Exhibit 4

Medical Officer Review, Integrated Summary of Efficacy, Oxycodone Controlled Release, NDA 20553, Curtis Wright, M.D. and Medical Officer Review, OxyContin Study 0402B-Cancer Pain, Curtis Wright, M.D.

MEDICAL OFFICER REVIEW (MOR)

Integrated Summary of Efficacy
Oxycodone Controlled Release

"OxyContin"

NDA #: 20-553
Sponsor: The Purdue Frederick Company
Type of Submission: NDA Submission
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Reviewer: Curtis Wright, M.D.

Summary

OxyContin is a controlled release dosage form (10, 20 & 40 mg) that is intended to support BID dosing as an alternative to the usual QID marketed forms for the drug substance. There is substantial evidence, based on controlled clinical, pharmacodynamic and pharmacokinetic studies that the new BID formulation provides equivalent pain control to the same daily dose of the current QID formulation, with an equivalent adverse effect profile There is some evidence, both pharmacokinetic and clinical, that reduced acute opioid adverse effects may be expected in some patients, but there is not enough evidence to support an AE superiority claim against other marketed products.

Background

Oxycodone is an old opioid that has been on the market for many years in pre-38, USP, brand and generic immediate-release forms as a QID drug both singly and in fixed combination wth NSAIDS. Purdue Frederick is a small firm that specializes in modified release dosage forms of already established drug substances. They have conducted a development plan that included bioequivalency testing, population pharmacokinetics, clinical trials in acute and chronic pain models and population pharmacodynamics.

They wish to establish that equivalent daily doses of BID Oxycontin (10, 20 & 40 mg) and QID immediate release oxycodone provide equivalent analgesia with as great, or greater, a margin of safety

Table of Studies

PHARMACOKINETIC STUDIES

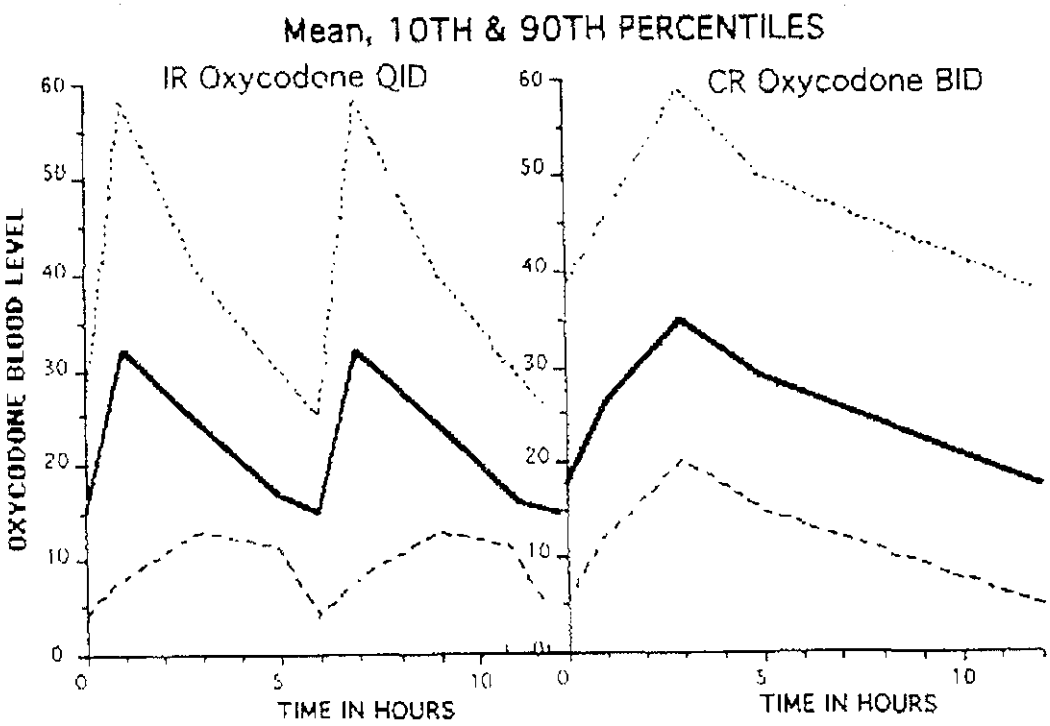
Study Name	Indication	Comparison
OC90-0708	SINGLE-DOSE PK STUDY	CR V. IR
OC91-0102	STEADY STATE PK	CR V. IR
OC92-0903	DOSE PROPORTIONALITY	10 V. 20 MG CR
OC93-0801	FED-FASTED PK	IR, 20 & 40 MG CR
OC93-0301	FILM COATING PK	10 MG CR UNCOATED/COATED
OC93-0103	SINGLE DOSE PK	IR V. MARKETED PRODUCT
OC93-0101	SINGLE DOSE PK (ELDERLY)	20 MG OLD & YOUNG
OC87-0105	DOSE PROPORTIONALITY	30 MG CR V. 3 X 10 MG CR V. IR
OC87-0501	FED & FASTED	10 MG CR
OC87-1003	STEADY STATE	IR V. CR
OC89-0702	CR V. SOLUTION	20 MG CR V. IR
OC93-0203	HEPATIC IMPAIRMENT	20 MG NORMAL/ABNORMAL
OC93-0307	RENAL IMPAIRMENT	20 MG NORMAL//ABNORMAL
OC94-0501	PER RECTUM	20 MG PO & PER RECTUM

CLINICAL STUDIES

Study Name	Indication	N	Comparison	Duration	PK/PD?
Controlled Trials					
OC91-0402A	CANCER	57/54	CR V. IR	5 DAY + / -	
OC91-0402B	CANCER	81/83	CR V. IR	5 DAY + / -	
OC93-0202	CANCER	50	CR V. IR	7 DAY X-O	PK/PD
OC92-1102	OA	44/44/45	10,20 CR V PLC	14 DAY	PK/PD
OC92-1201	LOW BACK	57	CR V. IR	7 DAY X/O	PK/PD
OC88-1105	POSTOP	30/30/30 30/31/31	10,20,30 CR IR, PLC PCT	SINGLE DOSE	none
Follow-on/ Compassionate Use					
OC91-0907A	CANCER	30		3 MONTHS	
OC91-0907B	CANCER	56		3 MONTHS	
OC92-1103	OA	100		ONGOING (18 MONTHS)	
OC92-1101	ALL DX	46		ONGOING (TILL APPROVAL)	

PHARMACOKINETICS

The reader is directed to the pharmacokinetic review for an expert analysis of the data. From the clinical perspective, the data from study 1201, a multi-dose comparison of plasma levels after IR and CR oxycodone is typical.



MEAN PLASMA OXYCODONE CONCENTRATIONS (adjusted to 40 mg/day)

	IR Oxycodone					CR Oxycodone				
	0 Hour	1 Hour	3-4 Hr	5-6 Hr	Mean	0 Hour	1 Hour	3-4 Hr	5-6 Hr	Mean
Mean	14.93	32.34	24.85	16.82	22.24	17.68	26.5	35.42	29.65	27.33
S.D	13.42	19.78	14.98	11.33	12.86	12.42	15.61	15.11	14.81	13.52
C.V	90%	61%	60%	67%	58%	70%	59%	43%	50%	49%

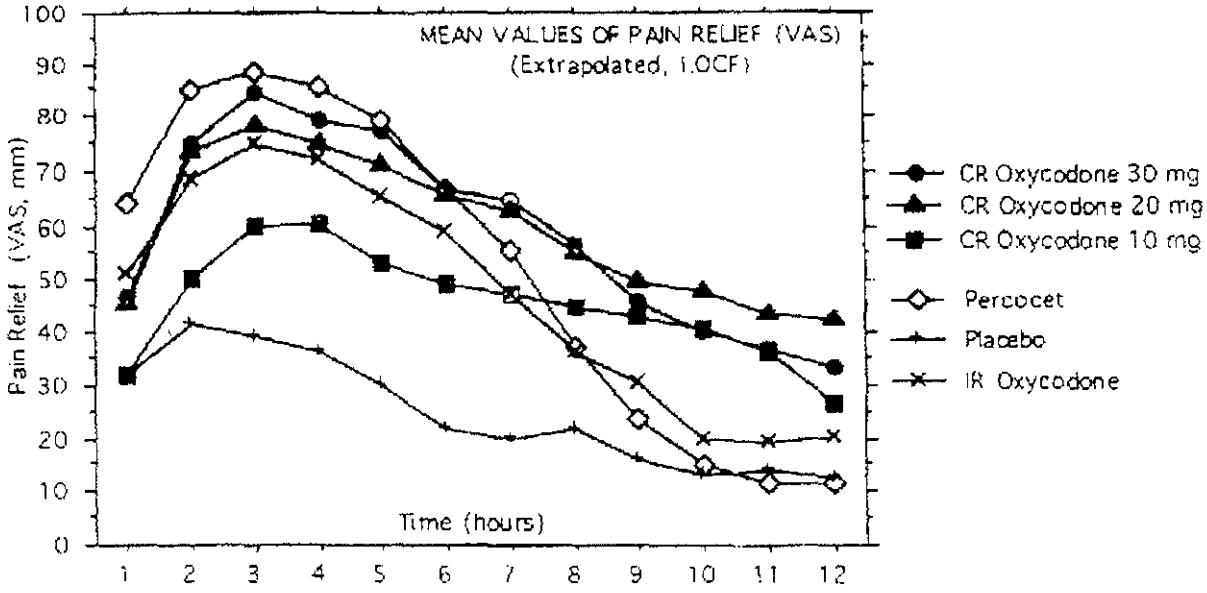
Both treatments appear to be similar with respect to peak, trough, mean and extreme values in clinical populations. The clinical question is if the process of stretching out the QID profile to BID substantially alters the clinical efficacy

Clinical Study Results

The efficacy of Controlled-Release Oxycodone tablets was studied in six controlled trials. The complete study reviews are attached, but the pertinent information about each trial is repeated below:

Study 1105 Post-Operative Pain

This was a single dose study of the efficacy and safety of CR Oxycodone (10, 20, and 30 mg) in comparison to immediate release oxycodone (15 mg), Percocet (2 tablets), and placebo for the management of post-operative pain.



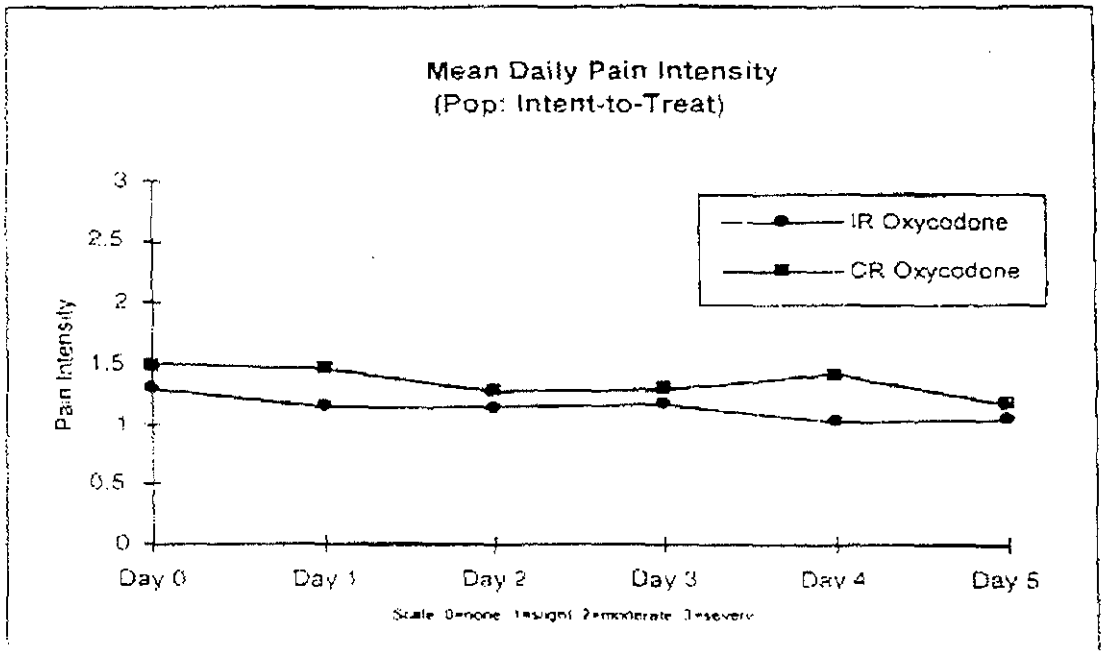
		Assessment Time Points (in hours)											
Treatment	Statistic	1	2	3	4	5	6	7	8	9	10	11	12
Placebo	Mean	32	41	38.9	36.3	29.6	21.6	19.9	21.6	16.1	13.1	14.1	12.6
	Std. Dev.	26	37	38	40	40	32	36	38	33	30	32	31
	N	30	26	24	19	15	9	8	8	6	6	6	5
IR Oxycodone	Mean	51.0	68.2	75.0	72.2	65.1	58.9	47.4	36	30.2	19.8	19.2	20.4
15 mg	Std. Dev.	34	35	37	39	43	42	43	39	38	34	34	36
	N	30	28	27	25	24	22	21	18	14	11	8	8
CR Oxycodone	Mean	31.8	50.3	60.0	69.2	53.3	49.5	47.5	45.0	42.7	40.4	36.2	26.4
10 mg	Std. Dev.	31	33	39	41	42	42	44	43	42	42	40	35
	N	30	28	22	22	21	20	20	17	17	17	15	14
CR Oxycodone	Mean	45.7	73.2	78.4	75.9	70.9	65.9	62.9	54.9	49.7	48.0	43.4	42.3
20 mg	Std. Dev.	29	26	28	32	37	41	42	45	46	46	45	45
	N	30	30	29	28	28	24	23	20	19	17	17	15
CR Oxycodone	Mean	46.9	73.1	84.6	79.0	77.2	66.3	64.9	56.3	45.8	40.2	36.5	33.6
30 mg	Std. Dev.	31	28	29	33	36	41	41	43	43	43	42	43
	N	30	30	29	28	26	25	25	22	20	19	16	13
Percocet x2	Mean	64.3	83.1	88.5	85.6	79.4	66.7	55.7	39.1	23.5	15.1	11.3	11.5
	Std. Dev.	31	21	14	24	31	38	42	40	37	32	29	30
	N	30	30	28	30	28	25	22	18	13	8	5	5
ANOVA P-value		< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .01	< .01	< .001	< .01	< .01

Conclusions

Controlled-release oxycodone at the 20, and 30 mg strengths (10 mg was marginal) appeared effective at relieving post-operative pain. Peak effects were observed at from two to five hours. A dose response was observed in which placebo was <10mg <20mg <30mg of controlled release oxycodone

OxyContin Study 0402A - CR & IR Oxycodone as an Alternative to Fixed Combination Opioids in Cancer Pain.

This was a double-blind, multi-center, randomized, repeated-dose, parallel group study in cancer patients who were receiving stable doses of fixed combination opioid analgesics for chronic pain. Patients were randomly assigned to either CR Oxycodone (30 mg, BID) or IR Oxycodone (15 mg, QID) for 5 days. In order to maintain the blind, all medication appeared identical (encapsulated: 00 capsules tested for dissolution).



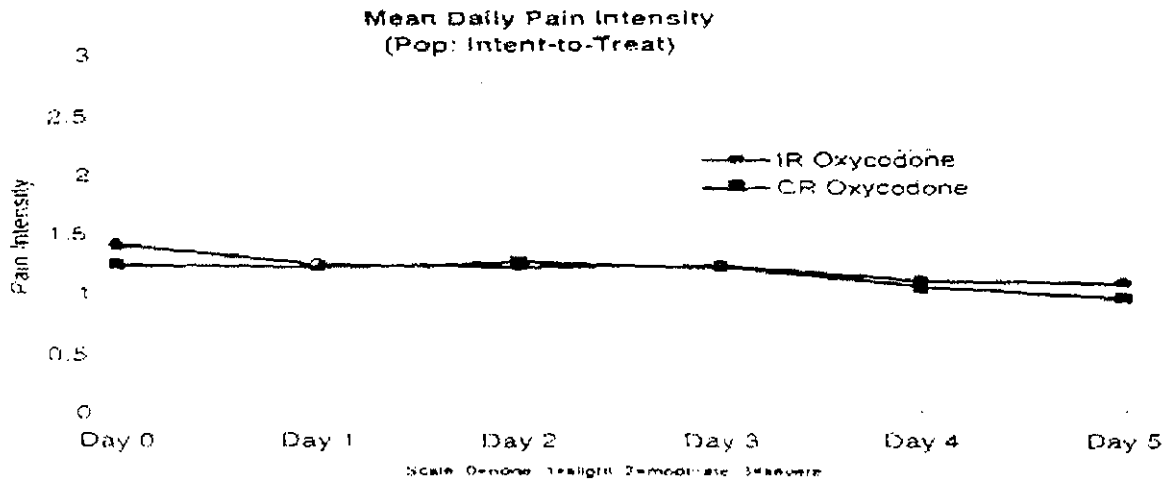
		Mean	Std. Error	N
DAY1_AVG,	CR Oxycodone	1.458	.122	52
	IR Oxycodone	1.147	.097	51
DAY2_AVG,	CR Oxycodone	1.268	.137	45
	IR Oxycodone	1.134	.096	41
DAY3_AVG,	CR Oxycodone	1.297	.146	41
	IR Oxycodone	1.162	.108	39
DAY4_AVG,	CR Oxycodone	1.399	.150	39
	IR Oxycodone	1.014	.094	37
DAY5_AVG,	CR Oxycodone	1.160	.139	36
	IR Oxycodone	1.046	.116	34

Conclusion

In patients with cancer pain receiving fixed-combination analgesics, conversion to both CR Oxycodone (BID) and IR oxycodone (QID) in equivalent total daily doses provded equivalent pain control. The fixed dose conversion rate was 30 mg CR bid/15 mg IR qid proved too small for patients taking more than 10 tablets of fixed-combination analgesics per day, but was acceptable for patients taking 6-9 tablets a day. The trial provided clear evidence of the need for individualization of dosage.

OxyContin Study 0402B- IR & CR Oxycodone in Cancer Pain Patients Previously Taking Strong Opioids.

This was a double-blind, multi-center, randomized, repeated-dose, parallel group study of QID IR oxycodone against BID CR oxycodone in cancer patients previously using strong opioid analgesics. The equivalent total daily oxycodone dose was calculated from the patient's current daily dose of opioids. In order to maintain the blind, all medication appeared identical (encapsulated: 00 capsules tested for dissolution).



Mean Pain Intensity by Study Day
Population: Intent-to-Treat

	Treatment	Mean	Std. Err	N
Day1 Avg	IR Oxycodone	1.248	0.085	79
	CR Oxycodone	1.225	0.090	77
Day2 Avg	IR Oxycodone	1.232	0.087	68
	CR Oxycodone	1.264	0.102	66
Day3 Avg	IR Oxycodone	1.247	0.099	62
	CR Oxycodone	1.236	0.105	58
Day4 Avg	IR Oxycodone	1.116	0.106	53
	CR Oxycodone	1.070	0.110	49
Day5 Avg	IR Oxycodone	1.105	0.126	47
	CR Oxycodone	0.981	0.110	48

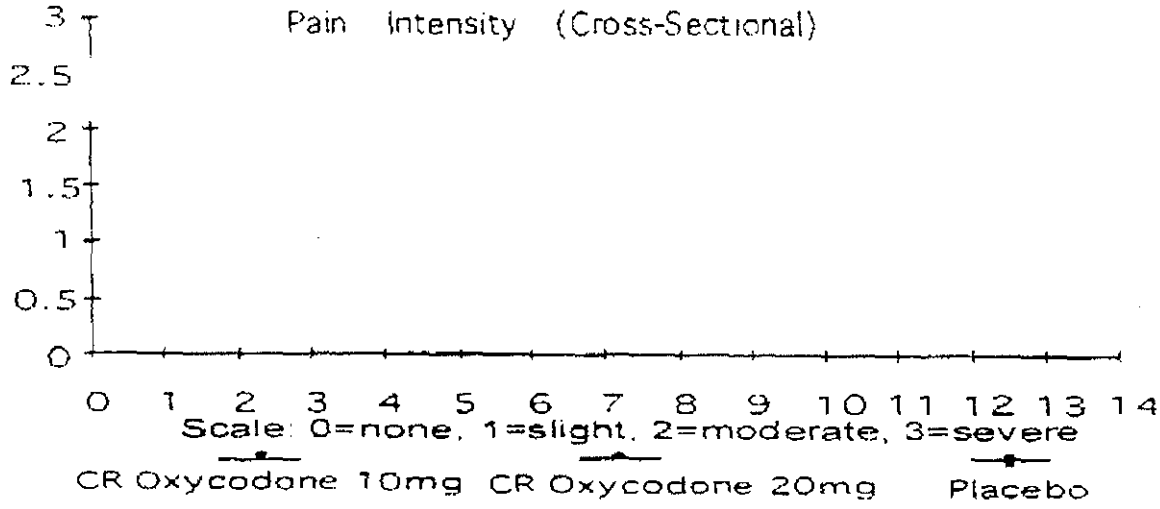
Conclusion

This trial provided substantial evidence that CR Oxycodone BID and IR oxycodone QID provided equivalent pain control in patients with cancer pain receiving high doses of fixed-combinations or strong opioid analgesics. The dropout experiences for patients enrolled before (3/1/92) and after (6/72) an amendment allowing individual titration (Amendment II) indicate that while the conversion ratios used by the sponsor are safe and appropriate, they are conservative (result in low doses of oxycodone in some patients). The label should use this data to highlight the importance of individual titration and use of rescue medication in successful pain management using this product.

OxyContin Study 1102- A Parallel Group Trial of Placebo and Two Doses of CR Oxycodone in an Osteoarthritis Chronic Pain Model.

This was a double-blind, double-dummy, randomized, repeated dose, placebo-controlled, parallel-group study in patients with moderate to severe chronic osteoarthritis pain (baseline pain = 2.5). The majority of these patients had pain judged to be inadequately controlled with non-opioid analgesics and were managed on opioid & NSAID combinations. Patients were randomly assigned to one of three treatments: Oxycodone 10 mg tablet plus a placebo tablet or two (2) Oxycodone 10 mg tablets, or two matching placebo tablets Q12H for 14 days.

The patients were instructed to take the first dose on day one at 8 AM (+/- 1 hr). The next dose was at 8 PM. For the remaining 13 days the patient was to take a dose at 8 AM and again at 8 PM . Four (4) visits were required for each patient: the baseline visit on day zero, the brief randomization visit on the morning of day one, a one week visit and a final visit within three (3) days after completing the study or dropping out.



Pain Intensity by Study Week (Evaluable Patients)

WEEK 1	N	Mean	Std. Dev.	Std. Error
Placebo	38	2.047	.614	.100
CR Oxycodone 10	37	2.023	.519	.085
CR Oxycodone 20	34	1.595 *	.706	.121

WEEK 2	N	Mean	Std. Dev.	Std. Error
Placebo	38	2.087	.708	.115
CR Oxycodone 10	37	1.905	.764	.126
CR Oxycodone 20	34	1.614 *	.761	.131

* "p" < 0.05

Conclusion

This double-blind, parallel-group, dose-response study provides substantial evidence of the short-term analgesic efficacy of CR Oxycodone (20 mg) in patients in this chronic pain model.

Study 1201- A Cross-Over Study of IR & CR Oxycodone in a Chronic Low Back Pain Model

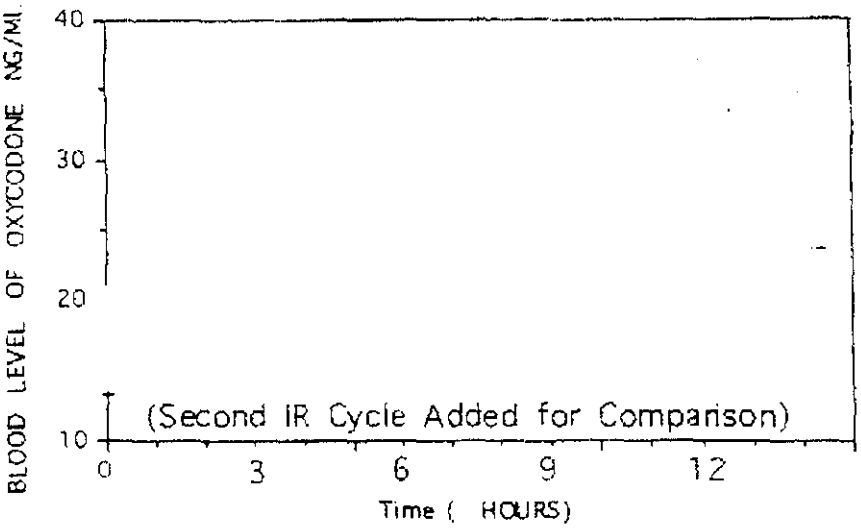
This was a multi-center, double-blind, randomized, repeated dose, two-period crossover study in patients with stable, chronic low back pain. Patients, initially, entered an open-label titration period and were randomly assigned to receive either open-label controlled-release (q12h) or immediate-release (qid) oxycodone to achieve pain control (titration). Following titration, patients were randomly re-assigned to a double-blind treatment sequence of either controlled-release oxycodone to immediate-release oxycodone (CR => IR) or the reverse (IR => CR). After completion of Period 1, patients received the alternate treatment.

One blood sample was drawn at trough at the end of titration (double-blind baseline). Blood samples were then drawn after 3-5 days on each treatment at trough, 1, 3 & five hours post dose.

PK Results

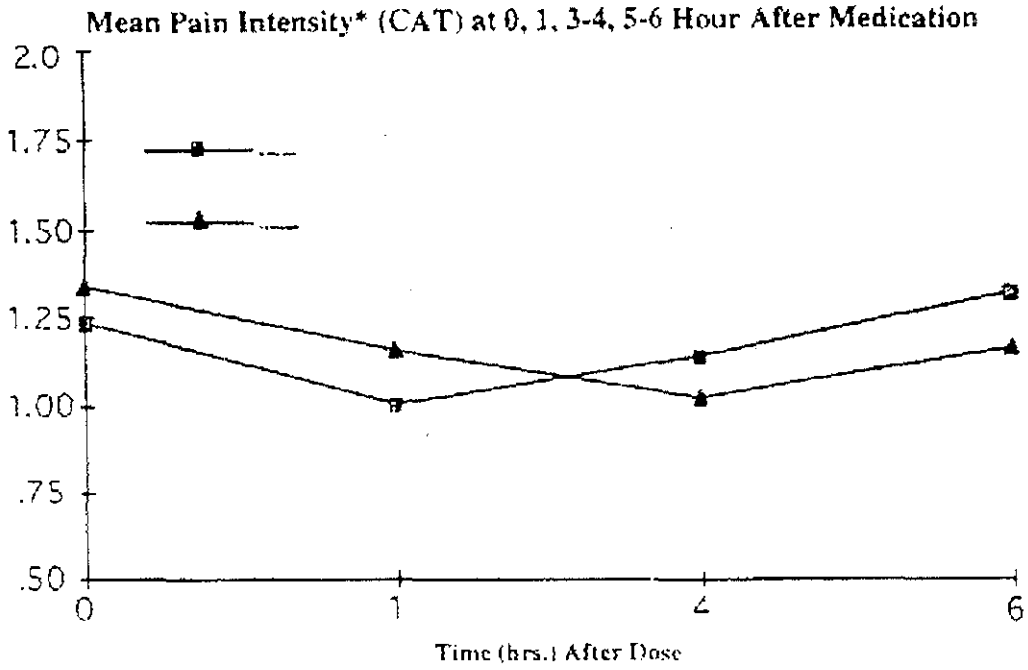
Because this was a cross-over study, each patient received the same dose of oxycodone in period 1 and period 2 . In order to facilitate cross-study comparisons, the concentration data were rescaled for each patient to a dose of 40 mg/day.

OXYCODONE AFTER ADJUSTMENT TO 40 MG/DAY



MEAN PAIN INTENSITY AND DRUG EFFECT RATINGS

	IR Oxycodone				CR Oxycodone			
Pain (CAT)	0 Hour	1 Hour	3-4Hr	5-6Hr	0 Hour	1 Hour	3-4Hr	5-6Hr
Mean								
S.D.	1.23	1.00	1.13	1.31	1.33	1.15	1.08	1.15
C.V.	.71	.51	.66	.66	.81	.75	.58	.67
	.57	.51	.58	.50	60	.65	.54	.58
Pain (VAS)								
Mean								
S.D.	29.97	21.69	26.26	29.79	35.05	29.15	25.85	29.41
C.V.	23.47	16.52	20.66	19.23	27.51	22.30	19.33	22.34
	.78	.76	.79	.64	79	.76	.75	.76
Subjective Effects								
Mean								
S.D.	9.10	15.38	15.59	11.08	14.77	12.77	17.31	13.62
C.V	15.03	17.86	20.95	16.76	21.61	14.40	19.49	19.79
	1.65	1.16	1.34	1.51	1.46	1 13	1.13	1.43



* Scale: 0=none, 1=slight, 2=moderate, 3=severe

Conclusion

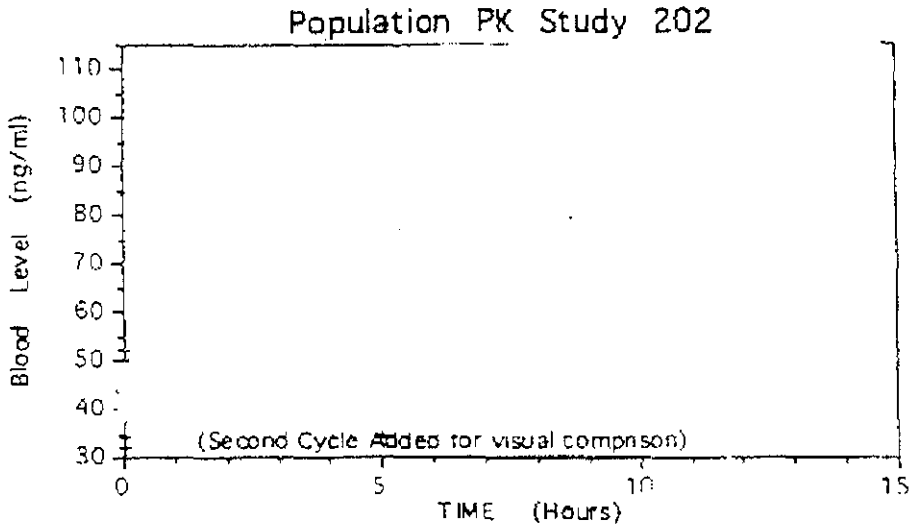
This was a small clinical trial, but a large PK/PD study. It provided strong evidence that the claimed PK peak-to-trough profile is similar to the IR in patient populations, and that the adverse effects and efficacy of the drug are not substantially changed by the switch from IR to CR.

It is notable in that it provided a head to head comparison with respect to an IR formulation. It alone does not meet the DDMAC standard for two-adequate head to head comparisons to make superiority claims, but it is supportive of expected future claims of comparability with "IR" oxycodone.

OxyContin Study 0202- A Cross-Over Study of IR and CR Oxycodone in Patients with Cancer Pain.

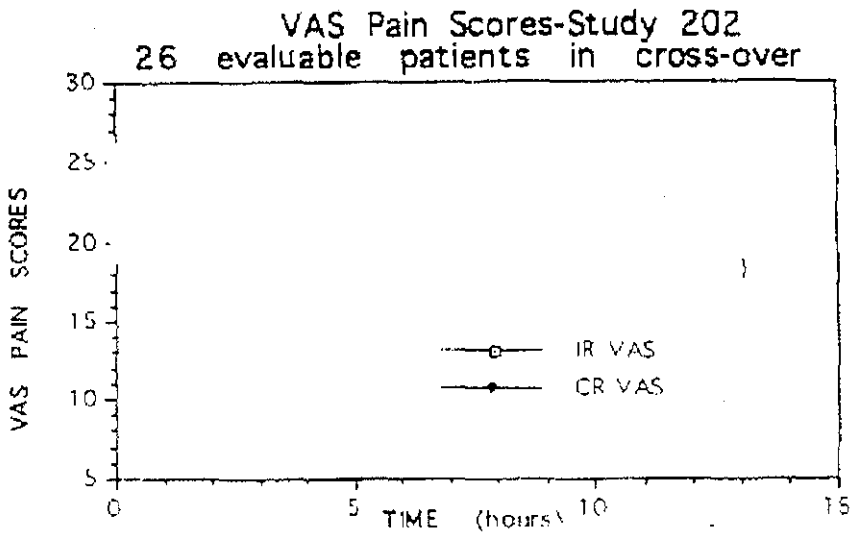
This was a multi-center, double-blind, randomized, repeated dose, two-period crossover study in patients with stable, chronic cancer pain. Patients, initially on a mixture of strong and weak opioids, were randomized to titration with either BID open-label controlled-release or immediate-release QID oxycodone to achieve pain control. Following titration to stable mild pain and low rescue use (see below), patients were randomly assigned to a double-blind treatment sequence of either controlled -release oxycodone to immediate-release oxycodone (CR =>IR) or the reverse (IR => CR).

When stable on each limb of therapy (on study Day 4 to 7 of the double-blind phases), each patient had four (4) blood samples drawn: zero hour (just prior to taking the 8:00 AM dose), at about 1 hour, 3-4 hours and 5-6 hours after dosing. At the same time the patient completed the Modified Specific Drug Effects Questionnaire (MSDEQ), a categorical (CAT) pain intensity scale (0 = none to 3 = severe) and a VAS pain intensity scale (0 mm = no pain to 100 mm = worst possible pain).



MEAN PLASMA OXYCODONE CONCENTRATIONS (unadjusted for dose)

	CR Oxycodone					IR Oxycodone				
	0 Hr	1 Hr	3-4 Hr	5-6 Hr	Mean	0 Hr	1 Hr	3-4 Hr	5-6 Hr	Mean
Mean	43.15	79.58	89.88	95.48	76.34	41.43	93.58	65.34	48.01	61.78
S.D.	39.29	68.92	76.79	93.16	65.66	54.28	107.42	60.86	41.59	59.96
CV	.91	.87	.86	.98	.86	1.31	1.15	.93	.87	.97



Conclusion

This trial provided supportive evidence that the claimed PK profile is relevant to the treatment of cancer patients, and that the efficacy of the drug is not substantially changed by the switch from IR to CR.

It is notable in that it provided a head to head comparison with respect to an IR formulation. It does not meet the DDMAC standard for two-adequate head to head comparisons to make superiority claims against a marketed product, but it is strongly supportive of claims of comparability with "IR" oxycodone

Discussion (Is BID CR therapeutically equivalent to QID IR?)

(The reader is directed to the discussion of statistical power in the individual reviews).

The most applicable divisional standard is that the applicants must demonstrate a 95% confidence interval of 80-120% of reference to the control product for PK equivalence, and a 95% confidence interval of 60-140% in a clinical pain model (70-130% for a RA model).

The population pharmacokinetic data provides a persuasive case that the new CR product produces a blood level profile in BID dosing in clinical populations that lies within the usual therapeutic range of QID immediate-release oxycodone. The clinical data is similarly substantial in that the pain relief provided by both products could not be differentiated.

The intended population of use is in chronic painful conditions, and the testing in cancer, low back pain, osteoarthritis and postoperative pain all provide a broad spread of models that show no clinical distinction beyond the different dosing interval.

There is a theoretical possibility that the slower fall and slightly higher trough might result in greater development of tolerance and/or withdrawal phenomena. This was not seen in the dataset (see ISS), and the two daily troughs appear adequate based on the divisional experience with "trough-less" opioid dosage forms such as Duragesic.

Conclusion (Efficacy)

The efficacy of Oxycontin is supported, across six clinical studies, by a consistent pattern of equivalent outcomes.

Six of six double-blind studies, two of which are placebo controlled, demonstrate the analgesic efficacy of CR Oxycodone tablets.

Efficacy was equivalent to immediate-release oxycodone in 4 clinical trials in which these two dosage forms were studied in a multiple-dose fashion and in one single-dose postoperative study.

Special Issues

Pharmacokinetic/Pharmacodynamic (PK/PD) Outcomes

A total of 242 patients in seven of the eight protocols (this includes OC91-0907A & OC91-0907B, two open label protocols swept into the ISS) agreed to have phlebotomies for determination of oxycodone plasma concentrations. Pain intensity (CAT and VAS) were recorded at each sampling time by the patient in the controlled studies, and both patient and observer responded to a Drug Effect Questionnaire (MSDEQ) at each sampling time.

Peak/Trough Plasma Oxycodone Fluctuation- Blood sampling for oxycodone was done at the approximate times of peak and trough reveals that a two-fold fluctuation is common to both equivalent daily doses of BID CR Oxycodone and QID IR Oxycodone (see individual study reports for plots).

Samples were available across a fourfold daily dose range of 20, 40, and 80 mg in four populations of subjects of differing demographics and pain syndromes. This showed a consistent and predictable peak and trough plasma oxycodone concentration.

Conversion to CR Oxycodone- In order to initiate therapy in the chronic pain setting, an initial starting dose must be selected. Any conversion ratio should provide a dosage estimate for the safe initiation of therapy. The conversion tables utilized in the clinical studies are drawn from the standard "Foley" NEJM article used by nearly all sponsor's in the last five years.

The data from study 0402 B, (Cancer patients using strong opioids) showed that the recommended conversion doses are safe and appropriate (no overdoses) but many patients need titration within the first few days to increase the dose to meet the patient's individual need. This is an essential element in any proposed labeling.

Titration with CR Oxycodone Tablets - The proposed dosing interval and lack of significant accumulation suggest that the CR drug can be used for titration directly, without the need for an IR transitional form. This is supported by the data from the studies in which titration was done with both IR and CR with equivalent results within a few days, although the data do suggest that titration to stable pain control may be faster with IR than CR (as expected).

Rescue Use (Supplemental Analgesic)- Immediate release oxycodone was used as the rescue analagesic in these studies using the usual 1/4 to 1/3 of the Q 12 hour dose (1/8 to 1/6 of the total daily dose) WHO standard. Patients used about 1-2 doses of rescue a day and found it an important part of therapy

Subgroup Analyses- Equivalent improvement in pain intensity and acceptability of therapy were seen regardless of sex, age or race for CR Oxycodone

Overall Conclusion

CR oxycodone appears to be a BID alternative to conventional QID oxycodone. Approval is recommended. Care should be taken to limit competitive promotion. This product has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing.

Curtis Wright 10/16/95

Curtis Wright
Team Medical Review Officer
PDES (HFD-007)

D. Kramer for 10-24-95

Douglas Kramer
Peer Reviewer

CC: Original NDA
HFD-007 Division File
HFD-007 C Wright
HFD-007 CSO B McNeal

MEDICAL OFFICER REVIEW (MOR)

OxyContin Study **0402B**-Cancer Pain

NDA #: 20-553
Sponsor: The Purdue Frederick Company
Type of Submission: NDA Study Report
Protocol No.: OC91-0402B
Date of Submission: December 28, 1994
Date Received: January 30, 1995
Date of Review: January 31, 1995
Date Finalized: May 10, 1995
Working Time: 30 hours
Calendar Time: 5 months
Reviewer: Curtis Wright, M.D.

Title

Controlled-Release Oxycodone Tablets (q12h) v. Immediate-Release Oxycodone Tablets (qid): Comparative Efficacy, Safety and Acceptability in Patients Previously on Strong Opioid Analgesics for Cancer Pain

Summary

Study of Controlled-Release Oxycodone (CR) administered on a q12h dosing regimen compared to IR oxycodone. The protocol was amended to add titration prior to randomization. The amendment showed that oxycodone should be titrated to each individual patient's needs to be most acceptable. A small amount of PK/PD data from this study was consistent with results from study 0402A.

This study used CR Oxycodone Tablets from two 137 kilo batches (Lots CB21-12 & W7) See PK review for equivalency data.

Material Reviewed-Primary Data (CANDA).

Background

Oxycodone hydrochloride is an opioid analgesic similar to morphine. Purdue Frederick has developed oxycodone hydrochloride in a controlled-release single ingredient tablet. This is a Phase III repeated-dose trial in cancer patients previously stabilized on opioids for chronic cancer-related pain. It was an active-control efficacy study against marketed IR Oxycodone (the sponsor purchased Roxicodone) with a nested safety study looking at conversion doses, titration and safety

Protocol

Design

This was a five-day, double-blind, 17-center, randomized, repeated-dose, parallel group study of IR oxycodone against CR oxycodone in 156 outpatient cancer patients previously using strong opioid analgesics. The equivalent total daily oxycodone dose was calculated from the patient's current daily dose of opioids. In order to maintain the blind, all medication appeared identical (encapsulated: 00 capsules tested for adequate dissolution).

Study Modifications

There were two (2) amendments to the study.

Amendment I allowed the inclusion of patients who underwent radiation therapy. In addition, fixed-dose concomitant non-opioid analgesic medications were permitted during the study as long as the medication was given on a regular schedule.

Amendment II allowed:

a) blood samples to be drawn to measure plasma oxycodone concentrations and compare them to pain intensity and drug effect parameters

b) patients receiving 10 or more tablets per day of a fixed-combination opioid analgesics to enter the study

c) immediate release oxycodone tablets (5 mg) as a rescue analgesic (PK effect).

d) an open-label titration phase (up to 10 days) prior to randomization to treatment to lower the rate of dropouts.

Procedures

Following screening, eligible patients were randomly assigned to each treatment. Patients were instructed to discontinue, for at least 4 hours prior to entry, all non-opioid analgesics given on a PRN basis. For each enrolled patient, the study lasted a maximum of five (5) days. The study began at the first 8:00 PM dosing (Day 0) and ended after the 8:00 PM evaluation (last dose of medication given at 2:00 PM) on Day 5.

Patients were asked to assess their **pain intensity** four (4) times each day (morning, mid-day, evening and bedtime) on a four-point categorical scale (0 = none, 1 = slight, 2 = moderate, 3 = severe).

The patients were asked twice daily to assess their **acceptability of therapy** considering pain intensity and side effects over the previous 12 hour period (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). The first evaluation was taken in the morning, immediately prior to the 8 AM study dose. The evening evaluation was taken immediately prior to the 8 PM study dose

Adverse experiences were spontaneously reported by the patient or observed by the investigator and documented.

Statistical Methods

Primary Efficacy Variables

The following summary measures of efficacy were calculated

- Mean Pain Intensity by Day is the average of the four (4) ratings (morning, mid-day, evening, bedtime) for each study day
- Mean Acceptability by Day is the average of the AM and PM rating for each study day.

Pharmacokinetic/Pharmacodynamic (PK/PD) Variables

Patients who agreed to the phlebotomies had three bloods drawn at 0 hour(just prior to taking the 8:00 AM dose), at 1 hour (+/- 15 min.) and 3-4 hours (+/- 15 min.) after dosing on study day 3, 4, or 5 (these corresponded to the peak blood levels of IR & CR seen in the PK studies). Patient responses to pain intensity (CAT and VAS) and the items of the Modified Specific Drug Effect Questionnaire (MSDEQ) were obtained at each sampling time.

Analysis

Mean pain intensity and acceptability by day and overall were analyzed using repeated measures analysis of variance (for all five study days) with "day" and "treatment " as main effects in the model by the sponsor. They were checked by the reviewer from the primary data, using both cross-sectional (no extrapolation) data for the ITT population and with a LOCF extrapolation for the same population by the reviewer (which is not shown unless different from the cross-sectional data)

Patient Disposition

Of the 180 patients enrolled, 164 were randomized and entered the double-blind phase of the study. Of these 164, 12 violated protocol and 156 were evaluable (see "ITT" below).

Eighty-eight of all the 164 patients randomized completed the 5 day study. Seventy-six discontinued: 40 due to ineffective treatment *(34 pre-amendment II; 6 post-amendment II)*, 16 for adverse experiences, 12 for protocol violations, 3 for unrelated illness, and 5 for miscellaneous reasons. One hundred fifty-six patients were evaluable for intent-to-treat. There were no significant differences between the treatments for sex, height, weight, race, body frame, baseline concomitant therapy, primary oncological type, and predominant pain site.

Note on Amendment II (Titration)

A total of 72 patients were enrolled under Amendment II. Fifty-six patients (27 IR Oxycodone; 29 CR Oxycodone) entered the double-blind period. Forty-nine patients entered the optional titration phase, 16 of whom discontinued prior to randomization.

Patient Disposition

	Titration (only)	IR Product		CR Product		Total	
Patient Completion	N (%)	N	(%)	N	(%)	N	(%)
Enrolled	16 (8.9)	83	(50.6)	81	(45.0)	164	(100)
Intent-To-Treat		79	(95.2)	77	(95.1)	156	(95.1)
Completed		43	(51.8)	45	(55.6)	88	(53.7)
Discontinued	16	40	(48.2)	36	(44.4)	76	(46.3)
Ineffective RX	6	22	(26.5)	18	(22.2)	40	(24.4)
Adverse Experience	2	10	(12.0)	6	(7.4)	16	(9.8)
Protocol Violation	0	5	(6.0)	7	(8.6)	12	(7.3)
Protocol Violation	0	5	(6.0)	7	(8.6)	12	(7.3)
Illness-unrelated	4	1	(1.2)	2	(2.5)	3	(1.8)
Withdrew Consent	1	2	(2.4)	1	(1.2)	3	(1.8)
Other	2	0	(0.0)	2	(2.5)	2	(1.2)
Death	2	0	(0.0)	0	(0.0)	0	(0.0)

Patient Demographics for the Double-Blind Period

	IR Oxycodone		CR Oxycodone	
Characteristics	Mean	Std. Error	Mean	Std. Error
Age (yrs)	58.01	1.52	60.42	1.34
Height (cm)	166.86	1.28	168.38	1.33
Weight (kg)	66.53	1.58	68.71	1.86
Sex				
Male n (%)	48	(57.83)	47	(58.02)
Female n (%)	35	(42.17)	34	(41.98)

Study Conduct Issues

When in the course of the study it became clear that there was a high discontinuation rate, a blinded interim analysis was performed (as specified in the protocol) limited to discontinuation rates, and the protocol was subsequently modified, as it was clear that adequate analgesia required individual titration of dose. (No interim analysis of efficacy variables was performed)

In order to evaluate the treatment-by-center interaction, centers with less than 2 evaluable patients per treatment were pooled (resulting in two pseudo-centers). Patient data from one investigator were excluded from efficacy analyses due to evidence of medication unblinding at the site at the time of a medication error.

There were 81 patients enrolled in the study under the original protocol, 27 under Amendment I, and 72 under Amendment II. Due to the substantial protocol changes resulting from Amendment II, those patients should be viewed as a separate sub-group. This is because in the CR Oxycodone group the discontinuation rate for ineffective treatment (during the double-blind period) dropped ten-fold from 32.7% pre-Amendment II to 3.5% post-Amendment II

One investigator (#1196) enrolled one patient twice under patient numbers
As #4910 the patient discontinued due to an intercurrent illness prior to double-blind randomization. At another site (#1180) investigational IR Oxycodone tablets were incorrectly dispensed to patients not in the titration phase of the study (post-Amendment II). These patients were counted as having been enrolled in the titration phase of study in order to account for the investigational medication.

The Effect of Individualization of Dosage

A secondary goal of this study was to examine the conversion of patients from a variety of analgesics to fixed doses of either CR or IR oxycodone. The patients came in on the following therapies:

Drug Product	Patients in CR Group (N)	Patients in IR Group (N)	All Patients (N)
Oral Morphine	35	41	76
Parenteral Morphine	5	2	7
Oral Hydromorphone	7	10	17
Oral Oxycodone	7	6	13
Duragesic	1	0	1
Oxycodone/APAP	10	7	17
Hydrocodone/APAP	2	1	3
Codeine/APAP	2	2	4
Mixtures of Opioids	7	10	17

Prior to amendment II, the patients were evaluated, and their daily dose of oxycodone was calculated based on the NEJM article in 1985 by Dr. Foley on interconverson of opioids in cancer analgesia.

Prior Opioid	Conversion Factor
Parenteral Morphine	3
Parenteral Hydromorphone	20
Parenteral Meperidine	0.4
Parenteral Levorphanol	15
Parenteral Oxycodone	2
Parenteral Methadone	3

Prior Opioid	Conversion Factor
Oral Morphine	0.5
Oral Hydromorphone	4
Oral Meperidine	0.1
Oral Levorphanol	7.5
Oral Oxycodone	1
Oral Methadone	1.5

The conversion factor was used to calculate the dose of oxycodone. First the physician totaled the daily dose of the patient's previous medication, then multiplied the previous opioid dose by the conversion factor to get the patient's new 24 hour oxycodone dose This was then divided into 4 doses (q 6 hr) for IR oxycodone or 2 doses (q 12 hr) for CR oxycodone.

Pre-Amendment II

108 patients were enrolled to the original protocol and amendment I, and 72 enrolled under amendment II. Of the 108 patients enrolled prior to amendment II, all had their dose of oxycodone fixed at the time of trial entry using the method described above, and had no access to rescue medication. Of the 108 patients in this category, 34 dropped out due to ineffective treatment. Under Amendment I all could receive concurrent fixed dose NSAIDS.

Post-Amendment II

Of the 72 patients who were enrolled after amendment II, all could have their dose increased prior to randomization, and all could have rescue medication. Of the 72, 49 had their initial dose increased prior to randomization, while 23 entered the study at the initial dose.

Of the 49 who increased their dose (titrated) prior to randomization, 6 dropped out due to ineffective treatment and 10 dropped out for other reasons. Of the 33 who entered the double blind period, 1 patient dropped out for ineffective treatment during the double blind period.

Of the 23 who entered the double blind period without titration, 5 dropped out for ineffective treatment.

Titration was performed with open-label IR oxycodone in this study.

Intent to Treat Population (ITT)

There were 180 patients enrolled in the study, of which 16 dropped out in the titration phase (as described above) and were never randomized. Of the 164 left, eight (8) patients were unevaluable. Of these, three never reached a stable level of pain control prior to randomization, three took unapproved medications or changed the dose of concurrent meds and two failed to complete the rating form properly ("at all"). They were:

1196-4019:	NOT ON RX	Not Stabilized prior to Randomization
312-17040:	NOT ON RX	Not Stabilized prior to Randomization
1180-15009:	NOT ON RX	Not Stabilized prior to Randomization
355-5040:	CR	Changed concomitant analgesic during study
1180-15008:	CR	Changed concomitant analgesic during study
355-5038:	IR	Changed concomitant analgesic during study
711-3006:	IR	Failed to complete form
345-11002:	IR	Failed to complete form

As noted above, the ITT population of 156 patients was evaluated both in a cross-sectional (all patients present @ the assesment time) and in an LOCF extrapolation.

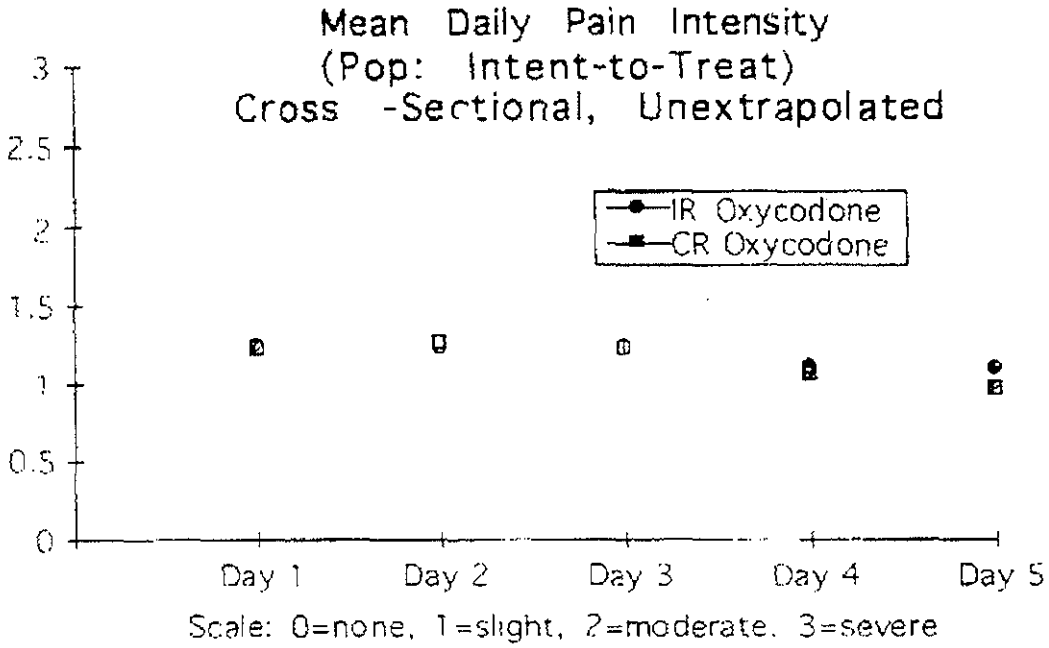
Doses used during the Double-Blind Period

Approximately 75% of the patients in the double-blind study had total daily doses of less than or equal to 120 mg oxycodone. The total daily dose of oxycodone during the study was 114-116mg for CR Oxycodone compared to 126-127 mg for IR Oxycodone (CR doses were slightly lower than IR, $p > 0.05$) due to a differential rate of dropouts for CR patients (44%) than IR patients (48%). The expected effect is to bias the study slightly in favor of IR oxycodone.

Parallel-Group Efficacy Results

There were no significant differences between the treatments with respect to overall discontinuation, discontinuation for ineffective treatment, or rescue use. (There were marked differences due to amendments as described above).

There were no significant differences between the treatments with respect to pain intensity at baseline, although the "previous day" baseline pain intensity tended to be slightly greater for the IR group while the "right now" baseline pain intensity was slightly higher for the CR group. There were no significant differences between the treatments on any of the five study days or over the entire period. There was the usual overall reduction in pain for both groups due to selective discontinuation of patients with poor pain control.



Mean Pain Intensity by Study Day

Population: Intent-to-Treat

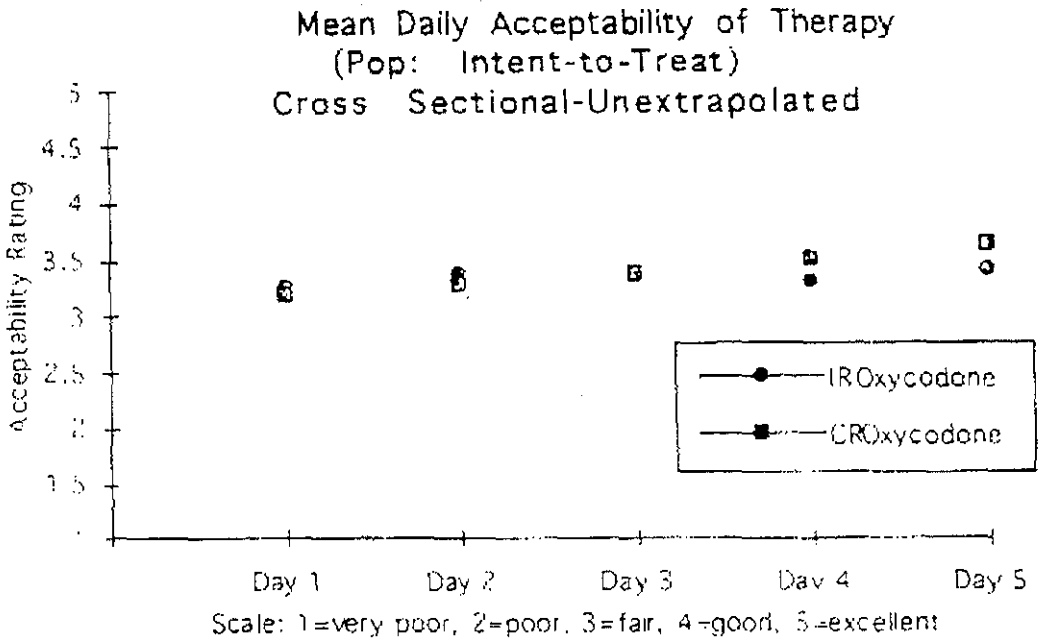
			Cross-Sectional		ITT Extrapolated	
Study Period	Treatment	N	Mean	SE	Mean	SE
Day 1	IR Oxycodone	79	1.248	0.085	1.28	0.086
	CR Oxycodone	77	1.225	0.090	1.22	0.085
Day2	IR Oxycodone	68	1.232	0.087	1.31	0.091
	CR Oxycodone	66	1.264	0.102	1.30	0.092
Day3	IR Oxycodone	62	1.247	0.099	1.34	0.091
	CR Oxycodone	58	1.236	0.105	1.35	0.092
Day4	IR Oxycodone	53	1.116	0.106	1.33	0.093
	CR Oxycodone	49	1.070	0.110	1.31	0.094
Day5	IR Oxycodone	47	1.105	0.128	1.34	0.095
	CR Oxycodone	48	0.981	0.110	1.30	0.096

Overall Pain Intensity

Population: Intent-to-Treat

			Cross-Sectional		ITT Extrapolated	
	Treatment	N	Mean	Std. Error	Mean	Std. Error
Overall	IR Oxycodone	79	1.320	0.082	1.32	.086
	CR Oxycodone	77	1.283	0.087	1.30	.086

Both treatment groups rated acceptability of therapy as fair-to-good at baseline (current) and throughout the study. There were no significant treatment differences for mean daily, AM, PM or overall acceptability of therapy.



Scale: 1=very poor, 2=poor, 3=fair, 4=good, 5=excellent

The CR Oxycodone group consistently required less than one dose of rescue per day over the study period, while the IR Oxycodone group required slightly more than one dose. Approximately (36/77) 46.8% of the CR Oxycodone group and (41/79) 76% of the IR Oxycodone group took at least one rescue.

Power Calculation

This study requires the same power analysis performed in study 402A, using a power calculation based upon the difference of the treatment and reference means. Given the agency tradition of accepting "QI'L" of greater than 60 (the lower end of the confidence interval for the efficacy of the new drug is at least 60% of control) it is reasonable to accept the sponsor's "a-priori" convention that a new formulation would have to have a two-sided 95% confidence interval within 60-140% of the standard to be equivalent.

Now assuming that the patients had a "pseudobaseline" pain score of moderate to severe pain (2-3 points or roughly 2.5), the observed mean pain scores on treatment of 1.3 would mean a range of possible values of roughly 1-1.5 points between ineffective treatment and effective treatment (pain intensity difference). If one treatment was 40% less effective than the other this would be a difference in the means of about 0.4-0.6 points. The observed standard deviation in the studies was about twice this (0.7-0.8), so the effect size (mean1-mean2)/SD we are looking for is about 0.5 SD.

For a more detailed analysis see the statistical review, but a 160 patient study using a two-sided "t" test with a postulated alpha of 0.05 & an expected effect size of 0.50 would have a > 95% power with a single outcome measure, more with the repeated measures taken here (although how much more I am loath to speculate).

PK/PD

Twenty patients (8 IR Oxycodone; 12 CR Oxycodone) underwent PK/PD phlebotomy. The mean plasma concentrations and pain intensity ratings are presented below. Since only a subset of patients had blood drawn, the average total daily dose for the CR Oxycodone group was 103 mg and 130 mg for the IR Oxycodone PK groups.

	CR OXYCODONE			IR OXYCODONE		
PLASMA OXYCODONE CONCENTRATION	0 HOUR	1 HOUR	3-4 HOUR	0 HOUR	1 HOUR	3-4 HOUR
N	10	12	11	7	7	7
Mean	45.7	52.7	75.7	30.4	65.5	79.0
Std. Dev.	23.0	32.6	36.6	22.3	47.7	72.8
Min						
Max.						
Coeff. of Var.						
PAIN INTENSITY (CAT.)						
N	11	12	12	8	8	7
Mean	1.4	1.0	0.9	1.3	0.8	0.7
Std. Error	0.3	0.2	0.2	0.4	0.3	0.3
PAIN INTENSITY (VAS)						
N	11	12	12	8	8	7
Mean	36.3	26.7	19.4	35.0	15.4	17.7
Std. Error	9.8	9.5	7.3	11.3	5.9	7.3

Safety Results

There were no significant differences between the treatments with respect to discontinuation due to an adverse experience (ADE) (n=6, CR; n=10, IR) . There were a total of 295 reports of adverse experiences at least possibly related to study medication by 104 patients. The IR Oxycodone group reported 186 ADEs by 55 patients and the CR Oxycodone group reported 109 ADEs by 49 patients. The greater number of reports with IR Oxycodone were primarily due to reports of nausea, vomiting, and dizziness. The ADEs with patient incidence > 10% (across the treatments) were somnolence, nausea, constipation, vomiting and dizziness

There were no deaths during the double-blind portion of the study. Two deaths occurred during the titration phase. One was an 81 year old female (#1180-15914) with lung cancer, rapidly progressing disease and pulmonary metastases. The second patient was a 76 year old male with lymphoma. With signs of impending death he was given IR Oxycodone for breakthrough pain and received several doses per rectum.

Of the 16 patients who discontinued due to ADEs, noteworthy were signs of withdrawal in one patient who was inadvertently underdosed and signs of hallucination and irritability in one patient who was inadvertently overdosed (pharmacy errors).

Conclusion

This trial provides substantial evidence that CR Oxycodone (q12h) and IR Oxycodone (qid) provided equivalent pain control in patients with cancer pain receiving opioid analgesics. The dropout experiences for patients enrolled before and after Amendment II indicate that while the conversion ratios used by the sponsor are safe and appropriate as general instructions, they are conservative (result in low doses of oxycodone in many patients). The label should use these data, highlight the importance of individual titration, and advocate the use of rescue medication in successful pain management using this product.

The trial appears to meet the DDMAC standard for a well-controlled trial comparing the CR product to the new product. No superiority for CR was shown, but the CR BID appeared to provide equivalent analgesia to QID IR.

cc: Original NDA
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