A randomised, double-blind, active-controlled, double-dummy, parallel group study to determine the safety and efficacy of oxycodone / naloxone prolonged release tablets in subjects with moderate to severe, chronic cancer pain

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To determine the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN) compared to subjects receiving oxycodone prolonged release tablets (OXY) based on the Bowel Function...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34017

Source
ToetsingOnline

Brief title
OXN in moderate to severe, chronic cancer pain.

Condition

- Other condition
- Gastrointestinal motility and defaecation conditions
- Miscellaneous and site unspecified neoplasms benign

Synonym
chronic cancer pain; cancer related background pain

Health condition

pijnbestrijding

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma
Source(s) of monetary or material Support: farmaceutisch bedrijf: Mundipharma

Intervention

Keyword: oxycodone naloxone obstipation maligne pain

Outcome measures

Primary outcome

Efficacy Assessments:

Bowel Function Index (BFI), recorded in the Case Report Form (CRF) at each assessment visit. The Bowel Function Index is the mean value of the 3 single items included in the BFI. Ease of defecation (numerical analogue scale [NAS], 0=easy/no difficulty; 100=severe difficulty); Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100= very strong); Personal judgement of constipation (NAS, 0=not at all, 100= very strong).

Amount of laxative medication use recorded at each assessment visit. Total number of bisacodyl tablets used per week, and the number of Bisacodyl tablets used per day will be recorded in the CRF.

Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's pain (worst, least, average, right now), pain relief

from medication and pain interference over the last 24 hours.

Amount of rescue medication recorded on the OXY IR wallet.

Secondary outcome

Safety Assessments:

Adverse Events (collected via spontaneous reports, subject interview)

Vital signs (at Visits 1, 2, 6, 6, 9 and 13)

Clinical laboratory test results (at Visits 1, 6, 9 and 13)

ECG (at Visits 1, 9 and 13)

Physical Examination (at Visits 1, 9 and 13)

Study description

Background summary

Opioid bowel dysfunction is an adverse event associated with OxyContin®/ Oxygesic® and other opioid analgesics that limits the continuous treatment of pain subjects and is therefore one of the main reasons for insufficient pain therapy in general. Naloxone is a narcotic antagonist used as a solution for injection in the treatment of opioid overdose. When administered orally, it can reduce opioid-induced constipation due to a local action in the gut. It has a high first-pass metabolism, which is an advantage as the laxative effect can be achieved due to the local action in the gut, without significant antagonism of the narcotic analgesic effect of the oxycodone.

Study objective

To determine the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN) compared to subjects receiving oxycodone prolonged release tablets (OXY) based on the Bowel Function Index (BFI) and laxative use.

To demonstrate the comparability of oxycodone/naloxone prolonged releaase tablets (OXY) for the management of chronic cancer pain as assessed by the Brief Pain Inventory (BPI) and rescue medication use recorded by subjects.

Other objectives:

To assess bowel function and bothersomeness based on the PAC-SYM(b) questionnaire.
To assess safety of treatment with OXN compared with OXY based on the Modified Subjective Opiate Withdrawal Scale (SOWS), Adverse Events (AEs), Electrocardiograms (ECG) and laboratory tests.
To assess quality of life based on EuroQol EQ-5D and EORT QLQ-C30 (European Organization for Research and Treatment of Cancr Quality of Life Questionnaire-Core).

Study design

This is a randomized, double-blind, active-controlled, double-dummy, parallel group study using OXN and OXY to trat moderate to severe, chronic cancer pain. Subjects must have a medical history of constipation that was induced by, or worsened by their opioid therapy.

Intervention

At V2 subjects will stop their pre-study opioid and laxative medication.
Subjects will be randomized to receive either OXN or OXY at V2. Subjectw will receive the double-blind medication for a period of 4 weeks. Investigators will change the subject's dose of pre-study opioid to a dose os oxycodone prolonged release (PR). The starting dose of oxycodone PR will be based on subject's prior dose of opioid and whether subjects need an increase in opioid dose to control their pain. During the double-blind treatment phase study medication will be titrated up to a maximum of 120mg/day of oxycodone PR. Open label oxycodoneimmediate release capsules (OxyIR) will be available to subjects as rescue medication throughout the double-blind treatment phase. OxyIR will be taken at a dose of approximately1/6 of the oxycodone PR daily dose, and will be taken as required by subjects to treat breakthrough pain. A maximum of 6 doses of OxyIR can be taken in 24 hours. If a subject regularly requires more than 2 uses of rescue medication per day, the investigator should increase the subject's dose of double-blind medication by 10 mg/day of OXN/OXY in a double-blind, double-dummy manner. If a subject requires greater than 120 mg OXY/OXN PR or 120 mg OXY/OXN PR and more than the maximum OxyIR allowed by the protocol e.g. regularly requires more than two rescue doses of OxyIR, then the subjects must be withdrawn from the study (see Section on Concomitant Medication Inclusing rescue-Analgesics).
Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication. On the day of randomisation pre-study laxatives hould be discontinued. If no bowel movement (BM) occurs within 3 days after the start of the double-blind phase, bisacodyl laxative intake will be commenced, which means that a laxative should be taken at that time. However investigators can instruct their subjects that if they exhibit discomfort during this period they can take oral bisacodyl as a laxative earlier than after 3 days as required to treat constipation. After that first 3 day period,

bisacodyl tablets may be used no sooner than 72 h after the subject's most recent BM. However investigators can instruct their subjects that if they exhibit discomfort during the 72 hour period they can take oral bisacodyl as a laxative earlier than 72 hours after theuir most recent bowel movement as required to treat constipation. The maximum allowed number of bisacodyl intakes is 5 dosages within 7 consecutive days.

Open label extension phase:
Subjects who complete the double-blind phase or who discontinue due to constipation and still comply with all screening inclusion and exclusion criteria will have the option to enter the 24 week extension phase. Subjects will receive open-label OXN for up to 24 weeks. Rescue medication (OxyIR) and laxative medication (bisacodyl) will be supplied for the first 7 days of the extension phase. Visits will be performed after 1 day (V10), 1 week (V11), 12 weeks (V12) and 24 weeks (V13). Monthly visits for dispensing of medication will be conducted according to law.

Study burden and risks

Physical examination (maximum of 3 times); blood and urine samples (maximum of 4 times); questionnaires (maximum of 10 times: BFI, EDRTC; EQ-5D, PAC-SYM (b), SOWS, BPI-SF, Bowel Movements; Vital Signs; gewicht; ECG (maximum of 3 times).

The patient is not allowed to use a different laxative than Bisacodyl during the study and not earlier than 72 hours after the most recent BM. If the patient is using another painmedication than Oxycodone, the patient willbe asked to switch to a dose of Oxycodone relative to an equivalent effect as the former painmedication.

Since former studies have shown positive results with respect to the frequence of laxation of the treated patients, it is expected that the invasive treatments in this study will be in good balance with the benefits the patient can expect.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female subjects at least 18 yearsor older with a diagnosis of cancer.
2. Females less than one year post-menopausal must have a negative urine pregnancy test recorded at the screening visit, be non-lactating, and willing to use adequate and highly effective method of contraception throughout the study. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly uch as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (hormonal), sexual abstinence or vasectomised partner.
3. Subjects who are receiving WHO step II or STep III analgesic medication who have constipation induced, or worsened by their opioid medication, as shown by:
a. the subject's medical need of regular intake of laxatives to have at least 3 bowel evacuations per week, or having less than 3 bowel evacuations when not taking a laxative,respectively.
b. the subject's self-assessment that their constipation was induced or worsened by their current pre-study opioid medication.
4. Documented history of moderateto severe, chronic cancer pain that requires around-the-clock opioid therapy (starting dose at the beginning of the double-blind phase of oxycodone PR between 20-80 mg/day) and are likely to benefit from WHO step III opioid therapy for the duration of the study. Subjects must be willing to discontinue their current opioid analgesic routine.
5. Subjects are willing to discontinue pre-study laxative medication and take study specific laxative medication.
6. Subjects taking daily fibre supplementation or bulking agents are eligible if they can be maintained on a stable dose and regimen throughout the study, and in the investigators opinion are willing and able to maintain adequate hydration.

7. Subjects willing and able (e.g. mental and physical condition) toparticipate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinicl visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.

Exclusion criteria

1. Subjects that require a dose >80 mg/day oxycodone PR at the start of the double-blind phase.
2. Any history of hypersensitivity to oxycodone, naloxone, bisacodyl, related products, and other ingredients.
3. Subjects with any situation in which opioids are contra-indicated, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, paralytic ileus.
4. Evidence of clinically significant cardiovascular, renal, hepatic or psychiatric disease, as determined by medical history, clinical laboratory tests, ECG result, and physical examination, that would place the subject at risk upon exposure to the study medication or that may confound the analysis and/or interpretation of the study results.
5. Abnormal aspartate aminitransferase (AST; SGOT), alanine aminotransferase (ALT;SGPT), or alkaline phosphatase levels (>3 times hte upper limit of normal) or an abnormal total bilirubin and/or creatinine level(s) (greater than 1.5 times the upper limit of normal).
6. Subjects with known or suspected unstable brain metastases or spinal cord compression that may require changes in steroid treatment throughout the duration of the study.
7. Subjects with uncontrolled seizures.
8. Subjects with increased intracranial pressure.
9. In the investigator's opinion, subjects who are receiving hypnotics or other central nervous system (CNS) depressants, that may pose a risk of additional CNS depression with op ioid study medication.
10. Subjects with myxodema, not adequately treated hypothyroidism or Addisons disease.
11. Active alcohol or drug abuse and/or history of opioid abuse.
12. Subjects receiving opioid substitution therapy for opioid addiction (e.g. methadone or buprenorphine).
13. Subjects with myxodema, not adequately treated hypothyroidism or Addisons disease.
14. Subjects who have a confirmed diagnosis of ongoing irritable bowel syndrome.
15. Subjects suffering from diarrhoea and/or opioid withdrawal.
16. Surgery completed prior to the start of the Screening Period, or planned surgery during the study that would influence pain or bowel function during the study or preclude completion of the study.
17. Cyclic chemotherapy in the two weeks before the screening visit or planned during the core study that has shown in the past to influence bowelfunction. If subjects are having theur first cycle of chemotherapy during the 2 weeks before the screening visit or during the double-blind phase of the study they should be excluded from the study.
18. Radiotherapy that, in the investigator's opinion, wpuld influence bowel funstion or pain during the double-blind phase of the study.
19. Subjects presently taking, or who have taken, naloxone =<30 days prior to the start of

the Screening Period.
20. Subjects who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry (defined as the start of the Screening Period). Concurrent enrolment in another clinical trial is not permitted unless the sole purpose of the trial at the time of OXN2001 screening is for long-term follow-up/survival data.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-02-2008
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Oxycodone/naloxone prolonged release tablets 10/5 mg
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Oxycodone/naloxone prolonged release tablets 20/10 mg
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Oxycodone/naloxone prolonged release tablets 40/20 mg

Product type:	Medicine
Brand name:	OxyContin 20 mg prolonged release tablets
Generic name:	Oxycodone hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	OxyContin 40 mg prolonged release tablets
Generic name:	Oxycodone hydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-08-2007
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	19-09-2007
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	21-09-2007
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	20-03-2008
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 27-05-2008

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 08-08-2008

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 06-11-2008

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 18-11-2008

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 18-02-2009

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 24-02-2009

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	1
EudraCT	EUCTR2007-001313-42-NL
CCMO	NL18431.098.07