

The risk of drug dependence is high.

Restricted Benefit

Chronic severe disabling pain not responding to non-narcotic analgesics.

Note:

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(i) chronic severe disabling pain associated with proven malignant neoplasia; or

(ii) chronic severe disabling pain not responding to non-narcotic analgesics where the total duration of narcotic analgesic treatment is less than 12 months; or

(iii) first application for treatment beyond 12 months of chronic severe disabling pain not responding to non-narcotic analgesics where the patient's pain management has been reviewed through consultation by the patient with another medical practitioner, and the clinical need for continuing narcotic analgesic treatment has been confirmed. The date of the consultation must be no more than 3 months prior to the application for a PBS authority. The full name of the medical practitioner consulted and the date of consultation are to be provided at the time of application; or

(iv) subsequent application for treatment of chronic severe disabling pain not responding to non-narcotic analgesics where a PBS authority prescription for treatment beyond 12 months has previously been issued for this patient.

Dental Schedule:

Caution:

The risk of drug dependence is high.

Restricted Benefit:

Chronic severe disabling pain not responding to non-narcotic analgesics.

Note:
Prescribing of drugs of addiction by dentists is not permitted in some States/ Territories.

Maximum quantity: 10
Number of repeats: 0

## 13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 14. Sponsor's Comment

The sponsor welcomes the PBAC's recommendation as the availability of hydromorphone prolonged release tablets will allow physicians to tailor treatment to individual requirements by rotating different long acting opioids when side effects or treatment tolerance occurs.