PALLADONE 2MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 10MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 20MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 50MG/ML, SOLUTION FOR INJECTION OR INFUSION

PL 16950/0163-6

UKPAR

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LAY SUMMARY

On 19 November 2012, the MHRA granted Napp Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Palladone 2, 10, 20 and 50mg/ml Solution for Injection or Infusion (PL 16950/0163-6). These are prescription-only medicines (POM) to relieve severe pain.

These products contain the active substance hydromorphone hydrochloride, which is a potent analgesic (strong “painkiller”) of the opioid group.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Palladone 2, 10, 20 and 50mg/ml Solution for Injection or Infusion outweigh the risk, hence Marketing Authorisations have been granted.

PALLADONE 2MG/ML, SOLUTION FOR INJECTION OR INFUSION
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Palladone 2, 10, 20 and 50mg/ml Solution for Injection or Infusion (PL 16950/0163-6) on 19 November 2012 to Napp Pharmaceuticals Limited.

These were applications made under the national procedure, according to Article 10(3) of Directive 2001/83/EC, as amended, hybrid applications of the reference products Palladone Capsules 1.3 and 2.6mg Capsules (PL 00337/0238-9), and Palladone SR 2, 4, 8, 16 and 24mg SR Capsules (PL 00337/0242-6), which were initially granted to Napp Laboratories Limited in February 1997. Following the grant of a Change of Ownership, the marketing authorisation holder became Napp Pharmaceuticals Limited from June 2000 for Palladone Capsules 1.3 and 2.6mg Capsules (PL 16950/0049-50), and Palladone SR 2, 4, 8, 16 and 24mg SR Capsules (PL 16950/0051-55).

These products contain the active substance hydromorphone hydrochloride. Hydromorphone hydrochloride is a natural opioid alkaloid. It bears very close structural similarity to morphine. Hydromorphone is a μ-selective, full opioid agonist. Hydromorphone and related opioids produce their major effects on the central nervous system and the intestine. The effects are primarily analgesic, anxiolytic, antitussive and sedative.

These products are indicated for the relief of severe pain in cancer.

All non-clinical studies performed by the Marketing Authorisation Holder were conducted in-line with Good Laboratory Practice (GLP).

No new clinical studies have been conducted in support of these applications. This is considered to be acceptable as there is extensive published literature to support the use of intravenous and subcutaneous hydromorphone. In addition, the products are aqueous solutions to be administered intravenously or subcutaneously, and the excipients are not expected to interact with the drug substance or otherwise affect the disposition of the drug substance.

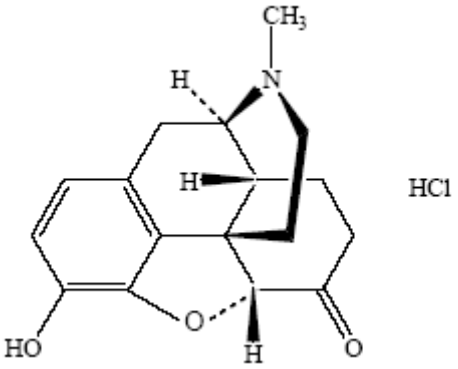
PHARMACEUTICAL ASSESSMENT

S. Active substance – Hydromorphone hydrochloride

rINN: Hydromorphone hydrochloride

Chemical name: 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride

Structure:



Molecular formula: $C_{17}H_{19}NO_3HCl$

Molecular weight: 321.8

Hydromorphone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydromorphone hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely anhydrous citric acid, sodium citrate, sodium chloride, sodium hydroxide solution (4%), hydrochloric acid (3.6%) and water for injections.

All excipients are controlled to their European Pharmacopoeia specifications.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a range of aqueous injections containing either 2mg/ml, 10mg/ml, 20mg/ml or 50mg/ml hydromorphone hydrochloride, to complement the prolonged- and immediate-release oral dosage forms that are currently available.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the finished products. The manufacturing process has been validated using full-scale batches and has shown satisfactory results.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished products are packaged in Type I clear neutral glass ampoules, in pack sizes of 5 x 1ml ampoules

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with parenteral products.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years unopened, with storage conditions of "Do not store above 25°C" and "The ampoules should be stored in the outer carton to protect from light."

There are additional instructions on use after opening the ampoule, including the following:
"The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at ambient temperature (25°C)."

"From a microbial point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution, dilution, etc has taken place in controlled and validated aseptic conditions."

Bioequivalence/bioavailability
No bioequivalence studies were submitted with these applications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive

manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

NON-CLINICAL ASSESSMENT

Pharmacology
Hydromorphone was discovered by the German chemical company Knoll, A.G. in 1924 and has been in clinical use since 1926. There are now over 70 years of clinical experience with this drug. Since the pharmacology of hydromorphone has been well-established, the applicant has not conducted any novel investigations into the mode of action of the products.

Pharmacokinetics
Published literature has also been used as a source of information on the pharmacokinetics of hydromorphone but a considerable number of studies have also been conducted by the applicant. The published literature and the applicant's own pharmacokinetic studies are also backed up by toxicokinetic information derived from toxicology studies conducted by the applicant, including by the oral, intravenous and subcutaneous routes of administration. GLP compliant acute toxicity studies have been conducted in rats and mice by the intravenous and oral routes of administration. Data are also available from the literature for these species/routes as well as for the subcutaneous route in mice and rats and the intravenous route in rabbits and cats. Repeat-dose toxicity studies have been conducted in rats by the intravenous route for up to 14 days and by the oral route for up to 6 months. Genotoxicity was assessed by means of a bacterial (Ames) assay, an in vitro assay using cultured mouse lymphoma cells and in *in vivo* bone marrow micronucleus assay in mice.

Additional data were used from a chromosome aberration assay in human lymphocytes. Carcinogenicity studies have not been conducted. A Segment I type fertility and early embryonic development study in rats, investigative teratology/developmental toxicity (Segment II type) studies in rats and rabbits and a Segment III type pre- and post-natal toxicity study in rats comprised the package of reproductive toxicity studies. These were all to full regulatory and GLP standard. Local tolerance studies have been conducted in the rabbit by the intravenous, subcutaneous, intra-arterial, perivascular and intramuscular routes of administration following single and/or repeated treatment; and after single intravenous, intramuscular, intra-arterial, paravenous and subcutaneous injection in beagle dogs. All but the range-finding studies were conducted in compliance with GLP. There was also an investigation of sensitisation potential in guinea pigs.

Toxicology

The toxicology of hydromorphone is broadly identical to that of morphine and other opioids. Hydromorphone was not genotoxic in the *in vitro* bacterial reverse mutation assay, in the *in vivo* mouse micronucleus assay, or in the in vitro mouse lymphoma assay without metabolic activation. A positive genotoxic effect was observed in the mouse lymphoma assay after S9 activation. However, negative findings have been obtained in a further mammalian cell *in vitro* assay in human lymphocytes both with and without metabolic activation. Findings such as these are not unexpected since genotoxic effects have been found with other opioid and related analgesics, including morphine and meperidine (pethidine). Overall, the weight-of-evidence indicates that hydromorphone does not pose a mutagenic risk to man. Carcinogenicity studies have not been conducted by the Applicant and there appear to be no relevant published reports in the literature. The long history of clinical usage of hydromorphone (in excess of 70 years) and its mode and duration of usage, i.e. generally short-term duration would lead to the conclusion that oncogenicity studies would not be required.

No effects on male or female fertility were seen in rats following oral administration at the highest dose tested of 5 mg/kg/day. No developmental toxicity has been seen by the Sponsor in studies in pregnant rats and rabbits using the oral route of administration. Developmental anomalies have been reported in the literature for the hamster and mouse dosed subcutaneously. As the relevance of these data to pregnant humans is not clear, it should be presumed that hydromorphone could pose a risk and pregnancy should be contraindicated unless the potential benefits outweigh any possible risk. In the rat pre-and post-natal toxicity study, there were no effects on the course or outcome of pregnancy, on the duration of pregnancy or on parturition but there was increased pup mortality and reduced pup body weights in the immediate post-natal period. No other effects on the offspring were observed. Cross-fostering studies showed this effect to be due to intra-uterine exposure of the offspring rather than to effects on the mother. Local intolerance and dermal sensitisation studies gave no rise to concern.

Environmental Risk Assessment

As recommended in the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/CHMP/SWP/4447/00), the predicted environmental concentrations in the aquatic compartment were calculated.

Although the worst-case calculated predicted environmental concentration (surface water) for hydromorphone hydrochloride exceeded the value of 0.01µg/l, patient use of the products is reasonably expected to replace that of other hydromorphone products. Therefore, no increase in environmental burden is anticipated and no further testing is required.

Conclusion

The non-clinical safety investigation of Hydromorphone Injection has not identified any particular issues that were not already known and it is concluded that Hydromorphone Injection should be safe when used in accordance with the proposed product labelling. As hydromorphone and opiates in general have been in clinical use for an extensive period of time, the non-clinical information has become of secondary relevance in the assessment of the risk/benefit compared to the vast clinical experience in man.

CLINICAL ASSESSMENT

Introduction

No new clinical studies have been conducted in support of these applications. This is considered to be acceptable as there is extensive published literature to support the use of intravenous and subcutaneous hydromorphone. In addition, the products are aqueous solutions to be administered intravenously or subcutaneously, and the excipients are not expected to interact with the drug substance or otherwise affect the disposition of the drug substance.

Clinical Pharmacology – Pharmacokinetics

Pharmacokinetic studies have been conducted to compare the pharmacokinetics of hydromorphone after administration via a number of routes, including subcutaneous and intravenous. Pharmacokinetic data obtained by a number of investigators in healthy males consistently show rapid C_{max} after intravenous dosing; these studies clearly show the tri-exponential nature of the plasma concentration vs. time relationship and also that the pharmacokinetic parameters are linear across the dose ranges tested. One study in particular showed that the pharmacokinetics of hydromorphone were independent of dose across the range studied. The average distribution and terminal elimination half lives were 1.27 min ($t½\pi$), 14.7 min ($t½\alpha$) and 184 min ($t½\beta$), respectively. Systemic clearance, central compartment volume and steady state volume of distribution were 1.66 L/min (Cl), 24.4 L (Vc) and 295 L (Vdss). The data from this study confirm the linearity of parenteral hydromorphone pharmacokinetics from 10 to 40 μg/kg.

Soon after intravenous administration of hydromorphone peak plasma levels occur, but levels decline rapidly due to rapid distribution to the skeletal muscle, liver, spleen and kidney and the central compartment, declining by as much as 63% within 3 minutes of administration (90% after 10 min). The onset of analgesia occurs within 5 minutes after administration, the maximum analgesic effect occurs 8-20 minutes after the plasma level peak. This lag time is most likely due to the hydrophilic properties and hence a low penetration of the blood-brain barrier.

The liver is the main site of hydromorphone metabolism but there is evidence of extrahepatic metabolism, especially in the gastrointestinal tract and the kidney.

Excretion of hydromorphone is relatively insignificant in limiting its effect. It takes place predominantly via the kidneys through glomerular filtration and is preceded by biotransformation of the parent compound to metabolites mainly glucuronides that are excreted more rapidly. Three metabolites have been isolated in the human urine. Major portions are excreted during the first 24 hours as 35% H-3-G, 6% unchanged, 1% dihydroisomorphine and 0.01% dihydromorphine.

After subcutaneous administration of hydromorphone, its availability is about 78 % to 100% of that of an intravenous infusion in patients with severe cancer pain (HMI1001). As the individual differences are much greater and the dosage has to be titrated again after any change of the administration route 1:1 conversion doses are usually recommended. There are minimal pharmacokinetic data available in the literature following subcutaneous administration. However, as adequately summarised in a number of reviews, subcutaneous hydromorphone shows a faster onset of action

and a shorter duration of about 3-4 hours compared to morphine, with a subcutaneous dose of between 1 mg and 5 mg of hydromorphone considered to be equinalgesic to 10mg morphine. Owing to the numerous studies conducted with hydromorphone via the subcutaneous route to generate efficacy and safety data, the lack of formal pharmacokinetic studies is not considered to significantly impact upon the ability to ensure adequate dosing instructions are available for the physician.

Following administration of intravenous hydromorphone to manage mucositis pain in children, mean observed plasma hydromorphone concentrations were similar to those observed on other studies in the adult population, although the mean clearance was greater than that observed in other studies. There was considerable variation in the mean hydromorphone plasma concentrations and clearance values, and only 10 children were studied. This variability was attributed by the investigator to either underlying disease or other treatment variables (such as concomitant medications) that could result in accelerated renal excretion or metabolic clearance.

There are no studies of the effect of age on the pharmacokinetic properties of hydromorphone; however, it is theoretically possible that the effects of the normal aging process may cause physiological changes, in particular, differences in metabolism, which, along with reduced kidney blood flow, may prolong the effect of the hydromorphone. It is, therefore, recommended that elderly patients may require a lower dose of hydromorphone to ensure adequate analgesia.

The inactivity of the metabolites of hydromorphone in the context of analgesia provides some degree of reassurance of its safe use in patients with renal failure, there being less clinical significance to their accumulation. Even when the mean ratio of H-3-G to hydromorphone is as high as 100:1, as can be the case in patients with renal failure, no toxic adverse drug reactions were reported (in one patient); furthermore, a specific retrospective study in this patient population further supports its safe use, leading to the general acceptance of the similarity of hydromorphone's safety profile to that of morphine.

Hydromorphone is extensively metabolised by the liver and has a variety of renally excreted, water-soluble metabolites. Hydromorphone bioavailability may change in patients with liver failure or changes in liver blood flow, especially with oral formulations. A lower dose of, and longer administration intervals for, opioids were recommended for patients with liver disease, following an observation of reduced metabolism in these patients. By extrapolation to the class in general, it is possible that repeat dosing with hydromorphone could lead to an increased risk of drug accumulation in the body. As with the currently authorised products, the Applicant duly proposes that hepatically impaired patients may require administration of lower doses. Pharmacokinetic interaction studies have shown that hydromorphone, at clinical concentrations, will have minimal effect, if any, on the activity of human CYP450 activities.

Specific interaction studies have not been conducted by the applicant. The pharmacokinetic and pharmacodynamic activities of hydromorphone and related opioids are well-characterised and the clinical experience with these drugs to date allows the applicant to call upon a body of data in the literature to adequately support the prescribing information with regard to known or potential interactions with other

medicinal products. It is well-established, for example, that in pain treatment, opioids are often used in combination with other analgesics and co-analgesics, as well as other drug groups due to comorbidity in the patient population.

Clinical Pharmacology – Pharmacodynamics

The applicant has not conducted any pharmacodynamic studies with hydromorphone. Given the structural similarity to morphine, and the evidence available in the literature, specific studies concerning the pharmacodynamics of hydromorphone are not necessary to support these applications.

The precise mechanism of action of opioid analgesics is not known, but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS). Interaction with the μ-opioid receptor subtype is believed to be responsible for most of hydromorphone's clinical effects in the CNS and in organs containing smooth muscle, such as the bowel. Its effects on the CNS influence a number of important organs of the body, including lungs and kidney; however, prominent binding sites and subsequent effects can also be observed in the gastrointestinal and cardiovascular systems.

These actions have been extensively studied and reviewed. Hydormorphone hydrochloride, the drug substance, is approximately seven times more soluble than morphine in aqueous solution and is therefore capable of being more highly concentrated in solution.

Hydromorphone shares with other opioids the actions, toxicity, and potential for development of tolerance, physical dependence, and, in susceptible individuals, psychological dependence. As a class, opioids product dose-related respiratory depression, nausea and vomiting as well as sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, euphoria, anxiety, dysphoria, and other mood changes. Physical responses to the presence of opioids include miosis, urinary retention, decreased biliary and pancreatic secretions, and increased biliary tract pressure. Constipation occurs frequently and with extended use opioids may decrease intestinal motility and gastric secretions.

Studies of intravenous and subcutaneous administration in both healthy volunteers and patients demonstrate that hydromorphone is 5 to 10 times as potent on a milligram basis as parenteral morphine. The onset of action from IV administration is approximately 5 minutes, with a duration of action of 3-5 hours. Onset is predictably slower at approximately 20 minutes with subcutaneous injection. There is no ceiling effect with hydromorphone, and thus the applicant has not proposed an upper dosage limit for Hydromorphone Injection. This is consistent with the approved dosing instructions for the authorised hydromorphone products currently available in the Community.

As with all opioids, the appropriate dose of hydromorphone is highly individualised and depends on the patient's age, pain syndrome, and the systemic dose of the drug needed for analgesia. As a general rule, patients with neuropathic pain may require higher doses than normally seen with nociceptive pain, and elderly patients usually require fewer doses than patients who are younger.

The dosing in all patients, however, should be individualised. It is not necessary to measure blood levels, but to rely on pain measurement in patients; a comparison of intravenous and subcutaneous constant infusion found no difference in normalised plasma levels, dosage need, and efficacy.

Clinical Efficacy

Twenty-two studies are included in this application in support of the efficacy of hydromorphone for the relief of severe pain in cancer. Not all of the studies described are in cancer pain but these applications are for cancer pain only in-line with other hydromorphone products in the UK. Most studies are not placebo-controlled, but use morphine as a comparator.

A Cochrane Collaboration review of hydromorphone for acute and chronic pain included 43 studies with 2725 patients. Approximately half of the studies were of low quality, and the heterogeneity of the studies precluded a meta-analysis. 11 studies involved chronic pain conditions (all cancer) and 32 acute pain. Studies involved various routes of administration (oral, parenteral, and epidural). The authors concluded that hydromorphone was a potent analgesic, with little difference between it and morphine in terms of analgesic efficacy, adverse effect profile and patient preference. A number of other non-randomised studies have been presented by the applicant in the arena of pain.

Twelve of the studies identified, two of which were conducted in the paediatric population, examined the efficacy of intravenous hydromorphone in comparison with an opioid comparator.

Hydromorphone was administered mostly to post-operative patients and patients with mucositis pain in these studies at doses of up to 140 mg/h for durations of just over two years via the subcutaneous route and at least 13 days for the intravenous route to a total of 1007 subjects; doses in the 49 patients participating in the two paediatric studies were generally lower at 3 mcg/kg for up to 35 days.

A further four studies of hydromorphone via the subcutaneous route were highlighted from the literature searches. These studies, however, were conducted solely in the adult population and included 302 patients with post-operative, cancer or acquired immune deficiency syndrome (AIDS) pain although the highest dose studied (where known) was 24.1 mg/h for a mean of 94.4 days.

Finally, the remaining six studies, conducted in a total of 207 patients, compared various routes of administration of hydromorphone; all of these studies employed intravenous and subcutaneous administration, with two additionally studying administration via the epidural route.

The 22 studies presented by the applicant in support of this application are detailed in the table below.

Pain model	Mean age	Gender (% male)	Dosage regimen of hydromorphone	Duration of treatment
Intravenous hydromorphone versus a comparator opioid - adults				
Acute severe pain	41.5	36	0.015 mg/kg IV	2 hours
Post-operative pain	60	3	0.1-0.2 mg with a 6 minute lock out PCA IV	48 hours
Post-operative pain	44.1	8	Mean 49.9 mg/day PCA IV	24-48 hours
Post-operative pain	60	83	0.1 mg/h with a 5 minute lock out up to 1.2 mg/h PCA IV	3 days
Post-operative pain	unk	unk	0.5 mg, 1 mg and 2 mg IV	1 day
Mucositis following bone marrow transplant	39.7	42	14.71 mg/day PCA IV	13 days
Cancer pain	59	46	0.4-140 mg/h IV infusion	Unk Study was over a three year period
Mucositis following bone marrow transplant	39.9	53	Max 14 mg/day PCA IV	at least 2 days
Ureteral Colic	Age range 18-75 yrs	77	1 mg IV	120 minutes
Post-operative pain	Age range 11-100 yrs	39	0.5 mg IV	4 hours
Intravenous hydromorphone versus a comparator opioid - paediatrics				
Mucositis following bone marrow transplant	14.5	unk	0.004 mg/kg with 5 minute lock out up to 0.014 mg/kg/h PCA IV	9 days
Pain associated with bone marrow transplant	Age range 4-12 yrs	54	3 mcg/kg with a 8 minute lockout PCA IV	up to 35 days
Subcutaneous hydromorphone versus a comparator opioid - adults				
Post-operative	45.8	0	1 mg SC	single dose
Cancer or AIDS pain	69	45	unk SC	72 hours
Cancer pain	52	52	Mean maximum dose of 24.1 mg/h	Mean 94.4 days (range 12 to 741 days)
Cancer Pain	58	37	Between 40 and 4024 mg/day SC	up to 156 days
Comparison of various routes of administration of hydromorphone				
Severe cancer pain			Mean dose of 56.3 mg/36 hours or 39.5/36 hours (SC infusion with and without PCA)	
Cancer pain			Mean dose of 168 mg/day or 181 mg/day (SC infusion with and without PCA)	
Cancer pain			1 mg/h to 35 mg/h (SC and IV infusion)	
Post-operative pain			0.2 mg IV administered every 5 minutes followed by 0.2 mg IV PCA with a 10 minute lockout or 0.2 mg SC PCA with a 15 minute lockout (SC PCA and IV PCA)	
Post-operative pain			1050 mcg initial dose 150 mcg increasing to 300 mcg with a lockout period of 15 minutes decreasing to 10 minutes (IV PCA and epidural PCA)	
Post-caesarean pain			0.15 mg IV PCA with a 10 minute lockout or loading dose of 0.9 mg followed by 0.15 mg epidural PCA with a 30 minute lockout or loading dose of 0.225 mg followed by 0.15 mg epidural PCA with a 30 minute lockout (IV PCA and epidural PCA)	

There were no significant differences in the results between studies; the potency ratio of hydromorphone to morphine with regard to pain relief was consistently demonstrated, both in the adult and paediatric populations. No differences in the effects of hydromorphone were observed between extremely ill patients (those with cancer and AIDS pain) and the otherwise healthy individuals undergoing elective surgery. No differences were observed between male and female patients, or between races, although the demographic data are scant. No further reports of differences between races have been identified in wider literature searches.

Three studies involving paediatric patients have been presented. One investigated hydromorphone versus morphine administered via patient-controlled analgesia in 10 children for the management of mucositis pain following bone marrow transplant. The age range of the participants is not provided, but the mean age was 14.5 years. The median pain scores were 4 (Visual Analog Scale) in both groups, with no significant differences between side effects. The second paediatric study was a retrospective observational study which examined the use of hydromorphone and morphine administered via PCA for the management of mucositis pain following bone marrow transplant. Thirty-nine (39) children between the ages of 4 and 12 years were included; 95% of children were managed effectively with patient-controlled analgesia. Most were started on morphine; 20% were switched to hydromorphone after starting on morphine, to control side effects or to enhance analgesia. An unknown (but small) number of boys aged 11 years and over were also treated with hydromorphone in a double-blind, controlled study. However, the indication in this trial was post-operative pain, and pain-relief was scored on a 4-point scale, with no measurements of pre-treatment pain.

Clinical Safety

A range of industry-sponsored clinical and independent published studies have been presented in support of the safety of hydromorphone, involving in excess of 1300 patients and healthy volunteers.

The most common adverse events observed in the clinical studies included gastrointestinal, nervous system and skin events, manifesting mainly as nausea, vomiting, dizziness, sedation, somnolence and pruritus. The adverse events profiles were similar across all pain aetiologies, and the profile was also similar to that of opioids as a class. The highest incidence of nausea, where reported, was observed by Urquhart et al in 77.7% of post-operative patients who received 0.2 mg subcutaneous patient-controlled analgesia with a 15-minute lockout. Incidentally, this study also reported a high incidence of pruritus, at 40%. Constipation is also generally considered to be a common adverse drug reaction of hydromorphone therapy, owing to the decreased intestinal resting tone with periodic spasm and decreased amplitude of non-propulsive contraction it causes, which prolongs gastric emptying, thus increasing oesophageal reflux and delaying the passage of gastric contents. Use in situations where paralytic ileus is possible is not recommended. Hydromorphone may cause biliary colic by constriction of the sphincter of Oddi. The most common sign relating to the system organ class psychiatric disorders reported across the studies was confusion, which occurred in up to 44% in patients and healthy volunteers. Euphoria was also reported in the healthy volunteer study, and anxiety, hesitancy, mental cloudiness and hallucinations were reported in the patient studies, thus supporting both the approved and proposed SmPCs for Hydromorphone Injection. Effects of

hydromorphone on the central nervous system, such as sedation, dizziness, and somnolence, are dose-dependent and are common to opioids as a class.

Hydromorphone has no direct effect on the heart, except bradycardia, but it may cause orthostatic hypotension and fainting postoperatively due to peripheral arteriolar and venous dilatation. Hydromorphone is highly unlikely to increase QT interval and, as such, presents a low risk for arrhythmogenic potential. From the adverse events reported from the clinical studies of hydromorphone, the most common cardiovascular adverse event was hypotension following single doses of over 1 mg administered to patients. The significant clinical experience with hydromorphone does not indicate a problem with QT prolongation and arrhythmia. For the class of opioid receptor agonists as a whole, extensive use, including use in the intensively monitored setting of the operating theatre, has failed to raise significant concerns with regard to QT-interval prolongation.

Respiratory depression is also perceived to be an adverse drug reaction of hydromorphone therapy but has been reported to be rare with analgesic doses. Respiratory depression was only reported in one study, and in this case is aetiology was unclear.

Hydromorphone inhibits the release of gonadotropin-releasing hormone. It decreases levels of luteinizing hormone, follicle-stimulating hormone and adrenocorticotropic hormone. Hydromorphone increases prolactin and growth hormone release, thus decreasing cortisol and testosterone levels. Altered sexual function, decreased testosterone and amenorrhea have been reported for hydromorphone as with other opioid treatment.

There have been case reports of local adverse reactions following administration of hydromorphone, including reddening, swelling, induration and even subdermal necrosis during subcutaneous infusion. A prospective study with a mean concentration of 30mg/ml hydromorphone highlighted cases of erythema, swelling and bleeding which did not require treatment. Such adverse reactions are anticipated with parenteral products and are manageable within the clinical environment for hydromorphone use.

Two paediatric studies have been identified. Safety results from the two paediatric studies are presented below. In a 10-patient cross-over study comparing morphine and hydromorphone, patients were treated with doses up to 0.014mg/hg/hour via intravenous patient-controlled analgesia. Adverse drug reactions of nausea/vomiting, pruritus and sedation were assessed against a numerical scale every 4 hours (if patient was awake). Patients in the study remained on antiemetic regimens that were started while on chemotherapy and that pruritus was treated with diphenhydramine every 6 hours, as needed. No significant difference between the safety profile and adverse drug reactions reported for morphine and hydromorphone was observed. One patient experienced urinary retention requiring catheterisation. This adverse event occurred on a washout day following the second crossover in the study and persisted until completion of the study.

In a 39-patient study examining preteens (age 4-12 years) ability to use patient-controlled analgesia pumps, 10 patients were treated with hydromorphone at a rate of

3mcg/kg every 8 minutes, remaining patients received hydromorphone although there was some switching between groups. Switching was primarily from morphine treatment to hydromorphone treatment in an attempt to improve undesirable effects. Two children enrolled in the study died. In both cases a long period of slowly progressive organ failure preceded death. Opioid requirements in these patients declined with deterioration of mental status but increased if respiratory failure requiring intubation interceded and the opioids were used for sedation. The only other adverse reaction noted was daytime sedation.

One further study enrolled children, adults and elderly patients. The author did not comment on any difference in adverse reactions between these groups.

Patients with moderate renal impairment require more careful dose titration. Those patients with severe renal impairment could be expected to acquire high levels of the 3-glucuronide, with possible toxic consequences. Patients with hepatic impairment also require more cautious dose titration. No data are available for patients with severe hepatic impairment, therefore no dosing recommendation can be made for this group.

In a retrospective study of 55 patients, switching from morphine to oral hydromorphone to control undesirable effects, 29 patients were defined as having impaired renal function.

There was no significant difference between the improvement in undesirable effects in the renally impaired group of patients and the patients with normal renal function. The authors concluded that hydromorphone can be used safely in patients with renal impairment and may even be better tolerated than morphine in this patient population. There is one report of a case study of a 70-year-old patient with poor renal function. The patients had multiple myeloma and also suffered with back pain, due to lytic lesion on his thoracic spine. This necessitated treatment with opioid analgesics (in this case morphine), which worked well. However, the patient became increasingly drowsy over time. The authors concluded that patients with hepatic and renal impairment required careful titration with morphine and hydromorphone due to the altered pharmacodynamics and pharmacokinetics presenting a risk of toxicity due to metabolites.

Respiratory depression, muscle flaccidity, cold skin, somnolence progressing to stupor or coma, constricted pupils and hypotension characterise hydromorphone overdosage. Intravenous overdosing may lead to apnoea, circulatory collapse, cardiac arrest and death. Treatment requires cardio-respiratory support, with special attention to keeping the airway patent through intubation. The opioid antagonist naloxone is a specific antidote against respiratory depression. A dose of 0.4-2 mg naloxone intravenously should be given and can be repeated every 3 min if there is no response; this dose should be adjusted to 0.01 mg/kg body weight in children. Hydromorphone-tolerant patients should receive naloxone with caution to prevent the withdrawal syndrome. The proposed SmPCs for Hydromorphone Injection contains recommendations for the management of overdose, which is rare in patients under post operative care.

As with all opioids, there are numerous reports in the literature of hydromorphone abuse from as early as 1933. Despite earlier reports to the contrary, it is now acknowledged that hydromorphone is roughly equivalent to morphine as an abused substance. There is no evidence that hydromorphone has any greater abuse liability than other opioids. However, because the diagnosis of dependence (addiction) among chronic pain patients treated with opioids is difficult, the available data are not suitable to establish the true incidence of psychological dependence (addiction) in these patients. The proposed SmPCs for Hydromorphone Injection includes a number of warnings and precautions for physicians with regard to the development of dependence.

As with all opioids, tolerance occurs with repeated use of hydromorphone, defined as the administered dose having a decreasing effect or when a larger dose is needed to obtain the same analgesia. Tolerance develops to the respiratory depressant, analgesic, euphoric, and sedative effects, but not to pupil constriction and constipation. Physical dependence is the response to long-term opioid use. It is characterized by an abstinence syndrome after abrupt withdrawal.

Withdrawal effects due to physical dependence may occur after abrupt dose reduction in patients after treatment, rather than in the postoperative setting. Such effects, including yawning, mydriasis, lacrimation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep, restlessness, anorexia, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, goosebumps/flesh, vasomotor disturbances, and an increase in heart rate, respiratory rate, blood pressure and temperature, have also been reported in patients switched from one opioid to the other, even when using equianalgesic dosages. As with other opioids, dosage of hydromorphone should be tapered if lower dosage need is expected or treatment has to be stopped entirely.

There is little data published on withdrawal syndrome following intravenous or subcutaneous administration of hydromorphone in patients, with the exception of one case report in which the symptoms were relieved by methadone. Although withdrawal syndrome has been observed with hydromorphone, it has also been found to be useful in preventing withdrawal syndrome following dependence on other opioids.

A summary of adverse events from the latest Periodic safety Update Report (PSUR), covering reporting dates from 02 October 2004 to 31 March 2007, has been presented - although this includes both parenteral and oral formulations. This report provides data from approximately 80,058 patient treatment years with parenteral formulations and over 35,500 patient years with oral and rectal formulations. The drug reactions reported in the PSUR do not present any significant new findings over and above the data available in both the literature and in the current approved SmPCs for Hydromorphone Injection, with the tolerability profile appearing to mirror that currently known. Data from this PSUR do not include adverse events from licensed usage in children.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PILs and labels are clinically acceptable.

Marketing Authorisation Application (MAA) form
The MAA forms are clinically satisfactory.

Clinical Overall Summary (Expert report)
The clinical expert report has been written by an appropriately qualified person and is a suitable summary of the clinical dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Palladone 2, 10, 20 and 50mg/ml Solution for Injection or Infusion (PL 16950/0163-6) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new concerns were raised from the non-clinical data submitted. Hydromorphone and opiates in general have been in clinical use for many years.

CLINICAL PHARMACOLOGY/EFFICACY
The literature provided by the applicant is sufficient to support the efficacy and safety of the products in adults.

SAFETY
No new safety data were submitted with these applications and none are required.

No new or unexpected safety concerns arise from these applications.

The SmPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with hydromorphone hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk is, therefore, considered to be positive.

PALLADONE 2MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 10MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 20MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 50MG/ML, SOLUTION FOR INJECTION OR INFUSION

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 30 July 2008
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 5 August 2008
3	Following assessment of the applications the MHRA requested further information relating to the dossiers on 28 November 2008, 11 March 2010, 14 February 2011 and 14 April 2011
4	The applicant responded to the MHRA's requests, providing further information on 26 February 2010, 10 June 2010, 11 May 2011 and 13 July 2011
5	The applications were determined on 09 November 2012

PALLADONE 2MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 10MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 20MG/ML, SOLUTION FOR INJECTION OR INFUSION
PALLADONE 50MG/ML, SOLUTION FOR INJECTION OR INFUSION

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

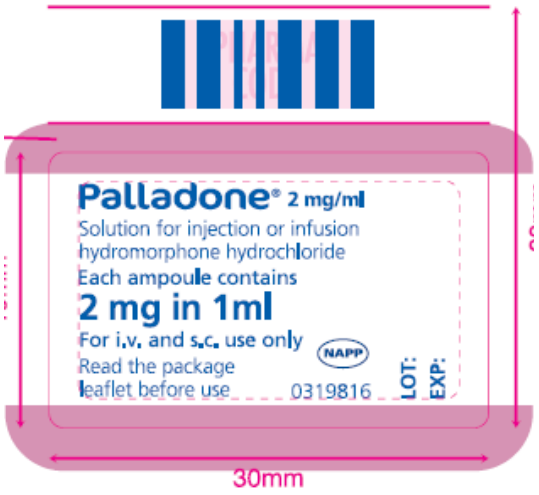
Summary of Product Characteristics and Patient Information Leaflet

The current approved UK versions of the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for these products is available on the MHRA website.

Labelling

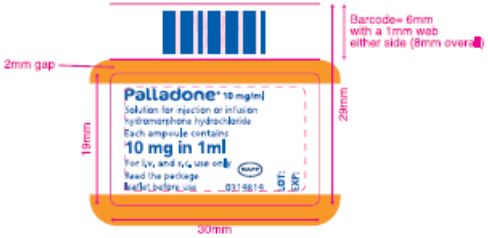

Palladone®
2 mg/ml
solution for injection or infusion
hydromorphone hydrochloride
for intravenous or subcutaneous use
5 x 1 ml ampoules
NAPP
5 012854 079335
0319818
APPLY PHARMACY LABEL IN THIS AREA
NAPP20
82x20x18mm
V2

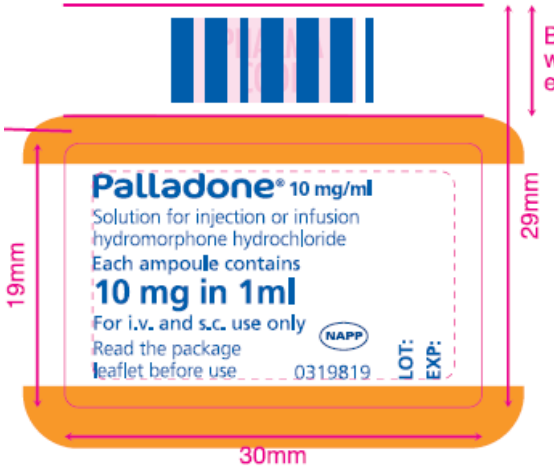

NAPP
Palladone® 2 mg/ml
Solution for injection or infusion
1 ml ampoule
each containing 2 mg hydromorphone hydrochloride


Palladone® 2 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
Each ampoule contains
2 mg in 1ml
For i.v. and s.c. use only
Read the package
leaflet before use
0319816
NAPP
LOT:
EXP:
30mm


Palladone®
10 mg/ml
solution for injection or infusion
hydromorphone hydrochloride
for intravenous or subcutaneous use
NAPP
5 x 1 ml ampoules
10 mg/ml solution for injection or infusion
hydromorphone hydrochloride 5 x 1 ml ampoules
for intravenous or subcutaneous use
5 012854 079342
APPLY PHARMACY LABEL IN THIS AREA
0319821
NAPP20
82x20x128mm
V2

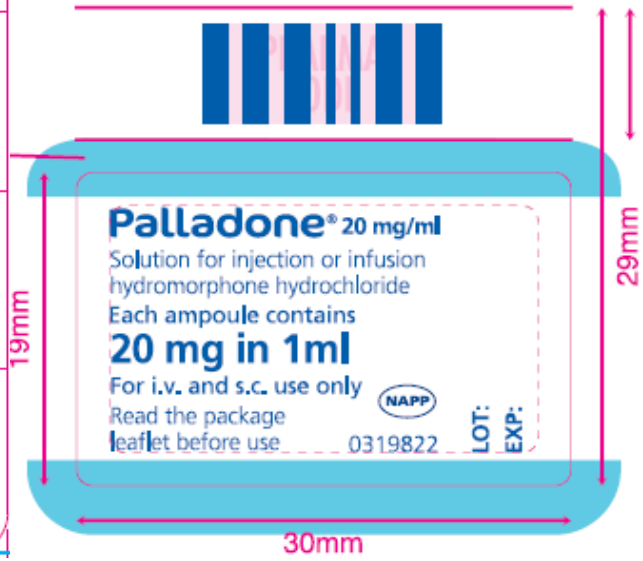

3mm
NAPP
Palladone® 10 mg/ml
Solution for injection or infusion
1 ml ampoule
each containing 10 mg hydromorphone hydrochloride


2mm gap
Barcode= 6mm with a 1mm web either side (8mm overall)
Palladone® 10 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
Each ampoule contains
10 mg in 1ml
For i.v. and s.c. use only
Read the package leaflet before use
0319819
LOT:
EXP:
19mm
29mm
30mm


Palladone® 10 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
Each ampoule contains
10 mg in 1ml
For i.v. and s.c. use only
Read the package leaflet before use
0319819
LOT:
EXP:
NAPP
19mm
29mm
30mm


Palladone®
20 mg/ml
solution for injection or infusion
hydromorphone hydrochloride
for intravenous or subcutaneous use
5 x 1 ml ampoules
NAPP
20 mg/ml solution for injection or infusion
hydromorphone hydrochloride 5 x 1 ml ampoules
for intravenous or subcutaneous use
5 012854 079359
APPLY PHARMACY LABEL IN THIS AREA
0319824
NAPP20
82x20x128mm
V2
Napp Pharmaceuticals Limited, Cambridge Science Park,
Milton Road, Cambridge, CB4 0GW, UK
PL 16950/0165
POM
® PALLADONE, NAPP and the NAPP device (logo) are
Registered Trade Marks.
™ The Palladone ampoule device is a trade mark.
© 2012 Napp Pharmaceuticals Limited.


NAPP
Palladone® 20 mg/ml
Solution for injection or infusion
1 ml ampoule
each containing 20 mg hydromorphone hydrochloride


Palladone® 20 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
Each ampoule contains
20 mg in 1ml
For i.v. and s.c. use only
Read the package
leaflet before use
0319822
LOT:
EXP:
NAPP
19mm
29mm
30mm


2mm gap
Palladone® 20 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
Each ampoule contains
20 mg in 1ml
For i.v. and s.c. use only
Read the package
leaflet before use
0319822
LOT:
EXP:
NAPP
19mm
29mm
30mm


Palladone®
50 mg/ml
solution for injection or infusion
hydromorphone hydrochloride
for intravenous or subcutaneous use
NAPP
5 x 1 ml ampoules
5 012854 079366
0319827
APPLY PHARMACY LABEL IN THIS AREA
NAPP20
82x20x126mm
V2


Palladone® 50 mg/ml
Solution for injection or infusion
1 ml ampoule
each containing 50 mg hydromorphone hydrochloride
NAPP
29mm


30mm
Palladone® 50 mg/ml
Solution for injection or infusion
hydromorphone hydrochloride
each ampoule contains
50 mg in 1ml
For i.v. and s.c. use only
Read the package leaflet before use
LOT:
EXP:
0319825
NAPP


30mm
18mm
2mm gap
Barcode= 8mm with a 1mm web either side (8mm overall)