CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Palladon injectie 2 mg/ml, 10 mg/ml, 20 mg/ml and 50 mg/ml, solution for injection or infusion Mundipharma Pharmaceuticals B.V., the Netherlands

hydromorphone hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 104833, 104836-104838

12 November 2012

Pharmacotherapeutic group:	natural opium alkaloids
ATC code:	N02AA03
Route of administration:	intravenous; subcutaneous
Therapeutic indication:	severe pain in cancer patients and severe post-operative pain
Prescription status:	prescription only
Date of authorisation in NL:	15 March 2011
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Palladon injectie 2 mg/ml, 10 mg/ml, 20 mg/ml and 50 mg/ml, solution for injection or infusion from Mundipharma Pharmaceuticals B.V. The date of authorisation was on 15 March 2011 in the Netherlands.

The product is indicated for the relief of severe pain in cancer and severe post-operative pain.

A comprehensive description of the indications and posology is given in the SPC.

Like morphine, hydromorphone is an agonist of mu receptors. The pharmacological actions of hydromorphone and morphine do not differ significantly. The oral analgesic potency ratio of hydromorphone to morphine is approximately 5-10:1. Hydromorphone and related opioids produce their major effects on the central nervous system and bowel. The effects are diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and alteration of the endocrine and autonomic nervous system.

This national procedure concerns a line extension to Palladon 2 mg, 4 mg, 8 mg, 16 mg and 24 mg prolonged-release capsules (NL license RVG 29655, 22162-22165) by Mundipharma, which have been registered in the Netherlands since 1999. These products have been authorised with a restricted indication for the treatment of severe cancer pain.

The MAH has not previously applied for a MA for a solution for injection or infusion in the Netherlands. However, the MAH holds an MA in Germany since 2007 for the solution for injection formulation of hydromorphone hydrochloride: Palladon® inject 2 mg/ml, 10 mg/ml, 20 mg/ ml and 50 mg/ml, indicated for the relief of severe pain in cancer and severe post-operative pain. This marketing authorisation has been recognised in a number of EEA member states through a decentralised procedure with Germany acting as Reference Member State (DE/H/1540/001-004/DC). This procedure was finalised with a positive outcome on 13 March 2009. The Netherlands was not involved as CMS in this procedure. In this national application for a line extension, the MAH thus sought to introduce the pharmaceutical form ‘solution for injection or infusion’ with the indication ‘relief of severe post-operative pain’ additional to the oral formulation.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinial and clinical data.
The active component of Palladon injectie is considered to be well-known and the clinical pharmacology of hydromorphone hydrochloride has been extensively studied. Parts of the data in the dossier of Palladon injectie were already submitted in the dossier of Palladon 2 mg, 4 mg, 8 mg, 16 mg and 24 mg prolonged-release capsules (NL license RVG 29655, 22162-22165). Only clinical data from published studies and reviews were presented to support the safe and effective use of Palladon Injection.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is hydromorphone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, crystalline powder. The substance is freely soluble in water, very slightly soluble in ethanol and practically insoluble in methylene chloride.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Palladon injectie is available in 2, 10, 20 and 50 mg/ml strength and is a clear colourless to pale yellow, isotonic, sterile solution of pH 4.

The solution for injection or infusion is packed in Type I Ph.Eur. clear, neutral glass ampoules with a fill volume of 1.1-1.2 ml.

The excipients are: anhydrous citric acid (E330), disodium citrate (E331), sodium chloride, sodium hydroxide solution (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies concerned optimisation of pH and osmolarity, photostability of

the solution and compatibility studies with commonly used solutions for infusion and other drug products which it is likely to be co-administered with. No overages are included in the formulation. The volume of fill into 1 ml ampoules is 1.1-1.2 ml to ensure delivery of at least 1 ml from each ampoule. This is acceptable. The pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process consists of mixing, filtering, filling into ampoules and terminal sterilization. The manufacturing process is performed under nitrogen atmosphere. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches of the 2 mg/ml and 50 mg/ml drug product strengths, and on 1 full-scale batch of the 10 mg/ml and 20 mg/ml drug product strengths.

Microbiological attributes

The product is terminally sterilized by autoclaving. Sterility and endotoxins testing are performed on every batch of finished drug product. This is acceptable. Stability data confirm that sterility and endotoxins comply with the specification throughout storage.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, pH, deliverable volume, clarity of solutions, identification, assay, related substances, sterility and bacterial endotoxins. The release and shelf-life limits are identical. The specification is acceptable. The proposed limit for the specified impurities is below the qualification threshold and agreed. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three full-scale batches of the 2 mg/ml and 50 mg/ml strengths and one full-scale batch of the 10 mg/ml and 20 mg/ml strengths, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three full-scale batches of the 2 mg/ml and 50 mg/ml strengths and one full-scale batch of the 10 mg/ml and 20 mg/ml strengths stored at 25°C/60% RH (up to 24 months), 30°C/65% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were packed in 1 ml Type I Ph.Eur. glass ampoules. Except for a slight increase in total impurities and some of the specified impurities, no changes or trends were observed at either condition. All parameters remained within the specified limits. Photostability testing demonstrated that the hydromorphone hydrochloride injection shows some sensitivity to light.

The claimed shelf life of 36 months could be granted, with the storage requirement ‘Keep ampoules in the outer carton to protect from light’.

Compatibility/In-use stability

Stability of the 50 mg/ml drug product was demonstrated for dilutions (1:17) to approximately 3 mg/ml with *0.9% saline*, *5% dextrose* and *water for injections* and diluted and undiluted with the infusion bag materials and syringe materials for 24 hours at 2-8°C and at 25°C. No changes are observed in appearance and assay. Furthermore, the compatibility was tested with a range of drug products likely to be co-administered with (hyoscine butylbromide/hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromzine hydrochloride, glycopyrronium bromide and ketamine hydrochloride) over a period of 24 hours at 2-8°C and 25°C. No evidence of incompatibility was observed. The compatibility of the drug product with commonly used solutions for infusion and with other possibly co-administered drugs was adequately demonstrated. The used dilution to approximately 3 mg/ml with solutions for infusion is considered adequate. Based on the compatibility studies, section 6.3 of the SPC describes the stability of undiluted and diluted drug product with 0.9% saline, 5% dextrose and water for injections for 24 hours at room temperature (25°C).

Furthermore, the compatibility with the above mentioned co-administered drug products is described in section 6.6 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This full application for marketing authorization involves hydromorphone hydrochloride, a μ- selective, full opioid agonist with well known pharmacodynamic, pharmacokinetic and toxicological properties. Hydromorphone has been marketed for many years as orally applied formulations as well as solutions for injection. The non-clinical submission contains an detailed and sufficient overview of published data concerning non-clinical pharmacology, pharmacokinetics and toxicology of hydromorphone hydrochloride.

Environmental risk assessment
The MAH submitted an environmental risk assessment, which is required for this new formulation. The predicted environmental concentrations were calculated as recommended in the guideline for environmental risk assessment of medicinal products (EMEA/CHMP/SWP/4447/00). The predicted environmental concentration in surface water ($PEC_{surfacewater}$) exceeds the action threshold of 0.01 μg/L. As requested, the MAH additionally initiated a phase II assessment.

II.3 Clinical aspects

Hydromorphone bears structural similarity with morphine. It is a second-line drug to morphine in the treatment of chronic pain and is to be classified in step III of pain therapy according to WHO recommendations. There are no known active metabolites from hydromophone in contrast with morphine. Hydromorphone has been available in the market since 1926.

No clinical trials using the intravenous or subcutaneous routes were performed by the MAH. Two phase III studies were included in the dossier. However, these have very limited significance as these were done using controlled-release capsules. Only clinical data from published studies and reviews were presented to support the safe and effective use of Palladon Injection.

Clinical pharmacokinetics
The MAH has submitted data from bioavailability studies in healthy volunteers: study HMI 1001 with 1 mg and 2 mg s.c. and i.v. bolus and infusion dose, and two other studies (HYDRO.PKIN0014 and D-101) establishing absolute bioavailability of different hydromorphone oral formulations which are not relevant to support this application.

Study HMI 1001
An open-label, six-treatment, four-part, randomised, incomplete block crossover study in healthy subjects to compare the pharmacokinetics of hydromorphone given orally, and parenterally as bolus doses or infusions. The test and reference treatments were taken under the cover of naltrexone to reduce opioid-related adverse events.

Test treatments
Hydromorphone HCl solution for injection or infusion 2 mg/ml administered as a bolus injection or continuous infusion as follows:

A: 1 x 0.5 ml s.c. injection (1 mg dose)
B: 1 x 0.5 ml i.v. injection (1 mg dose)
C: 1 x 0.5 ml i.m. injection (1 mg dose)
D: 1 x 1 ml s.c. infusion* (2 mg dose) over 8 hours
E: 1 x 1 ml i.v. infusion* (2 mg dose) over 8 hours

*The hydromorphone solution 2 mg/ml for s.c. and i.v. infusion was diluted with normal saline to deliver a 2 mg dose over 8 hours.

Reference Treatment
HCl capsules 2.6 mg (Palladone® capsules 2.6 mg) administered orally as follows.
Treatment F 1 x 2.6 mg capsule

Study population
Fourty-one healthy adult subjects were actually randomised and 28 subjects completed the study. Eight subjects withdrew their consent, 3 discontinued for administrative reasons (failed drug screen), and 2 discontinued due to adverse events (following naltrexone administration).

Study results

Table 10. Summary Statistics for Hydromorphone Pharmacokinetic Parameters by Treatment: Full Analysis Population for Pharmacokinetic Parameters (All Data)

PK Parameter	Statistic	Capsule p.o.	Bolus s.c.	Infusion s.c.	Bolus i.v.	Infusion i.v.	Bolus i.m.
AUCt (pg.h/ml)	n	21	23	26	22	24	25
	Geometric Mean	5469.1	9694.5	18801.4	14333.5	18412.9	9252.5
	Geometric SE	2.80	1.05	2.10	1.24	2.12	1.06
	Exponentiated LS Mean	5414.6	10067.0	18862.8	14325.0	18387.8	9677.0
AUCINF (pg.h/ml)	n	15	14	13	14	15	13
	Geometric Mean	6503.5	10269.2	18276.3	11568.4	18859.4	9242.9
	Geometric SE	2.83	1.06	2.16	1.08	2.14	1.06
	Exponentiated LS Mean	6126.6	10440.2	20383.1	11587.2	18877.4	9582.6
Cmax (pg/ml)	n	21	23	26	22	24	25
	Geometric Mean	1768.56	10648.87	2603.52	49256.89	2309.34	6787.39
	Geometric SE	2.911	1.110	2.116	1.117	2.181	1.125
	Exponentiated LS Mean	1836.09	10683.06	2677.22	52511.56	2304.26	6868.10
t1/2Z (h)	n	15	14	13	14	15	13
	Mean	11.3	6.7	11.1	8.3	12.3	8.2
	SE	0.61	0.94	2.02	1.45	1.85	2.35
	SE (Gini*)	0.63	0.96	2.03	1.46	1.80	1.85
	LS Mean	11.8	6.3	10.0	8.2	12.0	8.1
LambdaZ (1/h)	n	15	14	13	14	15	13
	Mean	0.064	0.138	0.093	0.130	0.075	0.144
	SE	0.0040	0.0193	0.0165	0.0237	0.0102	0.0251
	SE (Gini*)	0.0039	0.0198	0.0168	0.0236	0.0101	0.0253
	LS Mean	0.060	0.139	0.107	0.133	0.083	0.148
tmax (h)	n	21	23	26	22	24	25
	Median	0.66	0.16	8.08	0.03	6.00	0.08
	Min, Max	0.33, 2.50	0.08, 0.33	0.08, 8.16	0.03, 24.00	2.00, 14.00	0.03, 8.08

Summary of Ratios for Hydromorphone Pharmacokinetic Parameters: Full Analysis Population for Pharmacokinetic Parameters (All Data)

PK Parameter	Treatment Comparison	Ratio (%)	90% Confidence Interval -Lower-	-Upper-
AUCt/Dose	Bolus i.m. – Bolus i.v.	67.6	53.9	84.7
	Bolus s.c. – Bolus i.v.	70.3	56.2	87.9
	Capsule p.o. – Bolus i.v.	14.5	11.6	18.1
	Infusion i.v. – Bolus i.v.	64.2	51.3	80.4
	Infusion s.c. – Bolus i.v.	65.8	53.4	81.2
	Infusion s.c. – Bolus s.c.	93.7	76.3	115.1
	Infusion s.c. – Infusion i.v.	102.6	82.5	127.6
AUCINF/Dose	Bolus i.m. – Bolus i.v.	82.7	73.2	93.4
	Bolus s.c. – Bolus i.v.	90.1	80.4	101.0
	Capsule p.o. – Bolus i.v.	20.3	18.0	22.9
	Infusion i.v. – Bolus i.v.	81.5	72.5	91.5
	Infusion s.c. – Bolus i.v.	88.0	77.9	99.3
	Infusion s.c. – Bolus s.c.	97.6	86.9	109.6
	Infusion s.c. – Infusion i.v.	108.0	95.3	122.3
Cmax/Dose	Bolus i.m. – Bolus i.v.	13.1	10.5	16.3
	Bolus s.c. – Bolus i.v.	20.3	16.4	25.3
	Capsule p.o. – Bolus i.v.	1.3	1.1	1.7
	Infusion i.v. – Bolus i.v.	2.2	1.8	2.7
	Infusion s.c. – Bolus i.v.	2.5	2.1	3.1
	Infusion s.c. – Bolus s.c.	12.5	10.3	15.3
	Infusion s.c. – Infusion i.v.	116.2	94.1	143.5

Bolus s.c. gave significantly lower extent of absorption compared to bolus i.v., being 30% with regard to AUC_t but bioequivalent with regard to AUC_{inf}. C_{max} for bolus s.c. was 80% lower than that of bolus i.v.
The infusion of hydromorphone either by i.v. or s.c. route provided an equivalent bioavailability with regard to AUC_{inf}, but AUC_t was just outside the acceptance range for bioequivalence. In addition, C_{max} for i.v. infusion was 16% higher than after s.c administration, but is not expected to have significant clinical consequences. Based on these data, the same dose recommendation for iv and sc infusion is acceptable.

Clinical Efficacy
Twenty-two studies were presented, but only 16 were performed on the indications applied for. Seven of these studies were on cancer pain and 9 on post-operative pain. As for study design, there were 9 blinded, 4 open-label, 2 retrospective and 1 not clear whether blinded or not. The majority of the studies were done with parallel groups and a few had cross-over design. There were no placebo-controlled trials. As a method of drug administration, 8 studies used iv, 6 used sc and 2 used both routes. Two studies were long-term (156 days and 741 days) and the rest are short-term. Only 1 study included paediatric patients (≥11 years) and 5 studies included elderly patients (> 65 years).

Except for 2 studies (Deutsch, 1968; Chan et al., 1999) which used pethidine, all of the studies used morphine as active comparator. The conversion ratio varied from 1:2.5-20 with hydromorphone to morphine and 1:50 with hydromorphone to pethidine.

The 9 blinded studies are summarized in the table below.

				Dose			

Reference	N	Pain model	Age (ave.)	Ratio hydromorphone: comparator	Duration	Efficacy measure	Outcome
Intravenous hydromorphone versus a comparator opioid (morphine or pethidine)							
Larijani *et al, 2005* (blinded; not clear whether single or double blind; parallel groups)	60	Post-operative pain	60	0.1-0.2 mg with a 6 minute lock out **PCA** **1:5-10**	48 hours	Verbal Numeric Rating	75% of patients treated with hydromorphone reported good pain control.
Rapp *et al,1996* (DB, parallel groups)	61	Post-operative pain	44.1	Mean 49.9 mg/day **PCA** **1:5**	24-48 hours	Profile/mood states and Cognitive function testing	Equivalent analgesia and side effects; morphine caused less cognitive impairment while hydromorphone appeared to improve mood. Hydromorphone was deemed to be a suitable alternative to morphine.
Mahler and Forrest 1975 (blinded; not clear whether single or double blind; cross-over)	143	Post-operative pain	unknown	0.5 mg, 1 mg and 2 mg **bolus** **1:2.5-20**	1 day	Nurse/observer questionnaire	Both hydromorphone and morphine groups demonstrated good analgesic effects lasting up to 4.5 hours in duration. The relative potency for hydromorphone is 8.6. More sleepiness was noted with hydromorphone.
Deutsch, 1968 (DB; parallel groups)	200	Post-operative pain	Age range 11-100 years	0.5 mg **bolus** **1:50**	4 hours	Verbal report	Superior analgesia and equal incidence of side effects for hydromorphone compared to pethidine.
Subcutaneous hydromorphone versus a comparator opioid (morphine or pethidine)							

Miller *et al,1999* (DB; parallel groups)	74	Cancer or AIDS-related pain	69	unknown **1:5**	72 hours	Memorail Pain Assessment cards Assessed by proxy if the patient was too ill	Hydromorphone is as effective as morphine when delivered by continous sc infusion.
Chan *et al,1999* (DB)	60	Post-operative pain	45.8	1 mg **bolus** **1:50**	single dose	VAS	Subcutaneous hydromorphone is a good alternative to intramuscular pethidine for postoperative analgesia
Comparison of various routes of administration of hydromorphone							
Vanier *et al,1993* (DB; cross-over)	7	Cancer pain	Adults (age not given)	Mean dose of 56.3 mg/36 hours or 39.5/36 hours **SC infusion with and without PCA**	36 hours	VAS	Both modes of hydromorphone administration are effective and safe.
Moulin *et al,*1991 (DB; cross-over)	15	Cancer pain	61.9	1 mg/h to 35 mg/h **SC and IV infusion**	48 hours	VAS	No difference between sc and iv routes.
Liu *et al,1995* (DB; parallel groups)	16	Post-operative pain	59	1050 mcg initial dose followed by 150 mcg increasing to 300 mcg with a lockout period of 15 minutes decreasing to 10 minutes **IV PCA and epidural PCA**	3 days	VAS	Equivalent in terms of pain score and patient satisfaction.

DB = double-blind; IV = intra-venous; PCA = patient-controlled analgesia; SC = subcutaneous; VAS = visual analogue score

The above summarized studies showed that hydromorphone is effective in the treatment of post-operative and cancer pain. In addition, as with all opioids, tolerance occurs with repeated use of hydromorphone. Tolerance develops to the respiratory depressant, analgesis, euphoric and sedative effects but not to pupil constriction and constipation.

No dose-response studies were done by the MAH and the recommended doses were based on published studies. The table below compares the doses in the literature (a) and the proposed recommended doses (b) by the MAH.

Mode	**intravenous**		**Subcutaneous**	
	Studies (a)	Proposed (b)	Studies (a)	Proposed (b)

Bolus	0.5 mg – 2 mg	1 -1.15 mg/3-4h	1 mg	1-2 mg/3-4h
Infusion	0.4 – 140 mg/h	0.15-0.45/h; 0.004 mg/kg bw/h	1.7 mg/h – 24 mg/h; 4024 mg/day	0.15-0.45/h; 0.004 mg/kg bw/h
PCA	0.1 mg/h – 1.2 mg/h max 49.9 mg/day	0.2 mg	0.2 mg	0.2 mg

The dose required to provide effective analgesia is highly variable between individuals and sc administration generally required higher doses than iv administration. However, in the SPC of the medicinal product in question, the recommended doses are on the lower limit of those in the literature and the infusion doses for the 2 routes are the same. Hence, these recommended doses could be questionable.

In summary, the studies demonstrated that hydromorphone is, in general, as effective as morphine in the treatment of cancer and post-operative pain and that administration via sc and iv showed comparable efficacy to morphine and pethidine. The indications for treatment of severe cancer pain and severe post-operative pain are therefore acceptable.

Clinical Safety

The safety data is based on 34 published studies using sc and iv administration. The total safety population consisted of 1197 male and female patients and healthy volunteers. Studies included not only cancer pain and postoperative pain, but also other pain models like mucositis after BMT, ureteral colic and acute pain. The majority of the studies were short-term; only 3 were long-term (156 days to 741 days). Four studies included paediatric patients (youngest was 4 years old).

Summary of the common adverse events (average % of the pooled published data)

Adverse event	%
nausea	25
vomiting	19
dizziness	21
sedation	18
somnolence	24
pruritus	33
rash	3
itching	10
headache	9
constipation	5
bloating	5
anxiety	2
vertigo	3

As shown in the table, the most common adverse events observed in the clinical studies reported included gastrointestinal, nervous system and skin events, manifested mainly as nausea, vomiting, dizziness, sedation, somnolence and pruritus. The adverse events of hydromorphone were similar across all pain etiologies and were similar to that of opioids as a class.

The occurrence of pruritus (33%) is considerably high. However, this is comparable to the data reported on morphine and pethidine. Furthermore, local site reaction e.g. itching is also relatively high (10%). But based on the pre-clinical dermal sensitization studies and 3 PK/PD studies on the injection solution, local intolerance appeared not to be a major concern.

A number of deaths occurred with cancer-related pain and only in one case with postoperative pain. None of the deaths were considered hydromorphone-related. There is a high death rate, which could be

expected in trials involving patients who are terminally ill and, in some cases, in the last few hours or days of life. This could be a reason why the dose recommendations are on the conservative side.

In summary, the safety profile of hydromorphone administered via sc or iv is comparable to that of opioids as a class.

Benefit/risk assessment

Pros	Cons
• Several reported double-blind studies have shown a similar efficacy of hydromorphone to morphine in cancer and post-operative pain in 1:2.5-20 ratios. • Safety profile is comparable with that of strong opioids as a class. • Lack of known therapeutically active metabolites in comparison to morphine. Safe to be used in renal patients due to less accumulation. • Established clinical experience of almost 90 years with hydromorphone.	• No clinical studies with the formulation was done by the MAH. • PK is not well-established. • Doses are not systematically studied and based only on published studies. • The published studies were not placebo-controlled.

As could be expected from a strong opioid, hydromorphone is effective to treat post-operative and pain. The safety profile seems comparable to morphine.

Based on the pros and cons, it can be concluded that the benefit /risk ratio of hydromorphone solution for injection is considered favourable.

Risk management plan
In the safety specification the MAH outlines the advantages of the availability of a parenteral route of administration next to oral routes of administration of the product; i.e. there are situations in which oral administration is not possible, for instance in patients with dysphagia, nausea, vomiting, gastrointestinal obstruction or in post-operative patients. In these cases it is important to have continuity of analgesic treatment particularly during the terminal stages of disease.
The recommended starting doses have been derived from the published studies using parenteral hydromorphone. These recommended starting doses are intended as a guide as the SPC recommends the dose to be adjusted to the severity of the pain, condition of the patient and previous or concurrent medication. The higher concentrated products (10 mg/ml, 20 mg/ml and 50 mg/ml) are not indicated for use as starting dose or when initiating pain therapy with hydromorphone. In addition, elderly patients and patients with severe renal or hepatic impairment may require a lower starting dose.
Because hydromorphone is a well established and widely used strong opioid, its safety profile is well defined and identified risks are appropriately reflected in the SPC. The MAH addresses and will continue to address specific risks or situations as the potential for medication errors, overdose, potential for misuse, abuse/diversion and the potential for off-label use. With the already existing safety monitoring in place for all hydromorphone and other strong opioids marketed by the MAH, it is also possible to detect safety issues which may be related to certain dosage forms or dose strengths. Routine pharmacovigilance activities sufficiently cover these issues.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Palladon prolonged-release capsules and has been adapted with regard to the difference in pharmaceutical form and indication.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questionnaire contained 15 questions addressing the key safety issues and presentation of information. Four additional, solicited questions were asked to complete the questionnaire with regards to positive, negative and stylistic feedback about the readability of the PIL.
Both rounds of testing showed that, for each question, at least 90% of participants were able to find the correct information, and at least 90% of participants were able to answer the questions correctly.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Palladon injectie 2 mg/ml, 10 mg/ml, 20 mg/ml and 50 mg/ml, solution for injection or infusion have a proven chemical-pharmaceutical quality and are legitimate line extensions to Palladon 2 mg, 4 mg, 8 mg, 16 mg and 24 mg prolonged-release capsules. Palladon prolonged-release capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

The submitted studies demonstrate that hydromorphone is, in general, as effective as morphine in the treatment of cancer and post-operative pain and that administration via sc and iv showed comparable efficacy to morphine and pethidine. The safety profile seems comparable to morphine.

SPC, package leaflet and labelling are in the agreed templates and are in agreement with other hydromorphone containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered the benefit/risk balance positive and granted a marketing authorisation. Palladon injectie 2 mg/ml, 10 mg/ml, 20 mg/ml and 50 mg/ml, solution for injection or infusion were authorised in the Netherlands on 15 March 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval /non approval	Assessment report attached
Extension of the in-use shelf life of the finished product.	--	IB	28-6-2011	15-7-2011	Approval	N
Submission of a new or updated Ph. Eur. certificate of suitability; updated certificate from an already approved manufacturer.	--	IA	22-11-2011	22-12-2011	Approval	N