Information to be included with an application for inclusion, change or deletion of a medicine in the WHO Model List of Essential Medicines

1 Summary statement of the proposal for inclusion, change or deletion

This is a proposal for the inclusion of morphine modified release tablets (MMR) for the treatment of cancer related pain in the WHO Model List.

2 Name of the focal point in WHO submitting or supporting the application

Cecilia Sepuldeva Department of Medicines Policy and Standards.

3 Name of the organization(s) consulted and/or supporting the application

Cochrane Pain Palliative and Supportive Care Group
African Palliative Care Association, Entebbe, Uganda
Dr Peer Neleman, anaesthesiologist, University Hospital, Groningen, The Netherlands
Foundation for Hospices in Sub-Saharan African, Alexandria, VA, United states of America
International Hospice and Palliative Care Organisation, Houston, TX, USA
International Narcotics Control Board, Vienna, Austria
National Hospice and Palliative Care Organisation, Alexandria, VA, USA
PCH Pharmachemie BV, Haarlem, The Netherlands
WHO Collaborating Centre for Policy & Communications in Cancer Care, Pain & Policy Study Group, University of Wisconsin, Madison, WI, USA.

4 International Nonproprietary Name (INN, generic name) of the medicine

Morphine sulphate (or sulfate) modified release (INN does not appear to have been assigned).

5 Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Modified release tablets releasing morphine over 12 or 24 hours. Strengths: 10mg, 30mg and 60mg.

6 International availability - sources, if possible manufacturers

MS Contin (Purdue) is available in at least 100 countries (Appendix 1). Data for other brands could not be obtained.

7 Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine although other salts of morphine are available such as morphine hydrochloride.

8 Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

It is estimated that approximately two thirds of cancer sufferers experience moderate or severe pain. Over twenty epidemiological studies exist (60,000 participants) however most are from Europe, Japan or North America. The large studies indicate that moderate or severe pain occurs in a range of 33% to 75% depending on the cancer type. Following the publication of World Health Organization guidelines in the mid 1980s, the oral administration of aqueous morphine solution every four hours by the clock became commonplace for moderate or severe cancer pain (WHO 1986). Morphine in a modified release (also known as sustained release) tablet was first marketed around the same time, allowing the dosage interval to be extended to 12 hours. A number of products are now available in both 12 hour and 24 hour modified release. These allow regular dosing for those who are on a stable dose with immediate release available for breakthrough pain. Of particular value is that modified release provides pain relief throughout the night time sleeping period.

As the INCB pointed out in its Annual Report of 2003, six countries together accounted for 79 per cent of the global consumption of morphine. "Developing countries, which represent about 80 per cent of the world's population, accounted for only about 6 per cent of the global consumption of morphine."

Addition of MMR to the essential medicines list will hopefully promote greater appropriate use of morphine in developing countries.

The target population is cancer sufferers with moderate or severe pain.

9 Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

The following is quoted from the WHO guideline Cancer Pain Relief, with a guide to opioid availability, Second edition, WHO, Geneva, 1996. The document is now somewhat dated but the section on oral morphine is still relevant:

Morphine by mouth

Morphine can be given as: a simple aqueous solution of the sulfate or hydrochloride salt every four hours (an antimicrobial preservative may be added); tablets, every 4 hours;slow-release tablets, every 12 hours.(also 24 hr formulation) The effective analgesic dose of morphine varies considerably and ranges from as little as 5 mg to more than 1000 mg every four hours. In most patients, pain is controlled with doses of 10-30mg every four hours. The effective dose varies partly because of individual variations in systemic bioavailability. ***The correct dose is the dose that works.*** *The drug must be given "by the clock" and not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy. If the patient has a sudden attack of severe pain, a rescue dose of morphine should be given promptly (as immediate release PW) and repeated after one hour if necessary. After the pain has been relieved, the regular dose should be reviewed, and increased if necessary. Slow-release morphine tablets are available in some countries in strengths varying from 10 mg to 200 mg. These tablets usually need be given only every 12 hours.*

10 Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

A comprehensive search using Cochrane Pain and Palliative care group methods was undertaken on Medline, Embase and the Cochrane Central register of RCTS. Date of the last search was 14 July 2006.

A Cochrane review was published in 2004 which included a total of 45 studies (3061 participants). Of these 14 studies (420 participants) compared MMR with instant release. An interim update was carried out for this submission and a further 12 potential reports of 10 RCTs were identified. Eight of these (541 participants) have been assessed (2 Japanese papers await assessment). Two of the eight studies compare morphine immediate release (MIR) and MMR (56 participants)

Summary of available data (appraisal of quality, outcome measures, summary of results)

Morphine was shown to be an effective analgesic and pain relief was not different between MMR and MIR when used at appropriate doses. The studies were largely equivalence studies for registration purposes. Mean daily doses ranged from 100mg/day to 250mg/day. Some patients required as much as 2g/ day to achieve pain relief. Adverse effects were common and in the studies 4% of participants found that the adverse effects were sufficient to withdraw from treatment with morphine.

From the interim update, two of the studies compared MMR with MIR (56 participants). The findings in the new studies do not substantially alter the original review though one new study comparing treatments (Klepstad) reinforces the idea that dose titration to pain relief can be undertaken with MMR.

Summary of available estimates of comparative effectiveness

Data are available in the Cochrane review comparing morphine with oxycodone, hydromorphone, fentanyl transdermal patches, dextropropoxyphene and tramadol. Morphine provided equivalent pain relief in the majority of studies with similar adverse effect profiles. Patients on Fentanyl patches frequently report less constipation than with morphine.

11 Summary of comparative evidence on safety:

Estimate of total patient exposure to date
Primary care prescribing data for England indicates that over 900,000 prescriptions for MMR were dispensed in 2002. Extrapolating this data suggests that millions of patients have received this medicine worldwide.

Description of adverse effects/reactions
Adverse effects of the modified release formulation are similar to those for immediate release. The common adverse effects are : nausea, vomiting, constipation, drowsiness and confusion. Respiratory depression can occur but is rarely a problem if the drug is titrated to manage the pain. Addiction is a common fear but rarely occurs in practice. The list of adverse effects described in the eModel formulary is sufficient.

Identification of variation in safety due to health systems and patient factors
The main issue of concern is the quality of manufactured sustained release products. There is a theoretical risk that poor manufacture could lead to a 'dumping' of a large proportion of the dose within a tablet or capsule leading to the possibility of a patient being overdosed with morphine with subsequent respiratory depression.

Summary of comparative safety against comparators
The main comparator for a modified release product is the instant release formulation. The safety profile for both products is similar. With modified release, it is not possible to ensure bioequivalence between morphine modified release products and once on a stable dose, patients should not be changed to an alternative product without re-titration and clinical assessment.

12 Summary of available data on comparative cost1 and cost-effectiveness within the pharmacological class or therapeutic group:

Range of costs of the proposed medicine – priced per tablet
Data from the International Drug Price indicator gives the following prices (USD) for MMR
Morphine modified release 10mg tablets: 24c
Morphine modified release 30mg tablets: 97 c (range 90c to 1.35)

Mims India (Dec 2005) (USD)
Morphine modified release 10mg tablets: 7 cents
Morphine modified release 30mg tablets: 12 cents

Mims Indonesia 2005 (USD)
Morphine modified release 10mg tablets: 40.cents
Morphine modified release 30mg tablets: 1.06 dollars

13 Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

These parameters are not relevant as dose and length of treatment are impossible to predict. The most important comparison is with immediate release morphine. This is not listed on the International Drug Price indicator but where comparison prices could be found the costs are similar or in some countries the modified release product is slightly cheaper.

14 Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Morphine sulphate tablets are registered in virtually all WHO's Member States. See appendix 1.

Morphine modified release is available internationally in the following strengths: 5mg, 10mg, 15mg, 20mg, 30mg, 60mg, 100mg, and 200 mg morphine sulphate.

Legal classification morphine

In the United Kingdom, morphine is listed as a Schedule II, Class A drug under the Misuse of Drugs Act 1971.

In the United States, morphine is classified as a Schedule II drug under the Controlled Substances Act.

Internationally, morphine is a Schedule I drug under the Single Convention on Narcotic Drugs

15 Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Morphine is listed in all major pharmacopoeias. The USP has monographs for morphine Sulfate and also for morphine Sulfate extended release capsules. The BP has a monograph for morphine Sulphate and a monograph for Prolonged release morphine tablets. The EP has a monograph for morphine sulphate.

16 Proposed (new/adapted) text for the WHO Model Formulary

There is a current monograph on the 2004 e-Model version (appendix 2). This will need to be amended to include details of modified release formulations. A suggested text is as follows:

The optimal route of administration of morphine is by mouth. Ideally, two different formulations are required: immediate release (for dose titration) and modified release (for maintenance treatment).

The simplest method of dose titration is with a dose of immediate release morphine given every four hours and the same dose for breakthrough pain. This rescue dose may be given as often as required (for example, every hour), and the total daily dose of morphine can be reviewed daily. The regular dose can then be adjusted according to account for the rescue doses.

There is no standard dose of morphine nor a maximum dose. The dose must be titrated against pain relief and adverse effects for each patient, the starting dose to be determined by previous analgesic treatment. Patients changing from a weak opioid will usually start with 10 mg every four hours.

If pain returns consistently before the next regular dose is due the regular dose should be increased. In general, immediate release morphine does not need to be given more often than every four hours and modified release morphine more often than every 12 hours (or 24 hours if 24 hour formulation is used)

It is important to keep the drug regimen as simple as possible. Increasing the dose invariably allows a four hourly or 12 hourly regimen to be achieved without producing troublesome adverse effects associated with the increase in peak blood concentrations. There is no advantage in increasing the frequency of administration and a considerable disadvantage to the patient in terms of convenience and compliance.

References

Cancer pain relief : with a guide to opioid availability- 2nd ed. World Health Organization Geneva (1996).

Klepstad P, Kaasa S, Jystad A, Hval B, Borchgrevink PC. Immediate- or sustained-release morphine for dose finding during start ofmorphine to cancer patients: a randomized, double-blind trial.Pain. 2003 Jan;101(1-2):193-8.
PMID: 12507714.

P.J.Wiffen Sept 2006

Appendix 1, Availability of MS Contin- one of the lead brands of morphine modified release

90 countries listed. COMMERCIAL- IN CONFIDENCE

Albania
Argentina
Australia
Austria
Bahrain
Belarus
Belgium
Bosnia and Herzegovina
Channel Islands
Brazil
Bulgaria
Canada
Chile
China
Colombia
Costa Rica
Croatia
Cyprus
Czech Republic
Denmark
Egypt
El Salvador
Estonia
Finland
France
Gabon
Georgia
Germany
Ghana
Greece
Hong Kong
Hungary
Iceland
India
Indonesia
Iran, Islamic Republic of
Ireland
Israel
Italy
Ivory Coast
Jamaica
Japan

Jordan
Kazakhstan
Kenya
Korea
Kuwait
Latvia
Lebanon
Luxembourg
Macedonia, The Former Yugoslav Republic of
Malaysia
Maldives
Malta
Mexico
Mongolia
Morocco
Netherlands
New Zealand
Norway
Oman
Pakistan
Papua New Guinea
Peru
Philippines
Poland
Portugal
Qatar
Romania
Russia
Saudi Arabia
Senegal
Singapore
Slovakia
Slovenia
Solomon Islands
South Africa
Spain
Sweden
Switzerland
Taiwan
Thailand
Tunisia
Uganda
United Arab Emirates
United Kingdom
United States
Uzbekistan
Venezuela

Appendix 2

Current (2004) monograph on morphine

Morphine salts

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Tablets , morphine sulfate 10 mg

Oral solution , morphine hydrochloride or sulfate 10 mg/5 ml

Injection (Solution for injection), morphine sulfate 10 mg/ml, 1-ml ampoule

Uses:

severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia (section 1.5)

Contraindications:

acute respiratory depression, acute alcoholism, where risk of paralytic ileus; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions:

renal and hepatic impairment (Appendices 4 and 5); reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **overdosage:** section 4.2.2; **interactions:** Appendix 1

Dosage:

Acute pain, *by subcutaneous injection* (not suitable for oedematous patients) *or by intramuscular injection* **ADULT** 10 mg every 4 hours if necessary (15 mg for heavier well-muscled patients); **INFANT** up to 1 month 150 micrograms/kg, 1–12 months 200 micrograms/kg; **CHILD** 1–5 years 2.5–5 mg, 6–12 years 5–10 mg

Chronic pain, *by mouth or by subcutaneous injection* (not suitable for oedematous patients) *or by intramuscular injection* 5–20 mg regularly every 4 hours; dose may be increased according to need; oral dose should be approximately double corresponding intramuscular dose

Myocardial infarction, *by slow intravenous injection* (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary; elderly or debilitated patients, reduce dose by half

Acute pulmonary oedema, *by slow intravenous injection* (2 mg/minute), 5–10 mg

Note. The doses stated above refer equally to morphine sulfate and hydrochloride

Adverse effects:

nausea, vomiting (particularly in initial stages) constipation; drowsiness; also dry mouth, anorexia, spasm of urinary and biliary tract; bradycardia, tachycardia, palpitations, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, miosis; larger doses produce respiratory depression and hypotension

Appendix 3
Details of included studies in Cochrane review : Oral morphine for cancer pain

Study	Methods	Participants	Interventions	Outcomes	Notes
Arkinstall 1989	Design Randomised two phase cross over in 10 days treatment phase. No further dose adjustment allowed apart from MIR for break through. Mean age 63 yrs mean weight 61.1kg	Cancer pain Setting Hospital/Acute /Surgery/Community. 29 pts	Dosing regime MSR 12 h vs. MIR 4 hourly with MIR for break through. All pts treated under double blind conditions Length of treatment 20 days -(10 d crossover then 10 d)	Outcome measures Extra MIR and patient preference. Plasma morphine concentrations last 3 days of both phases. Side effects Analgesic outcome results: No sig difference between MSR & MIR pain scores. Rescue MIR No sig diff between groups. Preferred MSR-8, MIR-6 No Pref-3	Withdrawals and Adverse effects No sig diff for nausea or tiredness. 11/29 dropped out (10 during titration). Withdrawal due to AE 3 pts. 17 pts completed study QS 4 (R1,DB2,W1)
Cundiff 1989	Design MSC or MIR titrated upwards until not more than 20% total daily morphine given as rescue over a 2 day period (time to reach steady state 4:7 days). Crossover to start at one third pre study equivalent than titrate up. 23 pts Age 31-72 yrs mean 45yrs	Cancer pain Setting In & out patients 23 pts	Dosing regime MSC 30 mg every 12 hrs or MIR tablets 15 mg 4 hourly.15 mg MIR tablets as rescue Length of treatment 4-7 days per arm	Outcome measures Quality & frequency of rescue medication. Nurse assessed PI and frequency. A/E Analgesic outcome results	Withdrawals and Adverse effects Total morphine dose in last 24hrs significantly higher in immediate release group (496 mg MIR vs. 369 mg MSC) QS 4(R1 DB2 W1)
Deng 1997	Randomised parallel study of 7 days and pharmacokinetic study	Advanced cancer pain- hospital inpatients. 16 pts	Dose: MSC 30mg 12hourly or MIR 10mg 4 hourly for 7 days	Physician assessed pain relief	Withdrawals and Adverse effects 1 pt withdrew in MSC group (no reason

Study	Methods	Participants	Interventions	Outcomes	Notes
					stated) Chinese language paper
Deschamps 1992	Design Randomised cross over trial with titration phase. DB DD. MIR for break through. 2x7day phases. No other opioids/ analgesics allowed. Mean age 57yrs (40-72)	Cancer pain Cancer outpatients 20 pts	Dosing regime MSR 30, 60,100 mg vs. MIR 1mg/ml and 5mg/ml. MSR given 12 hourly (8am & 8pm) MIR 4 hourly with double dose at night Length of treatment: 14 days (2 x 7d)	Outcome measures VASPI, verbal (6 point) side effects severity. Patient preference Analgesic outcome results: No sig diff in pain scores or supplemental morphine.	Withdrawals and Adverse effects 4 died during titration and 2 withdrew due to AE. One withdrew consent. 8/20 dropped out QS 5
Finn 1993	Design Randomised DB DD crossover MSR - 30mg 12 hourly MIR 20 mg/ml. Severe pain required >60 mg IRM. Rescue: paracetamol, IRM or subcut/IM morphine. Non opioid medications continued. Mean age 59 yrs.	Cancer pain Outpatients. 37pts entered 34 pts completed	Dosing regime Day 1 Usual immediate release morphine Day 2&3 either MSC or MIR (with matched placebo) Day 4&5 crossover. (15/34 MIR/MSC) (19/34 MSC/MIR) Length of treatment 6 days	Outcome measures VASPI 3x day Cat PI (4 point) Karnofsky. S/E profile. Use of rescue & patient preference Analgesic outcome results: No sig diff between groups on VAS scores. No sig diff on breakthrough medication. All pts in both groups reported either no pain or mild/mediate pain. No diff in side effects between groups. Av daily dose 150 mg	Withdrawals and Adverse effects 3/37 withdrew-reasons not clear 1 death. QS 5

Study	Methods	Participants	Interventions	Outcomes	Notes
Gillette 1997	Design Randomised DB DD 6 days treatment then crossover. Initial dose titration 5 days. Mean age 61.3yrs weight 60 kg. Rescue: drugs other than morphine. Severe pain.	Cancer pain Setting Hospital 27pts	Dosing regime MSR Capsules 30 mg or 60 mg 12 hourly. MIR 5ml/ml 4h. No washout Length of treatment 12days (2 x 6d)	Outcome measures VASPI 4x daily. Verbal scale (5 point) S/E, Sleep quality (days 6 &12) Morphine concentrations on day 6 & 12 Analgesic outcome results: No sig diff between treatments. No breakthrough analgesia required by any subject. A/E similar in both groups	Withdrawals and Adverse effects Dry mouth, constipation, somnolence & nausea most frequently reported. Incidence AEs - none withdrew because of AE QS 4 (R1 DB2 W1)
Hanks 1987	Design Randomised DB DD crossover study 2 days each arm. Age mean male 72 (range 59-78) female 68 (53-82)	Cancer pain Setting Continuing care unit 27 entered but 18 completed	Dosing regime MSR twice a day vs. MIR 4 hourly Length of treatment 4 days (2 x 2d)	Outcome measures VASPI, VAS alertness, nausea, mood, sleep assessment & appetite. Global rating CATPI (5points) Analgesic outcome results: No diff in pain scores, but pts on MSR slept better. Base line PI MIR 86.1 (SE2.8) MSR 80.2 (SE5.0) Final PI MIR 82.4 (4.8) MSR 75.3 (7.2). Patient Preference: 14 no pref, 3 MIR, 1 MSR	Withdrawals and Adverse effects Need to unpick - 27 initially, 9 not entered. 18 completed (abstract) Withdrawals due to breakthrough pain :1 MIR AEs 1MSR (drowsiness) QS 4 (R1 DB2 W1)

Study	Methods	Participants	Interventions	Outcomes	Notes
Hanks 1995	Design Randomised DB DD crossover. Age 35-69yrs mean 56. 200 mg to 1000 mg MSR 12hrly	Cancer pain Advanced Malignant disease. At least 400 mg morphine/day 25 pts	Dosing regime MSR 100 mg vs. MSR 200 mg 3 day crossover Length of treatment: 6 days (2 x 3d)	Outcome measures VASPI , symptom score categorical 4 point. Scores taken four times on days 3 and 6. Morphine plasma concentrations in 4pts Analgesic outcome results: No sig diff in treatments except in the 12hr post dose ratings .Pts had less pain on 200mg formulation. No sig diff in rescue medication. Kinetic data shows no dose "dumping". No sig diff in use of rescue.	Withdrawals and Adverse effects 5 withdrew. 2 constipation, 1 dysphagia 1 increasing pain 1 anxiety. Sedation 15/23 100 mg 17/21 200 mg (Not Sig) nausea & vomiting 8/23 100 mg 10/23 200 mg (Not Sig). One pt excluded as unreliable data. QS 4 (R1 DB2 W1)
Hoskin 1989	Design Randomised DB study one dose of MSR together with either additional MIR or placebo	Cancer pain Setting Inpatients on MIR	Dosing regime 1st dose MSR with 4 hourly equivalent of MIR or placebo (1dose) Length of treatment Single dose 12 hour study	Outcome measures Plasma morphine levels VASPI and CATPI (4 point) VASPR. S/E categorical + nurse assessment Analgesic outcome results: No sig effect noted by giving a loading dose of MIR with 1st MSR dose. No sig diff in PI and PR scores.	Withdrawals and Adverse effects 1/20 withdraw - deteriorating condition QS 5

Study	Methods	Participants	Interventions	Outcomes	Notes
Klepstad 2003	Randomised D/B double dummy parallel group. Titration study to compare titration with MIR and MSC	Malignant disease and persistent pain on mild to moderate opioids. 40 pts	MIR or MSC (24 hour release) with ketobemidone as rescue analgesia. Initial dose 60mg morphine per day then titrated to pain relief. Study stopped 2 days after stable dose.	Outcome measures VASPI for pain , rescue medication, loss of sleep, tiredness, constipation and vertigo Analgesic outcome results 13/16 satisfied or better on MIR 10/13 satisfied or better on MSR. Acceptable pain relief in both groups	Withdrawals and Adverse effects 6 dropped out- none due to lack of pain relief QS 5
Knudsen 1985	Design Randomised double blind cross-over trial Pts were 'consecutively randomised'	Cancer pain Setting not stated. Chronic pain due to advanced cancer	Dosing regime MSR 12hrly vs. MIR tablets 4hrly Length of treatment 14 days	Outcome measures VASPI for pain & sedation Analgesic outcome results No sig diff for pain. Greater sedation on 1st 3 days of MSR which then resolved	Withdrawals and Adverse effects Not stated QS 2 (R1DB1)
Kossman 1983	Design Randomised parallel group	Cancer pain	Dosing regime MST vs morphine cocktail (MIR) Length of treatment 7 days	Outcome measures Daily PI, pain duration and quality of sleep. Analgesic outcome results: Marked fall in pain intensity on day one. Then majority either wholly pain free or only slight residual pain.	Withdrawals and Adverse effects Not stated QS 1 (R1)

Study	Methods	Participants	Interventions	Outcomes	Notes
Panich 1993	Design Randomised cross-over at 7 days. Single (observer) blind. paracetamol or narcotic injection for breakthrough pain. Mean age 53+/- 10, weight 46.5 kg +/- 10.6 kg. Severe Pain	Cancer pain Setting Pain clinic in Thailand 73 pts (49 reported)	Dosing regime MSR 10 mg or 30 mg every 12 hrs for 7 days then cross-over to MIR solution (local formula) 5-10 mg every 4 hrs (or reverse order) No wash out Length of treatment: 14 days (2 x 7d)	Outcome measures Nurse assessment of pain (VAS) nurse assessment - cat (4 point) duration of sleep Analgesic outcome results No sig diff between MSR & MIR. Pt preference for MIR (71%) All pts had improved sleep. Pain scores provided.	Withdrawals and Adverse effects Withdrawals not included in analysis. Constipation, nausea, vomiting dizziness - table 6 no sig diff between groups. QS 2 (R1 W1)
Thirlwell 1989	Design Randomised DB DD cross-over. Each phase > 5 days to stabilise morphine dose. No non study opioids allowed. Non-opioids were allowed.	Cancer pain Setting not stated	Dosing regime MSR 30 mg 12 hrly or MSR 30 mg 8hrly vs. MIR 4hrly. Length of treatment 10 days (2 x 5d)	Outcome measures Pain intensity PPI (4 pt CAT scale) x 4 daily. Breakthrough analgesia. Plasma morphine concentrations Analgesic outcome results No diff between treatments. Morphine bioavailability for MSR over 12 hrs similar to MIR 4hr Av daily dose 160mg	Withdrawals and Adverse effects 1 withdrew due to AE - somnolence + disorientation, 5/28 withdrew in total = 2 somnolence + disorientation, 2 difficulty in obtaining blood sample, 1 excluded as received extra dose of morphine on pharmacokinetic sampling day. MSR nausea 3 MIR nausea 3 QS 4 (R1 DB2 W1)

Study	Methods	Participants	Interventions	Outcomes	Notes
Ventafridda 1989	Design Randomised parallel group. Mean age 57 (28-88)	Cancer pain Cancer pain no previous strong opiates. 70 pts	Dosing regime MSR 20 mg/day to 120 mg/day (N=35); MIR 4% sol 24 mg/day to144 mg/day (N=35) also Diclofenac 75 mg 3x days Haloperidol 20mg in 2doses daily. Length of treatment 14 days	Outcome measures Integrated score pain intensity scale 0-240! S/E. Slight 1 troublesome 2.5 exhausting 5 terrible 7.5 killing 10 Analgesic outcome results No diff between groups for analgesia. S/E frequency lower in MSR	Withdrawals and Adverse effects MIR 2 died 1 withdrew - lack of analgesia, MSR 1 died 2 withdrew 1 with hallucinations & 1 morphine intolerant. QS 1 (R)
Walsh 1984	Design Randomised DB DD cross-over MIR vs. MSR Mean age 67 =/- 8yrs	Cancer pain Setting - hospital in-patients 36 pts (30 completed)	Dosing regime Pts stabilised on MIR randomised to MIR/MSR cross-over day 3,cross-over day 5, cross-over day 8 Length of treatment 10 days (crossover d3, d5, d8)	Outcome measures Pt reported VASPI. Mood. Nurse reported - pain sedation, N&V, constipation, orientated. Pain breakthrough. Assessment of blinding Analgesic outcome results No diff in pain, mood, sedation or anxiety. No evidence of pain breakthrough on MSR	Withdrawals and Adverse effects Not described QS 3(R1 DB2)
Walsh 1992	Design Randomised DB DD cross-over. Pre-study non opioids allowed. Rescue - morphine (IR), paracetamol, IM/SC morphine. Mean age 60yrs.	Cancer pain Setting Advanced Cancer Hospitalised 33 pts	Dosing regime MSR 30 mg 12hrly or multiple MIR equivalent mg/24hrs every 4 hrs cross-over @ 2 days then 3 days further treatment	Outcome measures VASPI. VAS for anxiety, depression, sedation, nausea, constipation & confusion. Pt preference, breakthrough pain	Withdrawals and Adverse effects A/E scores recorded - no sig diff. - 3pts - nausea which necessitated

Study	Methods	Participants	Interventions	Outcomes	Notes
	Pre-study morphine dose 92-108 mg/day. Required >60 mg IR oral morphine to enter study.		Length of treatment 5 days (crossover day 2)	Analgesic outcome results No sig diff in pain scores, no diff in breakthrough pain (table 3) No diff in side effects.	withdrawal, 1pt - protocol violation. 2pts - rapid deterioration in health. QS 5

AE-adverse effect:
Av - average
CAT- categorical scale;
CATPI-categorical pain intensity;
CATPR-categorical pain relief;
d - day
DB - double blind;
DD - double dummy;
EORTC - European organisation for research and treatment of cancer;
hrs-hours;
IR- immediate release;
M-morphine;
NSAIDs- non steroidal anti-inflammatory drugs;
PPI- Present pain intensity;
Pts -patients;
QOL- quality of life;
QS-quality score, max 2 for randomised , max 2 for double blind, 1 for description of dropouts. Max possible 5
S/E - side effects;
sig diff - significant difference;
soln - solution;
SPID-Sum of pain intensity difference;

SR- sustained release;
TOTANS-Total analgesic score;
TOTPAR- total pain relief:
VAS-visual analogogue scale;
VASPI-vas for pain intensity;
yrs - years

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