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Brief Synopsis of the Submission to the Pharmaceutical and Therapeutics Advisory Committee

for

Independent Pricing of OxyContin (Controlled Release Oxycodone Hydrochloride)

on the
PHARMAC Pharmaceutical Schedule

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BRIEF SYNOPSIS

INTRODUCTION

OxyContin is a controlled-release [CR], oral formulation containing oxycodone hydrochloride, a semi-synthetic congener of morphine, intended for 12-hourly administration for the treatment of opioid responsive moderate to severe pain. OxyContin is currently registered in New Zealand in tablet strengths of 10mg, 20mg, 40mg and 80mg.

A request has recently been made to Mundipharma to submit a tender for provision of OxyContin on the PHARMAC Pharmaceutical Schedule. Following subsequent discussions between representatives of PHARMAC and Mundipharma, it was suggested that the price for OxyContin should be linked to that of sustained-release [SR] morphine. Unfortunately, such a price is not commercially possible and Mundipharma would, therefore, not be in a position to agree to listing of OxyContin on the Pharmaceutical Schedule. Mundipharma noted that contemporary pain management recognises that opioids are not all the same, and that the availability of a range of different opioid entities is necessary for best pain management practices to be realized. Advice given to Mundipharma by PHARMAC was to provide a submission for review by the PTAC, outlining the differences between controlled-release oxycodone and morphine, and justifications for the independent pricing of OxyContin.

The listing of OxyContin on the Pharmaceutical Schedule would permit both pain and palliative care specialists access to an additional, and complementary, opioid analgesic necessary for the improved treatment of many of their patients suffering chronic moderate to severe disabling pain.

The Australian and New Zealand College of Anaesthetists [ANZCA] has recently articulated a *Statement on Patients' Rights to Pain Management* [2001]. ANZCA recognizes the rights of patients suffering chronic cancer and non-cancer pain to "...appropriate and effective pain management strategies". This submission, for consideration by PTAC, seeks to demonstrate the clinical and pharmacological differences between OxyContin and SR morphine, and describes in some detail the exigencies of contemporary pain management strategies and the key role that availability of a range of opioid entities [in particular, the availability of OxyContin in addition to SR morphine currently available on the Pharmaceutical Schedule] has in advancing best practice pain management in New Zealand, to provide justification for Mundipharma's request for independent pricing of this important opioid analgesic.

BACKGROUND

Use of Opioids in Chronic Pain

According to the World Health Organisation [WHO], opioid analgesics are the mainstay of moderate to severe chronic cancer and non-cancer pain. Morphine has traditionally been the most widely used opioid for the treatment of chronic pain [Goodyear-Smith et al, 2004], primarily due to its availability, familiarity to physicians, established effectiveness, simplicity of administration and relatively low cost. The use of oral morphine is however associated with a number of limitations, including the development of intolerable side effects, inadequate analgesia in some patients, and the development of tolerance to its analgesic effects following prolonged use. To maintain adequate analgesia in patients suffering from chronic severe pain, it is therefore necessary to have available alternative opioid medications with proven efficacy in the treatment of chronic cancer and non-cancer pain.

The WHO have devised a simple and effective method for the rational use of oral analgesia, referred to the WHO ladder [WHO, 1996]. The critical features of the recommended approach are that the treatment should be oral, should be given "around the clock" [i.e. at fixed intervals rather than "as needed"], and should be tailored to the patient's individual needs. Ideally, two types of formulation of the opioid are required for optimal pain management, an immediate-release [IR] formulation for dose titration and a CR formulation for maintenance treatment once the appropriate dose has been determined [Hanks et al, 2001]. During maintenance therapy, patients may still experience occasional episodes of breakthrough and/or incidence pain. For this reason, along with the regular CR formulation, the patient should also have access to an IR formulation to be used as "rescue therapy".

Opioid Side Effects

In clinical practice, opioid pharmacology for chronic pain relies on finding a satisfactory balance between analgesia and opioid-induced side-effects [McNicol et al, 2003]. With pure opioid agonists [such as morphine and oxycodone], the clinical dose-effect relationship shows no ceiling effect, with the upper limit of dosage being defined by toxicity. The common side-effects associated with opioid therapy are listed in Table S1

Table S1 Common Opioid-Induced Side Effects

Gastrointestinal	Nausea, vomiting, constipation
Autonomic	Xerostomia, urinary retention, postural hypotension
CNS	Drowsiness, cognitive impairment, hallucinations, delirium, respiratory depression, myoclonus, seizure disorder, hyperalgesia
Cutaneous	Itch, sweating

Source: Cherny et al, 2001, Table 1

Toxicity may increase over time without any change in the opioid dose. Cancer patients can develop severe, persistent adverse effects such as hyperalgesia, allodynia, confusion, sedation, hallucinations, nausea and emesis and respiratory depression even when they are receiving only small doses of morphine [Mercadante, 1999]. This is thought to be due, at least in part, to an accumulation of morphine metabolites following prolonged administration.

In general, four approaches to the management of opioid adverse events have been described. Due to the difficult nature of pain management and the requirement for an individual approach to achieve effective analgesia, the appropriateness of each of these approaches needs to be assessed for each patient.

1. Reduction of opioid dose
For patients with well-controlled pain, gradual reduction in opioid dose may result in resolution of opioid-related side effects, however, this may occur at the expense of maintaining adequate pain relief [Cherny et al, 2001]. In patients where relief of opioid-related adverse events cannot be achieved whilst maintaining adequate analgesia, secondary analgesics may have an additive effect. The use of secondary analgesics may however also be associated with the risk of additional of additive side-effects to those caused by the initial opioid drug.

2. Symptomatic Management of Adverse Events
Adjuvant drugs to prevent or control opioid induced adverse events are commonly used, however, this approach is generally based on anecdotal evidence rather than properly conducted clinical studies [Cherny et al, 2001]. As this approach involves the addition of new medications to the analgesia regimen, it may be associated with the risk of additional adverse events, drug interactions and diminished compliance due to additional pill burden.

3. Opioid Substitution
In patients experiencing intolerable adverse effects to a particular opioid it is often beneficial, and common practice, to switch to an alternative opioid. This practice is referred to as opioid substitution.

4. Switching Route of Administration of Opioid
Limited data indicate that some adverse effects among patients receiving oral morphine can be relieved by switching the route of administration to the subcutaneous route. This phenomenon has been reported for nausea, vomiting, constipation, drowsiness and nausea [Cherny et al, 2001]. The administration of parenteral boluses of opioid analgesics may also be associated with toxicity at high concentrations or breakthrough pain at low doses [McRae and Sonne, 1998].

Opioid Tolerance

The repeated administration of opioids can lead to the development of tolerance. Analgesic tolerance is defined pharmacologically as a reduced potency of the analgesic effect of opioids after repeated administration or the need for higher doses to maintain the same effect [Mercadante, 1999]. The development of tolerance occurs with continued exposure of an opioid receptor to its respective agonist, is time and dose dependent, and reversible if the agonist is removed [Scholes and Trotman, 1998]. In clinical practice, tolerance is frequently addressed by "rotation" of the patient to another opioid - when available.

Limitations of Morphine

Despite its widespread use for the treatment of chronic cancer and non-cancer pain, oral morphine is associated with a number of important limitations:

1. A substantial minority of patients treated with oral morphine [10% to 30%] do not have a successful outcome because of excessive adverse effects, inadequate analgesia or both [Cherny et al, 2001]. In such patients, a change to an alternative opioid or a change of route of administration should be considered. In some centres it has been found necessary, or beneficial, to change to an alternative opioid in up to 40% of patients, with several changes of drug being required in some patients before a suitable agent is found [Hanks et al, 2001].

2. The systemic availability of morphine by the oral route is poor, at around 15-64% [Anderson et al, 2001], and this contributes to the sometimes unpredictable onset of action and great interindividual variability in dose requirements and response observed with this agent [Hanks et al, 2001].

3. Morphine is predominantly cleared from the body via metabolism to morphine-3-glucuronide [M3G] and morphine-6-glucuronide [M6G]. M6G has a high binding affinity for the μ-opioid receptor, similar to that of morphine, and has been described to have analgesic properties from 4 to 200 times that of morphine. In contrast, M3G lacks affinity for the μ, κ or δ-opioid receptors, and has not been shown to possess any analgesic properties. M3G has however been shown to generate many of the side effects associated with prolonged morphine usage, including hyperexcitability, myoclonus, allodynia and confusion. It has also been suggested that morphine antagonism by high plasma concentrations of M3G may be responsible for "paradoxical pain", in which increasing doses of morphine appear to generate worsening pain behaviour and agitation [Ashby et al, 1997]. Concentration ratios of M6G and M3G to morphine are higher after prolonged use, as well as in patients with renal impairment. The increase in morphine glucuronides to morphine ratio observed following prolonged oral morphine therapy and in those with renal impairment would be expected to increase the potential for adverse clinical consequences from these metabolites [Mercadante et al, 1999].

4. Morphine has long been feared by both the general public and physicians. Underlying this fear, and associated stigma [Levy 2001], is the mistaken belief that the problems associated with abuse of opioids are inextricably linked to therapeutic use. Treatment with morphine, not infrequently, can lead patients to exaggerated perceptions regarding the seriousness of their condition. Concerns about addiction, excessive sedation and respiratory depression have resulted in widespread avoidance and under-dosing [Hanks et al, 2001].

REQUIREMENT FOR ALTERNATIVE OPIOIDS

Need for Alternative Agents for Opioid Substitution

Evidence exists that the occurrence of opioid-related adverse effects may differ substantially between individuals taking the same opioid, and that some individuals are unable to achieve adequate analgesia on commencement of therapy with a particular agent without the development of intolerable adverse effects. Nausea and vomiting, confusion and drowsiness are all common in patients with terminal malignancy, and the contribution of opioids to these symptoms is often difficult to quantify. Over recent years the practice of changing patients with unacceptable, refractory adverse effects of one opioid to another to improve the adverse effect profile while maintaining analgesia has emerged [Ashby et al, 1999]. This practice is often referred to as opioid substitution.

Nausea, vomiting, confusion and drowsiness adversely affect quality of life. Prior to the practice of opioid substitution, patients were urged to tolerate significant adverse effects in the belief that these would be similar for all opioids. Other patients refused opioid dose escalation and accepted poor pain control rather than risk exacerbating existing adverse effects. Opioid substitution is a relatively easy and applicable alternative for patients suffering intolerant adverse effects [Ashby et al 1999].

Need for Alternative Agents for Opioid Rotation

Opioid rotation refers to the practice of switching patients with an established opioid regimen to another opioid following development of analgesic tolerance or intolerable adverse effects following prolonged administration. This practice is based on the finding that different opioids differ in their side effect profile as a result of a number of factors.

Opioid tolerance is specific to the receptor activated. Animals rendered tolerant to morphine [a μ-receptor agonist] do not generally show loss of response to δ-receptor agonists. Rats infused with levorphanol [a μ, κ and δ-receptor agonist] become tolerant to both levorphanol and morphine, whereas those infused with morphine remain sensitive to levorphanol [Scholes and Trotman, 1998].

It is accepted that drugs working on the same receptor will show cross tolerance, however, cross tolerance may be incomplete, perhaps due to the existence of receptor subtypes or variation in the rate of development of tolerance.

As mentioned previously, metabolites play an important role in the development of opioid toxicity, and, at least in the case of morphine, increasing plasma levels of metabolites have been implicated in pathogenesis of late-stage toxicity following prolonged oral morphine therapy and in patients with renal impairment. The degree to which toxic metabolites are produced or eliminated is dependent on the opioid itself, the duration of therapy, and the patient's overall status, particularly with regard to renal and hepatic function [McNichol et al, 2003].

Three studies have been identified which address opioid rotation in patients with a history of opioid toxicity or other undesirable effects during opioid treatment for cancer pain. One study by de Stoutz et al [1995] found that, of 80 patients who underwent opioid rotation in a palliative care unit, 73% reported improved pain control as well as improvements in cognitive status, nausea and vomiting. In all cases, improvements were achieved with lower doses of the alternative opioid than that predicted. The authors also noted that rotation of between 2 and 3 different opioids was often necessary to obtain satisfactory long-term control of pain.

ARGUMENTS SUPPORTING THE AVAILABILITY OF OXYCONTIN ON THE PHARMAC PHARMACEUTICAL SCHEDULE

There is a clear need for alternative opioid agents to morphine for patients in whom morphine is either ineffective or contraindicated, or for patients who have developed tolerance to morphine. Both the WHO and the European Association for Palliative Care [EAPC] have recommended oxycodone as a suitable alternative to morphine in these patients [WHO, 1996; Hanks et al, 2001]. Several properties of oxycodone, and its modified release formulation, OxyContin, make it the ideal alternative to morphine for the treatment of moderate to severe chronic pain.

Oxycodone Fulfils the WHO Requirements for an Effective Opioid Analgesic

The WHO guidelines for opioid analgesia suggest that the critical features of a suitable opioid for treatment of chronic pain should be that it is oral, given around the clock, and should be tailored to a patient's needs [WHO, 1996]. Additionally, the ideal opioid would also be available in both immediate and sustained release formulations to allow for dose titration and long-term maintenance therapy, as well as to provide "rescue" therapy for breakthrough pain [Hanks et al, 2001].

This suitability of oxycodone as a treatment for chronic pain is supported by Levy [2002] who notes that "CR oxycodone has the characteristic of an 'ideal' opioid analgesic drug: short half-life, long duration of action, predictable pharmacokinetics, absence of clinically active metabolites, rapid onset of action, easy titration, no ceiling dose, minimal adverse effects and minimal associated stigma"

Mundipharma currently supplies oral oxycodone in both an IR [OxyNorm] and CR [OxyContin] formulation. It is understood, according to the Medsafe website [www.medsafe.govt.nz], OxyNorm and OxyContin are the only oral, oxycodone products currently registered in New Zealand [Proladone, oxycodone 30mg suppositories are registered in NZ].

OxyNorm is registered in New Zealand in a range of dosing strengths [5mg, 10mg and 20mg], allowing for easy dose titration in patients commencing opioid therapy or those switching from another opioid. This range of doses also allows for the provision of IR oxycodone to patients for use as rescue medication in the case of breakthrough pain, and for incidence pain.

Similar to OxyNorm, OxyContin is also registered in New Zealand in a wide range of dosing strengths [10mg, 20mg, 40mg and 80mg]. This range of strengths allows for flexibility in constructing a dosing schedule tailored to each patient's individual needs.

Neither OxyNorm nor OxyContin are currently listed on the PHARMAC Pharmaceutical Schedule.

Alternative Strong Opioids do not have the Same Clinical Utility in Pain Management as OxyContin

As well as oxycodone, a number of other alternative strong opioids are recommended by the WHO as alternatives for patients in whom morphine is inappropriate or ineffective. Whilst each of these alternative agents possess some of the characteristics required by the WHO guidelines for an ideal opioid, none of them fulfil all of the requirements of being available in:

- a range of dosing formulations, including oral;
- a wide range of dosing strengths; and
- both IR and CR formulations.

A brief discussion of each of these alternative opioids is given below.

Fentanyl is effective and well tolerated in the management of chronic cancer and non-cancer pain, however, due to it's pharmacological properties, it is generally less flexible than other opioids. Due to a rapid and extensive first-pass mechanism, fentanyl is not appropriate for oral use, and is supplied either as an injectable or, more commonly, a transdermal patch. Each transdermal patch is applied for three days and, following application, steady state is achieved at 72 hours. Although the 3-day duration may be an advantage for patients with stable opioid requirements it can complicate management of patients with unstable, chronic pain whose opioid requirements are fluctuating [Hanks et al, 2001]. Problems in obtaining adequate pain relief in the first 72 hours and unstable pain syndromes requiring rapid dose escalation or reduction are common limitations to the use of fentanyl [Mercadante, 1999].

Hydromorphone is a semi-synthetic congener of morphine and a potent μ-selective agonist similar to morphine and around 8 times more potent. There appears to be no major differences between hydromorphone and morphine in terms of efficacy and adverse effects when used in equianalgesic doses [Hanks et al, 2001]. However, there are no sustained release, oral hydromorphone preparations currently registered in New Zealand [www.medsafe.govt.nz].

Methadone is a synthetic opioid frequently used for maintenance and withdrawal of opioid dependency. It potential use in pain management is complicated by a discrepancy between the duration of its initial analgesic effect [4-6 hours] and its plasma elimination half-life [mean 24 hours, range 17 to 100 hours] [Hanks et al, 2001]. Steady-state levels may take up to 7-14 days to achieve [WHO, 1996] resulting in possible under-analgesia during this extended titration phase in some patients. Methadone accumulates on chronic dosing, and should therefore not be given more frequently than 8-hourly to avoid potential side effects and overdosing. When switching to methadone from another opioid, it is often difficult to accurately determine the equianalgesic dose, particularly in patients tolerant to high doses of opioids. Due to these complications associated with the use of methadone for the treatment of chronic pain, its use by non-specialist practitioners is not recommended [Hanks et al, 2001]. Again, it is understood that there are no sustained release, oral methadone preparations, suitable for chronic pain management, available.

Pethidine is a synthetic opioid analgesic, with similar effects to those of morphine, and only available orally as an IR tablet. It is generally shorter acting than morphine, with useful analgesia lasting up to three hours. Due to this, for treatment of severe chronic pain, pethidine may need to be given every three hours to maintain adequate analgesia. Consequently, this agent cannot be considered to be a practical alternative to SR morphine, or OxyContin, for the treatment of chronic moderate to severe pain [WHO, 1996].

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Clinical Support for Availability of OxyContin

Worldwide, leading pain and palliative care specialists strongly support the availability of OxyContin due to the requirement for a range of opioids, and consider OxyContin to be an indispensable tool in the management of chronic cancer and non-cancer pain. Whilst morphine continues in some cases to be the opioid of first choice for some patients, this is due to historical reasons rather than any scientific basis, and, with increasing exposure, many pain specialists now consider OxyContin to be the opioid of choice. This is particularly the case in elderly patients, patients with neuropathic pain, and those with renal impairment.

Commonly raised arguments to support the availability of IR and CR Oxycodone include:

- The need for a range of different opioids in both IR and CR formulations. Most clinicians acknowledge clinical observations that there is considerable variation in patient responses to different opioids, and that there is a need for alternative IR and CR opioid agents for patients in whom morphine is not appropriate [i.e. those in whom morphine is either not well tolerated or in whom pain control is inadequate]. It is common practice to change patients in whom morphine is not effective or poorly tolerated to OxyContin, providing practical support of its distinctive pharmacological properties.

- The wide range of OxyContin dosages available permit precise dosing.

- Many of the problems associated with the use of oral morphine [e.g. general hyperalgesia and excessive sedation, nausea and vomiting in those with renal impairment] are related to its active metabolites. Oxycodone does not have active metabolites, and therefore is not associated with the same problems as those seen with morphine.

- Oxycodone has specific pharmacological and pharmacokinetic properties that influence the clinical care of patients. Oxycodone has been shown to act on both the mu and kappa-opioid receptors, and recent evidence indicates that it has clinical utility in the treatment of neuropathic pain. Several clinicians have noted that they would choose OxyContin as the opioid of choice in patients in whom pain is at least partly neuropathic in origin, as clinical experience appears to indicate its superiority in the treatment of such patients.

- Many elderly patients with neuropathic pain receive very effective analgesia with regular doses of oxycodone as low as 2.5mg 3-4 times a day. The availability of the 5mg CR OxyContin allows for the convenience of 12 hourly dosing in these patients.

- [redacted]

The use of significant and adequate resources to facilitate pain relief at all stages of cancer is essential. The use of oxycodone, particularly in the form of OxyContin, allows patients to stay on oral pain medication for longer and to remain at home, and also avoid expensive interventions such as adjuvant analgesics and spinal opioids.

OxyContin is the Least Costly Alternative to CR Morphine

The only alternative long acting opioid to sustained release, oral morphine other than OxyContin currently registered in New Zealand is the fentanyl patch [www.medsafe.govt.nz]. It can therefore be assumed that, for those patients who are currently unable to use morphine either due to unacceptable side effects or the development of tolerance, these are the two drugs which are most likely to be prescribed. In major markets, the fentanyl patch is considerably more expensive than OxyContin, therefore, should this product be listed on the PHARMAC schedule, it is likely that the cost to the New Zealand government would be higher than if OxyContin were available and prescribed to these patients.

An alternative to opioid substitution in patients unable to achieve adequate analgesia without intolerable side effects is to reduce the dose of the opioid and provide concomitant analgesia with a non-opioid or adjuvant analgesic [Goodyear-Smith et al, 2004]. Alternatively, adjuvant drugs may be used to control the opioid-induced adverse effects [refer Section 2.3]. In both these cases, the cost of treatment is increased,

as it includes not only the cost of the opioid but also the cost of the concomitant analgesic or the drug[s] used to treat the opioid-induced adverse effects. Therefore, in cases where adequate analgesia without intolerable side effects cannot be achieved with morphine, substitution to OxyContin is the least costly alternative.

ARGUMENTS SUPPORTING THE INDEPENDENT PRICING OF OXYCONTIN ON THE PHARMAC PHARMACEUTICAL SCHEDULE

From the arguments presented above, it can be seen that, although sustained release morphine and controlled release oxycodone may have similar efficacy and safety profiles, the two agents cannot be considered therapeutically interchangeable. Consequently, as the availability of OxyContin will provide benefit to the New Zealand population in terms of best clinical practice for opioid usage, it is appropriate that the pricing of this important agent should be considered independently of the price of sustained release morphine.

Along with the clinical benefits of the availability of a range of opioid analgesics for the treatment of chronic cancer and non-cancer pain, a number of pharmacological aspects of OxyContin support the argument for its pricing independently of sustained release morphine.

OxyContin has Clinical Utility in Neuropathic Pain

Neuropathic pain represents a number of heterogenous conditions that cannot be explained by a single aetiology or by a particular anatomical lesion. Despite the different aetiology and multiple lesions giving rise to neuropathic pain, many of these conditions share common clinical phenomena such as no visible injury, paradox combinations of sensory loss and hyperalgesia in the painful area, paroxysms and a gradual increase in pain following repetitive stimulation. These observations have led to the proposal that neuropathic pain may be explained by the same or similar mechanisms. It has been suggested that hyperexcitability peripherally and at more central sites could be the mechanism by which these pains are explained [Sindrup and Jensen, 1999].

OxyContin has been shown in three placebo and randomized controlled trials to be effective in non-cancer related neuropathic pain - postherpetic neuralgia and diabetic neuropathy [Watson and Babul, 1998; Gimbel et al, 2003; Watson et al, 2003]. Statistical significant benefits were variously demonstrated in pain intensity, allodynia, disability, sleep quality and quality of life.

OxyContin has a Different Receptor Profile to Morphine

Opioid tolerance is specific to the receptor activated, with evidence of incomplete cross-tolerance between opioids acting on the same receptor. Morphine is primarily a μ- receptor agonist [McRae and Sonne, 1998]. The analgesic effects of oxycodone are mediated by both the μ and κ-opioid receptors [Ross and Smith, 1997] and it has been shown that co-administration of sub-optimal doses of oxycodone and morphine results in a much more pronounced analgesic effect than either agent alone [Ross et al, 2000]. Studies in rats have demonstrated that there is an incomplete and asymmetrical cross-tolerance between morphine and oxycodone. In animals tolerant to morphine there was either a low level or no discernable cross-tolerance to oxycodone, dependant on the route of administration. In contrast, a high degree of cross-tolerance was observed when morphine was administered to rats rendered tolerant to oxycodone [Nielsen at al, 2000]. This asymmetrical cross-tolerance was attributed to the different receptor profiles of the two agents. This finding has been confirmed in humans in a study that demonstrated that there is less cross-tolerance with a switch from morphine to oxycodone than one from oxycodone to morphine [Davis et al, 2003].

OxyContin has Predictable Oral Bioavailability

OxyContin has an oral bioavailability of 60-87% in humans and less plasma variation than morphine, which increases the predicability of its pharmacokinetics [Levy, 2001]. As mentioned previously, the oral bioavailability of morphine is poor and widely variable [15-64%], and this has been implicated in the unpredictable onset of action and great individual variability seen with this agent [Hanks et al, 2001].

OxyContin Lacks Active Metabolites

Oral oxycodone is absorbed through the gastrointestinal tract and is less subject to first-pass metabolism in the liver than morphine. It is metabolised by the liver and excreted primarily in the urine. Oxycodone is

metabolised to oxymorphone and noroxycodone as well as a variety of glucuronide conjugates, but the parent compound is primarily responsible for its pharmacodynamic effects, including analgesia.

Oxymorphone is biologically active [approximately 14 times as potent as oxycodone], however, it is produced in very small, often undetectable amounts in humans through metabolism of oxycodone [Anderson et al, 2001] and does not contribute to the analgesic effect of oxycodone.

Noroxycodone is clinically non-active and is excreted unchanged in the urine [Davis et al, 2003]. Due to the inactive nature of this metabolite, it is not implicated in the development of toxic adverse effects associated with oxycodone therapy. This is in contrast to morphine, in which both M6G and M3G have been implicated in both early and late-stage morphine-related toxicities [refer Section 2.5]. The lack of active metabolites associated with oxycodone may be responsible for the lower rate of treatment-related adverse events observed in patients treated with this agent in the clinical setting.

Dose Relativity of OxyContin and Sustained Release Morphine

Determination of the relative potency between oral oxycodone and morphine sulphate is problematic, primarily due to variations in the bioavailability of the two agents. There is significant inter-individual variation in the oral bioavailability of morphine sulphate, which ranges from 15-64%. Conversely, the oral bioavailability of oxycodone is 50% or higher. This disparity in oral bioavailability could result in at least a 1:1 to 2:1 equianalgesic ratio for morphine sulphate:oxycodone, i.e. depending on the individuals ability to absorb morphine sulphate, oxycodone may range from equipotent to twice as potent [Anderson et al, 2001].

Published data from randomised, controlled, cross-over studies comparing oral morphine sulphate and oxycodone have indicated dose ratios ranging from 1:1 to 2.3:1, a range which may reflect bioavailability differences and incomplete cross tolerance. Bioavailability differences could theoretically account for ratios as high as 3:1 for patients with widely variable morphine oral bioavailability [Anderson et al 2001].

Whilst it is accepted that the initial pricing of a new agent may be referenced to that of an existing product where available, due to the uncertainty surrounding the determination of the relative potency of oral oxycodone and morphine, it is uncertain how this can be adequately applied to controlled-release oxycodone and morphine.