CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-610

21-611

PHARMACOLOGY REVIEW

2nd Cycle

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-610 and 21-611
SERIAL NUMBER:	Original NDA submissions
DATE RECEIVED BY CENTER:	12/19/2002 and 12/22/2005
DRUG NAMES:	**OPANA™ ER (Oxymorphone Hydrochloride) Extended-Release Tablets (21-610)** **OPANA™ (Oxymorphone Hydrochloride) Tablets (21-611)**
INDICATIONS:	OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. OPANA is indicated for the relief of moderate to severe pain where the use of an opioid is appropriate.
SPONSOR:	**ENDO Pharmaceuticals, Inc.**
DOCUMENTS REVIEWED:	Electronic Submissions
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Mamata De, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham-Cruz, M.S.**

Date of review submission to Division File System (DFS): June 16, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. **Recommendation on approvability:** From the nonclinical pharmacology and toxicology perspective, NDA 21-610 and 21-611 may be approved.

B. **Recommendation for nonclinical studies:** None

Recommendations on labeling: The non-clinical sections of the labeling for both products should read as follows (blue text should be added to label and red struck-through text removed):

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-_____

[redacted]

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

In support of the NDA's for Oxymorphone ER and IR, the sponsor initially (Dec 12, 2002) submitted acute toxicology studies in the mouse and rat, 2-week and 13-week repeat-dose toxicology studies in the rat, mouse and dog models, and the full battery of genetic and reproductive toxicology studies.

There were three nonclinical pharmacology toxicology deficiencies described in the approvable letters sent to the sponsor after the first cycle. The letter noted the following (numbers correlate with the letter):

2. Assessments of the mechanism of oxymorphone-induced positive findings in the *in vivo* micronucleus assay and their relevance to patients. Although you have hypothesized that oxymorphone produces this result in a manner similar to that reported for morphine, this hypothesis has not been tested for oxymorphone. The Division is willing to review proposed study protocols.

   Reviewer Assessment: The Sponsor has provided adequate data suggesting that the increase in the incidence of micronuclei formation is indirectly related to activation of opioid receptors.

3. Adequate qualification of the impurities [redacted] via a minimal genetic toxicology screen (one *in vitro* gene mutation and one *in vitro* chromosomal aberration assay) or reduction of the specifications for each of these impurities to NMT [redacted] In addition, provide a repeat-dose toxicology study of at least 14-days duration for each compound in a single species.

   Reviewer Assessment: The sponsor elected to reduce the levels for these [redacted] impurities to below ICH qualification thresholds. The response is acceptable.

4. Control of the impurities [redacted] (structural alerts for mutagenicity) which are identified as impurities to levels well below (e.g., [redacted].) the current drug substance specification of NMT [redacted] is necessary. Coordinate with the DMF holder, [redacted], to submit a tightened specification acceptable to the agency, or provide adequate qualification of the impurities. For [redacted] this qualification should include a minimal genetic toxicology screen (one *in vitro* mutagenicity assay and one *in vitro* chromosome aberrations assay) testing each compound at the limit dose for the assay. Should a genetic toxicology assay yield a positive result, the specification for the impurity should be lowered to NMT [redacted] or the impurity should be adequately qualified via a carcinogenicity assessment in a single species. For [redacted], given the positive result in the *in vitro* chromosome aberrations assay, the specification for the impurity should be lowered to NMT [redacted] or the impurity should be adequately qualified via a carcinogenicity assessment in a single species.

> *Reviewer Assessment: The sponsor provided a minimum in vitro genetic toxicology screen for* [redacted]. *The* [redacted] *was negative in both genetic toxicology studies and therefore is considered qualified. Both the* [redacted] *were positive in the in vitro chromosome aberrations assay. The Division has an agreement in place with* [redacted] *(DMF holder) that for the reduction of the levels of these impurities over time. The response is acceptable.*

The Sponsor also submitted the carcinogenicity studies with the submission. These were previously agreed to be completed as a Phase 4 commitment.

The results of the 13-week repeat-dose toxicology studies demonstrate that oxymorphone produces a toxicity profile consistent with those of a potent opioid. The potential target organ of toxicity is primarily the CNS. In all species, excessively high doses of oxymorphone, like all full opioid agonists, can produce respiratory depression and death. In rats, the CNS effects include excessive chewing of cage and limbs/tail, hyperactivity, vocalization upon handling and hyperactive to touch. In mice, the CNS effects include the classical Straub tail, hypo- or hyperactivity, unkempt appearance, abnormal stance, muscle rigidity and even tremors. In the dog, oxymorphone produces excessive salivation, injected sclera of the eyes and decreased defecation. Dogs also displayed prostration, slow visual tracking, menace reactions, and impaired motor coordination at higher doses. In all species, oxymorphone produced a decrease in body weight and/or body weight gain which correlated with a decrease in food consumption.

In the 13-week repeat-dose rat study, oxymorphone produced mild regenerative anemia which was not associated with any corroborating histological changes. This reduction in red blood cells (maximum of 9%) was not noted in either the mouse or dog studies. The basis for the hematological findings in the rat are not known, however, as they were

minimal in nature and did not occur in either the dog or the mouse do not appear to be of toxicological concern. In males, absolute and relative liver weights were reduced; however, there were no corroborating histological changes indicative of toxicity. Likewise, in males, relative adrenal weights were increased at all doses. This is likely do to opioid-induced increases in corticosterone. There were no histological changes in the adrenal gland. Neither tissue was altered in the female rats. However, oxymorphone treatment was associated with decreased uterus weights and increased ovary weights. These changes are likely due to opioid-induced alterations in the estrus cycle.

In the 13-week dog study, ECG data was obtained at week 12 of dosing, 2 hours after drug administration. All electrocardiograms were within normal limits. Microscopic histology detected biliary hyperplasia in 2 of 8 high dose animals (one male and one female). The bile ducts were normal in appearance and were not evident in any of the recovery animals, suggesting that this was an adaptive change.

Oxymorphone hydrochloride was negative for the *in vitro* bacterial reverse mutation assay (Ames test) and the *in vitro* chromosome aberrations assay, both with and without metabolic activation. However, positive results were obtained for both the rat and the mouse *in vivo* micronucleus assay. Kinetochore analysis in the mouse indicated that the micronuclei formed following oxymorphone treatment did not contain centromeres, indicating that oxymorphone is not aneugenic. In their complete response to the original approvable action, the sponsor provided mechanistic studies that provide additional characterization of the positive findings in *in vivo* micronucleus assay. In these studies, oxymorphone was confirmed to induce increase in MNPCs. The data from the similar experiments showed that pretreatment with the antipyretic compound sodium salicylate did not increase the MNPCs in rats unlike that of the oxymorphone treatment alone. Other antipyretic compounds like naproxen and acetaminophen pretreatment did not block oxymorphone induced hyperthermia and therefore, were not tested for their potential ability to block oxymorphone-induced micronucleus formation. Since the sodium salicylate pretreatment did block the MPCE formation in rats, the concerned for the positive genotoxic finding is minimized.

Additional genetic toxicology studies have been conducted on — identified impurities in the drug substance that contain a structural alert for mutagenicity —

these impurities tested negative in the *in vitro* bacterial reverse mutation assay either with or without metabolic activation. In contrast, —

— tested positive in the *in vitro* chromosome aberrations assay, and therefore these —impurities should be considered as clastogens.

Reproductive toxicology studies were completed in support of the oxymorphone hydrochloride IR and ER NDAs and reviewed in the original NDA submission. The standard battery was completed. In the segment I study in rats (fertility and early embryonic development), oxymorphone was administered to male rats for 28 days prior to mating and continued throughout mating until one day prior to euthanasia. Female rats were treated for a total of 14 days prior to mating, throughout mating and through

gestation day 7. The results indicated that reproductive performance in males and females was not altered by oxymorphone treatment under the conditions tested. However, mean estrus cycle length was slightly but significantly increased in the 25 mg/kg/day group. In addition, early embryonic development was significantly altered by oxymorphone treatment. Specifically, the mean number of viable embryos and the mean number of implantation sites were reduced by 14% in the 10 and 25 mg/kg/day group. The mean number of corpora lutea was significantly reduced only in the high dose group (25 mg/kg/day). Overall, due to parental systemic toxicity, the NOAEL for parental toxicity was < 5 mg/kg/day. The NOAEL for reproductive performance in males was > 25 mg/kg/day. The NOAEL for reproductive performance in females was 5 mg/kg/day due to an increase in estrus cycle length.

Segment II (embryo fetal development) studies were completed in both the rat and the rabbit models. Female rats were treated with oxymorphone (5, 10 and 25 mg/kg/day) from gestation day 6-17 in the definitive segment II study. Clinical signs were evident in all treatment groups and were consistent with a high dose opioid and included CNS behavior such as Straub tail, rocking and lurching, hypoactivity, and exophthalmos. There was a dose-related and time-related decrease in body weight and food consumption in all dose groups. A NOAEL for maternal toxicity was not established and should be considered to be < 5 mg/kg/day. There was a slight but significant decrease in the mean fetal weights in the mid-dose and high-dose animals (5-6%) compared to control animals. There were no significant malformations (external, soft tissue or skeletal) between treatment groups, indicating that oxymorphone was not teratogenic under the conditions tested. There was a slight increase in the incidence of fetuses with variations (fetuses with unossified pubis, accessory skull bone(s), 27 presacral vertebra and bent ribs; however, these changes were not statistically significant and/or were within the historical control range. Overall the results suggest that the NOAEL for maternal toxicity was < 5 mg/kg based on findings consistent with exaggerated pharmacology associated with the opioid class of compounds. Developmental toxicity was noted at both the mid-dose and the high-dose groups based upon decreased mean fetal body weights. Therefore the NOAEL for developmental toxicity was 5 mg/kg/day (in agreement with the sponsor).

In the definitive segment II (embryo fetal development) study in the rabbit, female rabbits were treated with oxymorphone from gestation day 7 through gestation day 20. Clinical signs such as hypoactivity and decreased defecation were noted in all treatment groups in a dose-related manner. The mid-dose and high-dose group also demonstrated a few incidences of lacrimation, excessive chewing, exophthalmos and mydriasis. Maternal body weights were decreased in a dose-related manner at all doses tested during the first 3 days of treatment. Body weights of dams treated with 25 or 50 mg/kg/day remained reduced throughout the treatment period, while animals in the low dose group did not demonstrate an overall body weight gain during the treatment period. Food consumption followed a similar pattern. There was a significant decrease in the mean fetal weight of male pups (↓16%) born to the high-dose dams, but this decrease was not noted in the females (↓7%) of the combined fetuses (↓10%). There were no clear increases in the incidence of fetal malformations or variations. Some offspring malformations were noted (mandibular micrognathia, aglossia, lobular agenesis of the lung, sternebra fused or

forked rib), however, these were either not statistically significant or were within the range of historical controls. The NOAEL for maternal toxicity was < 10 mg/kg based upon the increased incidence of hypoactivity, decreased defecation, and body weight and food consumption. Based upon the presence of maternal toxicity, the study is considered to be valid. The NOAEL for fetal development was 25 mg/kg/day based upon a decrease in fetal body weights in males at the high dose (in agreement with the sponsor).

In a segment III study in rats, female rats (F_0) were treated with oxymorphone (0, 1, 5, 10 or 25 mg/kg/day) from gestation day 6 to lactation day 20. The results indicated that there were a significantly greater number of gravid females in the high dose group with total litter loss (13/25). Animals that died prior to scheduled necropsy exhibited typical clinical signs produced by high doses of opioids. Clinical signs in surviving F_0 females were noted 1 hour post-dose in all treatment groups, including Straub tail and exophthalmos. Animals in the 5, 10 and 25 mg/kg/day group demonstrated hyperactivity as well as abnormal posture. Higher doses produced whole body tetany, hypoactivity, rales, piloerection and salivation. Mean body weight losses in the F_0 females was significantly reduced early during treatment with the higher doses, however, as the treatment time progressed, a significant reduction in mean body weights were noted in all treatment groups. These effects were noted both during gestation and lactation. In surviving F_0 females, there were not differences between the number of pups born and the number of implantation sites between groups. Mean litter size in the F_1 generation born to the high dose F_0 females was 18% lower than controls (this reduction was not statistically significant, but is likely related to the drug treatment. Post-natal survival of the F_1 pus was reduced in the 25 mg/kg/day treatment group. Offspring mean body weights during the pre-weaning period were significantly reduced in the 25 mg/kg/day treatment groups compared to controls, whereas pups in the low dose group 1 mg/kg/day demonstrated a significantly higher mean offspring weight compared to controls. There were no treatment-related findings on PND 21 pups not selected for further study at necropsy. Developmental landmarks in the F_1 males indicated that balanopreputial separation in males from the 25 mg/kg/day group was delayed compared to controls, whereas males in the 1 mg/k/day group reached balanopreputial separation earlier than controls. There were no differences in the mean day of acquisition of vaginal patency in F_1 females between treatment groups. There were no treatment-related effects of oxymorphone in behavioral evaluation (acoustic startle, locomotor and Biel Maze Swimming Trials). Reproductive performance in the F_1 generation was not altered by F_0 generation oxymorphone treatment at any dose level tested. Body weights in the F_1 generation during the post-weaning period were significantly reduced in the 25 mg/kg/day groups on PND28, 35, 42, 49, 56, 62 and 70. Mean body weights were reduced in the 10 mg/kg/day groups on PND 49, 56, 63 and 70. Mean body weights in males in the 5 mg/kg/day group were also significantly reduced compared to controls on PND 63. There were no findings in the F_2 fetuses which could be attributed to F_0 maternal treatment with oxymorphone.

The carcinogenicity assessment of oxymorphone in rat (1, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) and mice (10, 25, 75, and 150 mg/kg/day) for 2 years is considered adequate. The executive carcinogenicity assessment committee

concurred with the sponsor's conclusions that the study was negative for drug-related neoplasms.

Non-tumor related toxicities were noted in both the rat and the mouse carcinogenicity studies. Although most of the doses tested appear to exceed the maximum tolerated dose for this duration of treatment, several findings should be noted due to the limited nonclinical data for any opioid for this duration. In the 2-year carcinogenicity study in rats nonneoplastic findings include increase in eye lesions and increase in the incidence of ulceration and scabs formation in skin. Ophthalmologic as well as histopathological observation showed increase in eye lesion which include corneal inflammation and retinal degeneration in all doses in females and mid and high dose in males, the incident is considered treatment related. Peer review of the ophthalmoscopic observations indicated that the findings might be related to the drug induced inhibition of the blink response. Reduce lubrication in the cornea and dryness of eye might be the likely cause for the inflammation noted. Excessive exposure of the retina in light due to the decreased palpebral closure might have been the reason for the retinal degeneration. Pupil dilation or mydriasis is widely reported in literature following morphine administration which might add into the retinal degeneration. Histopathological findings in skin showed dose related increase in the incidence of ulceration and scabs which may have resulted from self mutilation and excessive licking as observed in the clinical signs; the finding is considered treatment related. An increase in the incidence of pulmonary histiocytosis was observed in males and females given ≥5 mg/kg/day (mid and high dose males and low, mid and high dose females) compared with the control group. This was accompanied with an increase in the incidence of pulmonary granulomas and/or subacute inflammation which was often associated with the presence of foreign material (bedding) in the bronchi, bronchioles and/or alveoli. These changes were graded minimal to severe. The increase in the airway inflammatory lesions, and the associated plant material, was most likely the result of decrease in swallowing efficiency and/or suppression of the cough reflex coupled with inhalation of bedding material. Decreased respiratory function is a well characterized opioid effect and is monitorable.

In the mice carcinogenicity study, the clinical signs of self-mutilation of the skin, excessive grooming, and skin lesions were noted at all doses. Findings of the gross pathological observation include dilation of the pelvis, ureters, and urinary bladder wall in male mice receiving 75 or 150 mg/kg/day of oxymorphone HCl at an incidence that was greater than either controls or lower dose groups. Protrusion of the penis, commonly associated with obstructive uropathy, was also increased in males at these doses (75 and 150 mg/kg/day). Similar changes in the urinary bladder and pelvis were noted in females at the high dose. In male animals, some marginal increase was noted in transitional cell hyperplasia of the urinary bladder. In female animals an increase was noted in subepithelial edema and/or connective tissue thickening. The findings are treatment related and may be related to opioid-induced urinary retention in animals.

B. Pharmacologic activity:

Pharmacology:

Oxymorphone hydrochloride produces many of the same pharmacological effects as morphine. Oxymorphone is a phenanthrene-type opioid analgesic that binds with high affinity to μ-opioid receptors. Binding studies with oxymorphone in HEK-293 cells transfected with human recombinant opioid receptor subtypes have been reported in the literature (Metzger, et al., 2001) and are reproduced below:

Inhibition Constants (K_I nM)		
μ	κ	δ
17.4 ± 1.3	208 ± 36	730 ± 151

As indicated in the table above, oxymorphone shows approximately 42-fold higher affinity for μ than δ receptors and 12-fold higher affinity for μ compared to κ-opioid receptors. Endo Pharmaceuticals, who originally developed oxymorphone as an analgesic in the 1950s, conducted a NOVA-Screen (50 binding sites) for oxymorphone (10^{-8}M and 10^{-5}M). The percent inhibition of specific binding for the major binding sites is represented below:

Selected Results from NovaScreen Receptor Binding Study		
	Percent Inhibition (%)	
Concentration Tested →	**10^{-8}M**	**10^{-5}M**
δ1-opioid receptors	-18.26	89.03
δ2-opioid receptors (human recombinant)	7.76	72.74
κ-opioid receptors (human recombinant)	10.35	89.41
μ-opioid receptors (human recombinant)	85.42	100.39

Oxymorphone is about 10 times as potent as morphine when administered via the parenteral route. However, oxymorphone undergoes extensive first hepatic metabolism in humans. There are some differences in the metabolic products of oxymorphone between species and approximately 51% of the administered drug is not accounted for in human urine 5-days after the drug is administered. In the rat, only 14.9% of the drug is accounted for, indicating that there are unidentified metabolites and/or some of the drug is eliminated in the feces.

The analgesic effects of opioids such as oxymorphone are thought to occur primarily though interaction with opioid receptors at several sites within the central nervous system (CNS) including spinal and supraspinal sites.

In addition to analgesia, administration of opioids produces anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. High doses of opioids produce muscle rigidity possibly due to effects of opioids on dopaminergic transmission in the striatum. The euphoric effects of opioids are believed to be mediated in part via interaction with opioid receptors located in the ventral tegmental area (VTA) leading to the enhancement of dopamine release in the nucleus

accumbens. Opioid receptors in the locus coeruleus appear to inhibit the adrenergic neurons thought to play a role in feelings of alarm, panic, fear and anxiety. Opioids act within the hypothalamus to regulate body temperature (generally temperature decreases slightly, but at higher doses temperature may increase). Opioids inhibit neuroendocrine systems including gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF) thereby decreasing release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenal corticotrophic hormone (ACTH), and β-endorphin. This leads to decreased plasma levels of testosterone and cortisol. Opioids increase circulating levels of prolactin. Opioids such as fentanyl lead to constriction of the pupil (miosis) via increased parasympathetic nerve activity innervating the pupil. Pinpoint pupils are pathognomonic for toxic doses of μ-opioid agonists; however mydriasis can develop upon asphyxia. High doses of opioids can produce convulsions in animals, possibly via inhibition of GABAergic interneurons innervating the hippocampus. Opioids depress the central respiratory centers in the brainstem.

Non clinical safety issues relevant to clinical use:

The primary nonclinical safety issue related to the clinical use of any opioid such as oxymorphone is the risk of respiratory depression that may lead to death. It is thought that opioids, such as oxymorphone, act within the central nervous system respiratory center produce respiratory depression. Although highly significant, respiratory depression is a common and well characterized effect of opioids.

A nonclinical safety issue that is not well characterized is the positive *in vivo* micronucleus result with oxymorphone. Interestingly, the genetic toxicology profile of oxymorphone mirrors that reported in the literature for morphine (Swain, et al., 1980; Das and Swain, 1982; Sawant and Couch, 1995; Couch and Sawant, 1995; Sawant, et al., 2001). A positive *in vivo* genetic toxicity result is commonly considered to be of far more concern than a positive result in an *in vitro* assay. This positive finding has been further qualified via mechanistic studies in rats. It has been observed the oxymorphone induced micronucleus formation is blocked by an anti pyretic drug sodium salicylate. Although, other antipyretic drug naproxen and acetaminophen did not show similar effect and the hyperthermic effect of oxymorphone could not be correlated with its plasma concentration, the reduction of micronucleus formation by sodium salicylate indicate that the increase micronucleus formation by oxymorphone is at least partially induced via the prostaglandin mediated effect; therefore, genotoxic effect of the compound could be managed. The clinical relevance of the genotoxic finding; however, is not known. Carcinogenicity assessment for oxymorphone was conducted by the sponsor in rodents. The studies were found to be adequate. ECAC concurred with the sponsor that there is no treatment related neoplastic findings.

An additional nonclinical safety issue revolves around the impurity profile of the drug substance and the drug product. [redacted] . The molecule

contains an [redacted] moiety, which is a structural alert for mutagenicity. During the first cycle of the NDA review process, the sponsor tested [redacted] in a minimal genetic toxicology screen. The results indicated that the impurity tested negative in the Ames assay but tested positive in the *in vitro* chromosomal aberrations assay. At present, the MF holder for the drug product agreed to reduce the specification of these [redacted] impurities up to [redacted] level which is acceptable. All other non genotoxic impurities are qualified according to the ICH Q3B Guidance, therefore, raises no concern for safety evaluation for NDAs under recent submission.

NDA 11-738 Numorphan® Rectal Suppositories (ENDO, approved 5/31/1960)
NDA 11-737 Numorphan® IR Tablets (ENDO; 2 & 5 mg tablets approved 1959, 10 mg tablets approved 1961; after discontinued sales in 1967 due to low sales then withdrawn from the market in 1979. Sponsor opted not to undergo DESI review).

DMF 14502 Mallinckrodt (oxymorphone hydrochloride)
DMF 11868 Penwest (TIMERx®-N Controlled Release System)

Drug class: Opioid agonist; analgesic; narcotic.

Intended Clinical Use: The indication is for the "relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time."

Clinical formulation: Extended release tablet strengths of 5, 10, 20 and 40 mg will be produced with the following ingredients:

Ingredient	Function	Tablet Composition (mg/tablet)			
		5 mg	10 mg	20 mg	40 mg
Oxymorphone HCl, USP	Active Ingredient	5.00	10.00	20.00	40.00
TIMERx-N Delivery System	Release Controlling Agent				
Silicified Microcrystalline Cellulose					
Sodium Stearyl Fumarate, NF					
Coating:					
Total Theoretical Weight		**195.49**	**200.71**	**211.16**	**232.07**

Composition of the TIMERx-N Delivery System				
Ingredient	**Specification**	**%W/W**	**mg/tablet**	**mg/day**
Xanthan Gum				
Locust Bean Gum				

The immediate release product will be produced in doses of 5 and 10 mg and will contain the following ingredients:

Formulation for the Immediate Release Tablets (5 and 10 mg)			
Ingredient	**Function**	**Dose**	
		5 mg	**10 mg**
Oxymorphone HCl, USP	Active Ingredient	5.00	10.00
Lactose Monohydrate, NF			
Pregelatinized Starch, NF			
Magnesium Stearate, NF			
FD&C Blue #2 Aluminum Lake			
D&C Red #30 Aluminum Lake			
Total Theoretical Weight		**220.00**	**220.00**

All inactive ingredients are found at comparable levels in FDA-approved drug products that are administered for chronic indications.

According to Penwest, the manufacturer of TIMERx-N, the material is a component of nifedipine extended-release tablets, 30 mg, manufactured by Mylan Pharmaceuticals. This drug was approved by FDA via ANDA 75-108 on December 17, 1999. The ingredients used to make TIMERx-N are all used extensively in food products and are classified as GRAS (Generally Recognized as Safe). Each tablet contains [redacted] of TIMERx-N. Based upon the specifications, that would be [redacted] each of Xanthan Gum and Locust Gum. The DMF for TIMERx-N contains a summary report titled "TIMERx-N Controlled Release System (Granulation) Safety Evaluation: Nifedipine Extended-Release Tablets." This summary details all of the safety information on these excipients.

Based upon the composition of TIMERx-N and the previous experience with this excipient in the generic nifedipine drug product, there are no pharmacology/toxicology concerns with this ingredient.

[redacted]

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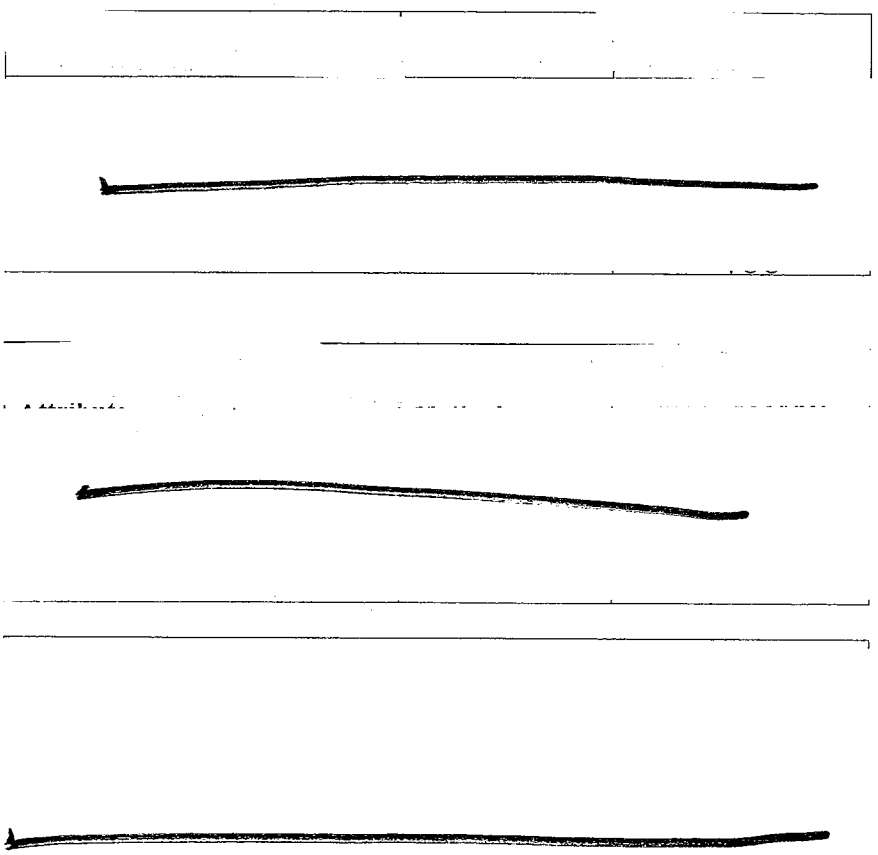


There are no novel excipients in the proposed drug product formulation.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: The current submission is a 505(b)(1) submission.

Studies reviewed within this submission:

EN3202-281-03 Effect of Different Oral Dosages of Naproxen (Antipyretic) on Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats

EN3202-271-03 Effect of Different Dosages of Sodium Salicylate (Antipyretic) on Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats

EN3202-261-03 Relationship between Micronuclei Formation and Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats

EN3202-252-03 Monitoring of Mouse Body Temperature Following Oxymorphone Administration

EN3202-251-03 Monitoring of Rat Body Temperature Following Oxymorphone Administration

EN3202-271a-03 Effect of Different Dosages of Sodium Salicylate (Antipyretic) on Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats - Higher Dosages and Varying Pretreatment Time

EN3202-261b-04 Relationship between Micronuclei Formation and Animal Body Temperature Changes Following Oxymorphone HCl and Sodium Salicylate (Antipyretic) Administration

EN3202-261a-03 Relationship between Micronuclei Formation and Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats – Repeat Study

[redacted] **Project No: 77069:** A 2-Year Oral Gavage Carcinogenicity Study Of Oxymorphone- HCl in the Albino Rats

[redacted] **Project No: 77070:** A 2-Year Oral Gavage Carcinogenicity Study Of Oxymorphone- HCl in the Albino Mouse

Studies not reviewed within this submission:

The following studies were reviewed during for the original NDA submission by Dr. R. Daniel Mellon. They have been incorporated into this document:

ADME Studies

Pharmacokinetic, Excretion/Balance and Metabolite Identification Studies with ^{3}H-Oxymorphone in the Rat

Profiling, Identification and Characterization of the Metabolites of Oxymorphone in Rat Plasma and Urine Using Radiodetection and LC/MS/MS

Pharmacokinetic, Protein Binding, Excretion/Balance and Metabolite Identification Studies with ^{3}HOxymorphone in the Mouse

In Vitro Characterization of the Inhibitory Profile of Oxymorphone Toward Cytochrome P450 Enzymes in Human Liver Microsomes

Non-GLP in Vitro Evaluation of Cytochromes P-450 Involved in the Metabolism of Oxymorphone to 6-Hydroxyoxymorphone

Non-GLP in Vitro Human Hepatocyte Enzyme Induction Study Using Oxymorphone

Repeat Dose Toxicology Studies

411003. A 13-Week Oral (Capsule) Study of Oxymorphone Hydrochloride in Dogs

Genetic Toxicology Studies

ENDO # SP0002-210-03. Bacterial Reverse Mutation Study with

ENDO # SP0002-220-03. *In Vitro* Chromosome Aberrations Study with in Chinese Hamster Ovary Cells

AA46XC.XD.123.BTL Mammalian Erythrocyte Micronucleus Test [oxymorphone HCl and morphine sulfate]: Mouse Study

AA46XC.125.BTL Mammalian erythrocyte micronucleus test [oxymorphone HCl] : Rat Study

Reproductive Toxicology Studies

411001. A Dose Range-Finding Study of the Effects of Oxymorphone Hydrochloride on Fertility and Early Embryonic Development to Implantation in Rats

411004. A Study of the Effect of Oxymorphone Hydrochloride on Fertility and Early Embryonic Development to Implantation in Rats

411006. A Study of the Effects of Oxymorphone Hydrochloride on Embryo/Fetal Development in Rats

411008. A Study of the Effects of Oxymorphone Hydrochloride on Embryo/Fetal Development in Rabbits

411009. Study of the Effects of Oxymorphone Hydrochloride on Pre- and Postnatal Development, Including Maternal Function in the Rat

Special Toxicology Studies

Dermal Sensitization Study in Guinea Pigs/Maximization Procedure Using Oxymorphone (Lot #R84-188)

The following studies have been previously reviewed by Dr. Kathleen Haberny for IND 56,919 (N 020). Dr. Haberny's summaries have been incorporated into this document.

T96-2-2: Oxymorphone HCl/[redacted] · Acute Intravenous Dose Toxicity in CD-1 Mice

T96-1-14: Oxymorphone HCl/[redacted] · Acute Intravenous Dose toxicity in Sprague-Dawley Rats

T96-2-1: Oxymorphone HCl/[redacted] · Two-Week Intravenous Dose Toxicity Study in CD-1 Mice

T96-1-7: Oxymorphone HCl/[redacted] Two-Week Intravenous Dose Toxicity Study in Sprague-Dawley Rats

The following studies were reviewed by Dr. Kathleen Haberny for IND 58,602 (N 046 SX and N 047 SX). Dr. Haberny's reviews have been incorporated into this document.

[redacted]-411011. A 13-Week Oral Study of Oxymorphone Hydrochloride in Rats

[redacted]-411012. A 13-Week Oral Study of Oxymorphone Hydrochloride in Mice

The following studies were reviewed for IND 58602 (N 067) by R. Daniel Mellon, Ph.D. (and included in this report under the genotoxicity section):

AA46XC.503.BTL and AA46XD.503.BTL. Bacterial Reverse Mutation Assay [for Oxymorphone HCl and Morphine Sulfate]

AA46XC-XD.341.BTL. In Vitro Mammalian Chromosome Aberration Test [for Oxymorphone HCl and Morphine Sulfate]

AA46XC-XD.123.BTL. Mammalian Erythrocyte Micronucleus Test [for Oxymorphone and Morphine Sulfate]

AA46XC.125.BTL. Mammalian Erythrocyte Micronucleus Test [for Oxymorphone HCl]

AA46XC.126.BTL. Mammalian Erythrocyte Micronucleus Test with Kinetochore Analysis [for Oxymorphone HCl]

The following studies were submitted by Mallinckrodt to their DMF for oxymorphone hydrochloride and were reviewed by R. Daniel Mellon, Ph.D.:

AA85YD.341.BTL. In Vitro Mammalian Chromosome Aberration Test [redacted]

AA85YD.503.BTL. Bacterial Reverse Mutation Assay [redacted]

Additional Toxicology Studies: The following studies were dose-range finding studies designed to determine dosing in the definitive studies. They were not formally reviewed for this NDA.

[redacted]-411002. An Oral (Capsule) Escalating Dose Range-Finding Study of Oxymorphone HCl in Dogs

[redacted]-411005. A Dose Range-Finding Study of the Effects of Oxymorphone Hydrochloride on Embryo/Fetal Development in Rats

[redacted]-411007. A Dose Range-Finding Study of the Effects of Oxymorphone Hydrochloride on Embryo/Fetal Development in Rabbits

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary:

Oxymorphone is about 10 times as potent as morphine when administered via the parenteral route. Oxymorphone undergoes extensive hepatic metabolism in humans. There are some differences in the metabolic products of oxymorphone between species and approximately 51% of the administered drug is not accounted for in human urine 5-days after the drug is administered. In the rat, only 14.9% of the drug is accounted for, indicating that there are unidentified metabolites and/or some of the drug is eliminated in the feces.

2.6.2.2 Primary pharmacodynamics:

Oxymorphone is a semi-synthetic opioid-receptor agonist. Oxymorphone is indicated for the treatment of moderate to severe pain.

Mechanism of action:

The mechanism of action of oxymorphone is thought to be mediated by interaction with μ-opioid receptors primarily in the central nervous system. Binding studies in opioid receptor transfected HEK-293 cells have recently been reported in the literature (Metzger, et al., 2001) and are reproduced below:

Inhibition Constants (K_I nM)		
μ	κ	δ
17.4 ± 1.3	208 ± 36	730 ± 151

As indicated in the table above, oxymorphone shows approximately 42-fold higher affinity for μ than δ receptors and 12-fold higher affinity for μ compared to κ-opioid receptors. Endo Pharmaceuticals conducted a NOVA-Screen (50 binding sites) for oxymorphone (10^{-8}M and 10^{-5}M). The percent inhibition of specific binding for the major binding sites is represented below:

Selected Results from NovaScreen Receptor Binding Study:

	Percent Inhibition (%)	
Concentration Tested →	**10^{-8}M**	**10^{-5}M**
δ1-opioid receptors	-18.26	89.03
δ2-opioid receptors (human recombinant)	7.76	72.74
κ-opioid receptors (human recombinant)	10.35	89.41
μ-opioid receptors (human recombinant)	85.42	100.39

At a concentration of 10^{-5}M, marginal inhibition (20 and 50%) was also noted at sodium channel site 1 (29.56%), sodium channel type 2 (22.98%) and Histamine H3 receptors (21.34%). Oxymorphone produced baseline inhibition of binding (-20 to 20%) in the following receptors: orphanin, adenosine, adrenergic (α1, α2, β), benzodiazepine, dopamine (D1, D2, nonselective), GABA A, glutamate (kainate, NMDA), glycine, histamine (H1, H2), muscarinic (M1, M2, non-selective), nicotinic, serotonin, sigma, calcium channels (L, N), potassium channels, angiotensin II, bradykinin B2, cholecystokinin (CCK1, CCK2), galanin, neurokinin NK2, neuropeptide Y, neurotensin, somatostatin, VIP or vasopressin V1A receptors.

Drug activity related to proposed indication: The analgesic effects of opioids such as oxymorphone occur though interaction with opioid receptors at several sites within the central nervous system (CNS) including spinal and supraspinal sites. Specifically activation of opioid receptors located on the terminals of sensory afferents inhibits substance P release and activation of opioid receptors located on interneurons inhibits the actions of substance P on output neurons within the spinal cord. Opioid receptors within the periaqueductal gray (PAG), locus coeruleus and raphe magnus also induce analgesia via enhancement of descending aminergic bulbospinal pathways which inhibit processing of nociceptive afferent signals. Continuous dull pain is relieved more effectively by opioids than acute sharp pain.

2.6.2.3 Secondary pharmacodynamics

In addition to analgesia, administration of opioids produces anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression. High doses of opioids produce muscle rigidity possibly due to effects of opioids on dopaminergic transmission in the striatum. The euphoric effects of opioids are believed to be mediated in part via interaction with opioid receptors located in the ventral tegmental area (VTA) leading to the enhancement of dopamine release in the nucleus accumbens. Opioid receptors in the locus coeruleus appear to inhibit the adrenergic neurons thought to play a role in feelings of alarm, panic, fear and anxiety. Opioids act

within the hypothalamus to regulate body temperature (generally temperature decreases slightly, but at higher doses temperature may increase). Opioids inhibit neuroendocrine systems including gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF) thereby decreasing release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenal corticotrophic hormone (ACTH), and β-endorphin. This leads to decreased plasma levels of testosterone and cortisol. Opioids increase circulating levels of prolactin. Opioids such as fentanyl lead to constriction of the pupil (miosis) via increased parasympathetic nerve activity innervating the pupil. Pinpoint pupils are pathognomonic for toxic doses of μ-opioid agonists; however mydriasis can develop upon asphyxia. High doses of opioids can produce convulsions in animals, possibly via inhibition of GABAergic interneurons innervating the hippocampus. Opioids depress the central respiratory centers in the brainstem.

2.6.2.4 Safety pharmacology

Neurological effects: In humans, opioids, such as oxymorphone, produce analgesia, drowsiness, changes in mood, mental clouding, and, in some individuals, euphoria. When individuals who are not in pain experience opioids such as oxymorphone, the experience is frequently unpleasant (nausea and vomiting is common). Depression of the cough reflex appears to be due to opioid actions in the medullary cough center; however these effects are less sensitive to naloxone than analgesia, suggesting a differential mechanism. Opioids also act within the chemoreceptor trigger zone for emesis in the area postrema of the medulla to stimulate nausea and vomiting. These effects are less likely in recumbent patients and increase and the individual becomes ambulatory suggesting a vestibular component.

Although formal behavioral studies were not completed by the sponsor, behavioral observations have been reported in dogs following the intravenous administration of oxymorphone (Copland, et al., 1987). Copland et al. report that following intravenous administration of 0.4 mg/kg oxymorphone, animals demonstrated panting or excessive respiratory effort, spasmodic muscle jerks, whining, and sudden movement in response to sound. Most dogs seemed restless or slightly anxious. After subsequent injections, some of the dogs began to have a positive response to the drug and showed arousal. Dogs were able to ambulate with mild ataxia, however, attitude, coordination, and responsiveness improved after naloxone administration.

Cardiovascular effects: The effects of opioids on the cardiovascular system are complex. In general, therapeutic doses of morphine produces peripheral vasodilation, reduced peripheral resistance and inhibition of baroreceptor reflexes and therefore orthostatic hypotension may occur. For morphine and meperidine, these effects may be partially mediated by peripheral histamine release. In contrast, oxymorphone and fentanyl do not appear to lead to histamine release (Hermens, et al., 1985; Robinson, et al., 1988). As a result, oxymorphone in the dog model produces an increase in systemic vascular resistance. It should be noted that the effect of morphine on skin mast cell histamine release does not appear to be mediated by classical opioid receptors, as the effect is not

blocked by naloxone. Cerebral circulation is not directly affected, however, opioid-induced respiratory depression and CO_2 retention can lead to cerebral vasodilation and increased cerebrospinal fluid pressure.

In Study [redacted]-411003, a 13-week repeat-dose toxicology study in dogs, oxymorphone was administered orally at doses up to 40 mg/kg/day. EKG evaluations were completed at 2 hours post dose, the time of maximal plasma drug concentrations. There were no treatment-related changes in the EGC, according to the independent review by Dr. Robert L. Hamlin, D.V.M., Ph.D., D.A.C.V.I.M.

Study Title: Effects of Oxymorphone HCl on cloned hERG Channel expressed in Mammalian Cells: Study Number: EN3202-501

The potential for oxymorphone HCl to inhibit potassium currents involved in cardiac action potential duration and QT interval prolongation was studied electrophysiologically *in vitro* using a human embryonic kidney cell line (HEK293) that stably expressed human ether-a-go-go-related (hERG) gene encoded potassium channel. Concentrations tested were 10, 30, 100, 300 μM.

Key Study Findings:

- Oxymorphone HCl inhibited hERG current by 6.3 + 0.8 % at 10 μM, 22.1 ± 1.6 % at 30 μM, 53.3 ± 1.0% at 100 μM, and 75.6 ± 1.2% at 300 μM with n=3. hERG inhibition at 10, 30, 100, and 300 μM were statistically significant, when compared to vehicle control values. Table The IC_{50} for the inhibitory effect of Oxymorphone HCl on hERG current was 95.3 μM with a Hill coefficient of 1.1 as shown in sponsor's Figure 3 reproduced below.
- The positive control, terfenadine at 60 nM resulted in 85.5 ± 0.4% (n = 2) block of hERG current. The results with terfenadine were consistent with ChanTest historical data which confirmed the validity of the assay system.

The result show that oxymorphone HCl inhibited hERG channel with an IC_{50} of 95.3 μM, the molecular weight of the test compound is 337, the maximum suggested initial daily dose is 40 mg. Although doses in human will be titrated and in vitro study doses could not be meaningfully converted to the *in vivo* dose, the data show that safety margin exists for the potential potassium channel blocking of the test compound under this experimental condition.

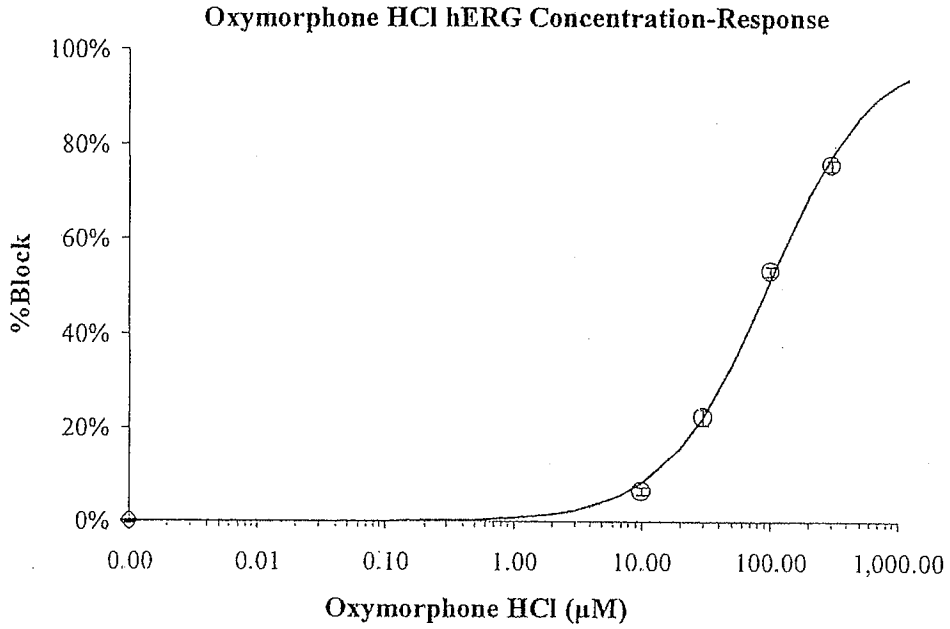


Figure 3: Concentration-response relationship of Oxymorphone HCl on hERG current.

Percent inhibition of hERG current at each concentration of Oxymorphone HCl (Mean ± SEM). hERG currents were not inhibited on exposure to vehicle control (blue rectangles). Number of observations for each concentration was three (n=3). The IC_{50} for the inhibitory effect of Oxymorphone HCl on hERG current was 95.3 μM with a Hill coefficient of 1.1.

Several published reports examine the potential cardiovascular effects of oxymorphone in the dog model (Copland, et al., 1987; Copland, et al., 1989; Copland, et al., 1992). Copland initially administered 0.4 mg/kg oxymorphone intravenously to 10 non-anesthetized, spontaneously breathing dogs. An additional 0.2 mg/kg oxymorphone was administered at 20, 40 and 60 minutes after the first dose. The effects of oxymorphone on the cardiovascular parameters examined are reproduced in the sponsor's table below:

Table 9. Cardiovascular Changes Following Intravenous Administration of Oxymorphone in Dogs.

Cardiovascular Parameter	Change	Maximal Effect[a]	Time of Maximal Effect[b]
Heart rate	Decreased	71%	5
Mean arterial blood pressure	Increased	120%	5
Stroke Volume	Increased	134%	150-270
Central Venous Pressure	Increased	192%	5-15
Pulmonary Artery Pressure	Increased	148%	5
Pulmonary Wedge Pressure	Increased	200%	5
Systemic Vascular Resistance	Increased	163%	5
Pulmonary Vascular Resistance	No change	NA	NA
Cardiac Output	Decreased	73%	5

[a] Mean value after oxymorphone injection as percent of mean baseline value (n=10). Calculated from Copland *et al.*, 1987, Table 2.
[b] Minutes after first injection. Oxymorphone (0.4 mg/kg) was administered intravenously at 0 minutes, followed by additional intravenous injections of 0.2 mg/kg at 20, 40 and 60 minutes.
NA=not applicable.
Reference: Copland *et al.*, 1987; Copland *et al.*, 1989.

The cardiovascular effects noted above were evident within 5-15 minutes of dosing (except stroke volume which did not increase until 120 minutes after the initial dose). The cardiovascular effects were also reversed by naloxone, indicating that they were mediated by classical opioid receptors. In addition, Copland demonstrated that the cardiovascular effects (and respiratory effects) were reversed by atropine, suggesting that overall parasympathetic tone contributes to the decrease in heart rate and cardiac output. The increase in systemic vascular resistance may be secondary to increased thoracoabdominal muscular rigidity, altered ventilatory pattern or secondary to bradycardia. The increase in mean arterial blood pressure is likely secondary to the increased systemic vascular resistance (Copland, et al., 1987).

Pulmonary effects: In the clinical setting, respiratory depression is a common side effect of μ-receptor agonists such as oxymorphone. Respiratory arrest due to depression of the respiratory centers in the brain stem is the primary cause of death due to opioid poisoning. Opioids depress respiratory rate, minute volume, and tidal exchange. In the absence of underlying pulmonary dysfunction, respiratory depression induced by therapeutic doses of opioids is rarely a problem. This depression appears to be due to decreased responsiveness of the respiratory centers to carbon dioxide. With large doses of opioids, patients may still breathe if told to do so, but without being told to do so will remain apneic.

The respiratory effects of opioids have been studied in dogs following intravenous administration (Copland, et al., 1987; Copland, et al., 1989; Copland, et al., 1992). In these studies, dogs were administered an initial dose of 0.4 mg/kg oxymorphone intravenously followed by 0.2 mg/kg injections at 20, 40 and 60 minutes later. Respiratory parameters were evaluated every 20-30 minutes for 5 hours. Under the conditions of the assay, oxymorphone produced mild respiratory depression generally within 5-15 minutes after the initial dose. This effect was reversed by naloxone. The sponsor's table 8 outlines the specific respiratory changes in the table below:

Table 8. Respiratory Changes Following Intravenous Administration of Oxymorphone in Dogs.

Respiratory Parameter	Change	Maximal Effect[a]	Time of maximal effect[b]
Apnea	Transient	NA	Lasting 45 seconds
Respiratory Rate	Increased	225%	15-35
Tidal Volume	Decreased	68%	15-35
Minute Ventilation	Increased	148%	15-35
PaCO2	Increased	125%	55-180
Physiologic Dead Space	Increased	121%	15-55
Base Deficit	Increased	253%	15-55
Alveolar Tidal Volume	Decreased	ND	ND
PaO2	Decreased	74%	5
Hemoglobin	Increased	124%	5
Arterial O2 content	Increased	116%	5-55
O2 Transport	No change	NA	NA
Venous admixture	Increased transiently	380%	5, 120-150

[a] Mean value after oxymorphone injection as percent of mean baseline value (n=10). Calculated from Copland *et al.*, 1987, Table 1.
[b] Time = Minutes after first injection. Oxymorphone (0.4 mg/kg) was administered intravenously at 0 minutes, followed by additional intravenous injections of 0.2 mg/kg at 20, 40 and 60 minutes.
NA=not applicable;
ND=not determined, effects were described in the text of this paper, but data was not presented.
Reference: Copland *et al.*, 1987; Copland *et al.*, 1989.

Renal effects: Opioids do not produce significant renal toxicity. Studies in the rat suggest that opioid microinjection into the PVN can lead to vasoconstriction in renal vascular (Lessard and Bachelard, 2002). These effects are mediated by alterations in the autonomic nervous system.

Gastrointestinal effects: Opioids have several effects on the gastrointestinal system. μ-Opioid agonists decrease secretion of hydrochloric acid in the stomach via diverse mechanisms. Opioids decrease gastric motility and thereby prolong gastric emptying time. This can lead to increased absorption of orally administered drugs. At the level of the small intestines, μ-opioids decrease biliary, pancreatic and intestinal secretions and delay digestion of food in the small intestine. The upper intestine (duodenum) is affected more than the lower intestine (ileum). At the level of the large intestine, μ-opioid agonists diminish or abolish the peristaltic waves of the colon and thereby causes increased water retention which leads to desiccation of the feces and retards their advance though the colon. Anal sphincter tone is increased and combined with inattention to normal sensory stimuli, constipation can result. In addition, opioids lead to constriction of the sphincter of Oddi and thereby increase the pressure of the common bile duct. Fluid pressure may also increase in the gall bladder leading to epigastric distress and typical biliary colic. Fentanyl produces fewer effects on the biliary tract than other opioids (Gutstein and Akil, 2002).

Abuse liability: Tolerance and physical dependence occurs with repeated use of opioids. Tolerance and dependence are physiological responses and do not appear to predict abuse of opioids. Patients in pain rarely develop abuse or addiction problems (O'Brien, 2001). Oxymorphone is a Schedule II drug (DEA 9652).

Other:

Immune System: Animal studies suggest that opioids can inhibit the cytolytic activity of natural killer cells (Shavit, et al., 1985; Weber and Pert, 1989; Yeager, et al., 2002) and enhance the growth of implanted tumors (Lewis, et al., 1983). In addition, morphine appears to inhibit the formation of human lymphocyte rosettes (Wybran, et al., 1979). Many of these effects appear to be due to interaction of opioids with the CNS (Mellon and Bayer, 1998).

Skin: Therapeutic doses of opioid lead to dilation of the cutaneous blood vessels. This can produce a flushing of the face, neck and upper thorax, possibly related to the release of histamine. This effect is noted with morphine and meperidine but is not seen with **oxymorphone**, methadone, fentanyl or sufentanil and is not mediated by naloxone-sensitive opioid receptors (Hermens, et al., 1985; Robinson, et al., 1988; Smith, et al., 2001).

Ureter and Urinary Bladder: Therapeutic doses of opioids can lead to inhibition of the voiding reflex via increased muscle tone in the ureter with increased tone of the sphincter and the volume of the bladder. Catheterization is sometimes required to assist in bladder emptying (Gutstein and Akil, 2002).

2.6.2.5 Pharmacodynamic drug interactions:

According to the current labeling:

[redacted]

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

[redacted]

In addition, CNS toxicity has been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; no clear-cut cause and effect relationship was established.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No pharmacology summary tables were provided by the sponsor.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The sponsor conducted *in vivo* PK studies in the rat and mouse as well as *in vitro* assessment of effects of the drug on liver enzymes. To characterize the pharmacokinetics of oxymorphone in the rat model, the sponsor administered ^{3}H-oxymorphone (25 mg/kg) via oral gavage to albino, male Sprague-Dawley rats and examined pharmacokinetics, excretion/balance and metabolism ([redacted] study # UK6052). For the PK study, animals were sacrificed via exsanguinations at 15 minutes, 30 minutes, 1, 2, 4, 8 and 24 hours post dose. Urine was collected predose and over the following intervals: 0-12, 12-24, 24-48, 48-72, 72-96 and 96-120. Feces were collected over the following intervals: 0-24, 24-48, 48-72, 72-96 and 96-120. Expired air was collected over the following intervals: predose, 0-6, 6-12, 12-24 and 24-48.

A second study was conducted in the mouse model similar to the rat model described above. Mice were dosed orally with ^{3}H-oxymorphone at doses of 100 or 300 mg/kg. Initial doses of 400 and 500 mg/kg oxymorphone lead to several deaths and thus the lower two doses were chosen for the PK study. The radioactivity total in the surviving mice

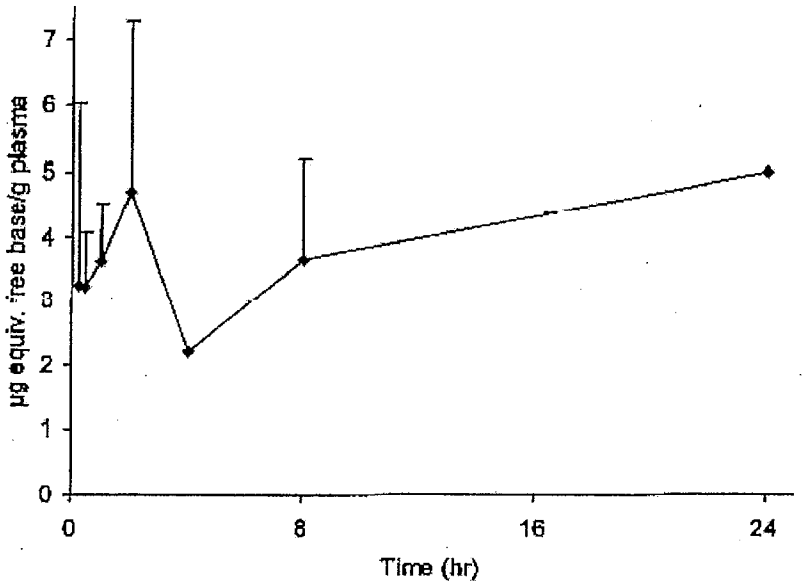
2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

Oxymorphone is absorbed following oral, intramuscular, rectal and subcutaneous administration. Quantitative bioavailability has not been reported in the literature. In [redacted] Study #6052, the plasma levels of ^{3}H-oxymorphone (25 mg/kg) following oral administration over time was determined. The figure below is reproduced from the sponsor's submission below:

Figure 2. Concentration of radioactivity (expressed as µg equiv. of ^{3}H-oxymorphone) in plasma following oral administration of ^{3}H-oxymorphone (mean dose 25.0 mg/kg body weight and 8.08 MBq/kg) to male rats.

For numerical values refer to Table 4



In the mouse, oral administration of ~100 mg/kg ^{3}H-oxymorphone produced the following plasma levels expressed as a factor of time. The figure below is reproduced from the sponsor's report ([redacted] Study #6083).

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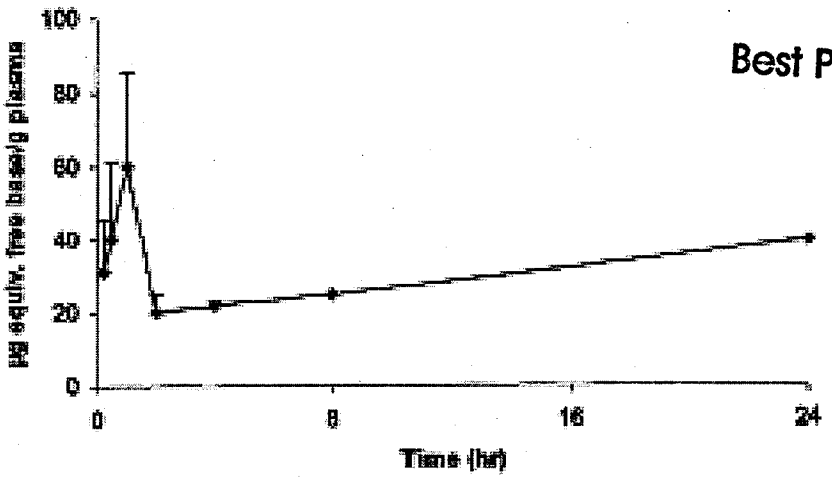
Figure 1. Mean concentration of radioactivity (expressed as µg equivalents of free base) in plasma following oral administration of ^{3}H-oxymorphone hydrochloride (mean dose 101 mg/kg body weight and 6.68 MBq/kg) to male mice

Mean of up to 3 animals per time point. Refer to Table 5 for individual values



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2.6.4.4 Distribution

Specific tissue distribution studies have not been completed for oxymorphone. A study conducted by [redacted] for Endo Pharmaceuticals ([redacted] Study #UK6052) examined the pharmacokinetics, excretion/balance and metabolite identification in the adult male rat following ^{3}H-oxymorphone (0.05, 0.5 and 5 µM) administered via the oral route of administration.

After oral dosing of oxymorphone (25 mg/kg) in the adult male rat a steady state volume of distribution was 3.08 ± 1.14 L/kg. Oxymorphone has low protein binding to human or rat plasma proteins (see sponsor's table below from [redacted] Study #6052):

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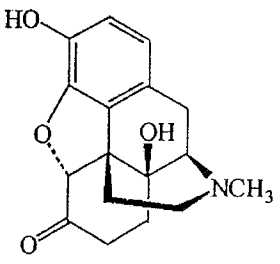
Table 8 Summary of binding of ^{3}H to plasma proteins following incubation of ^{3}H-oxymorphone hydrochloride (0.05, 0.5 and 5 µM free base) with rat and human plasma at 37 °C for 10 minutes

^{3}H-oxymorphone µM	% radioactivity binding to:	
	Rat plasma proteins*	Human plasma proteins*
5.0	9.4	12.9
0.5	8.4	4.5
0.05	11.7	0.1

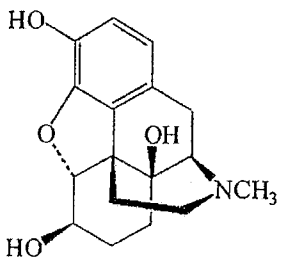
*Determined by difference in concentration values before and after ultrafiltration (50 K cut off)

2.6.4.5 Metabolism

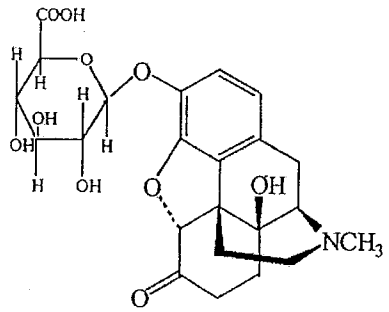
In the rat, a total of 4 putative metabolites of oxymorphone were detected in the urine and three in the plasma following oral administration. The major metabolite found in both urine and plasma is 3β-oxymorphone-glucuronide. The other possible metabolites are 6-OH-oxymorphone, N-demethyl oxymorphone, and N-demethyl oxymorphone glucuronide. The structures of the metabolites were confirmed by using MS/MS analysis. Chemical structures are presented below:



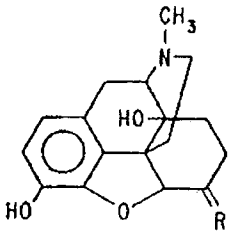
Oxymorphone
MW = 301
M+1 = 302



6ß-OH-Oxymorphone
MW = 303
M+1 = 304



3ß-D-Oxymorphone Glucuronide
MW = 477
M+1 = 478



OM: R = O
6βOM: R = 
6αOM: R = 

According to the package insert, Oxymorphone is metabolized by the liver in humans. After a 10 mg oral dose of oxymorphone, 49% was excreted over a 5-day period in the urine. Of this, 82% was excreted in the first 24 hours. The recovered drug-related products in humans included: oxymorphone (1.9%), the conjugate of oxymorphone (44.1%), the 6(β)-oxymorphol

produced by 6-keto reduction of oxymorphone (0.3%) and the conjugates of 6-(β)-oxymorphol (2.6%) and 6(α)-oxymorphol (0.1%). These data appear to be derived from published studies (Cone, et al., 1983). The image to the left depicts the structures of oxymorphone (OM) and the 6β-oxymorphol and 6α-oxymorphol metabolites (Cone, et al., 1983). According to metabolism studies published by Cone et al., the metabolism of oxymorphone shows some differences between humans, rats, dogs, guinea pigs and rabbits. Specifically, urinary excretion of unchanged oxymorphone is low except in the rabbit (see table 1 from the Cone paper below). In addition, conjugation of oxymorphone (presumably via glucuronidation) is highest in the guinea pig, but also fairly high in the human and the dog. Conjugated oxymorphone was lower in the rat and rabbit. The portion of the dose unaccounted for is likely to be either unidentified metabolites or eliminated in the feces (Cone, et al., 1983).

TABLE 1

Recovery of drug and metabolites from urine following a single dose of oxymorphone hydrochloride

These data represent the means of triplicate determinations and are expressed as percentage of administered dose. Conjugated (Conj) drug and metabolites were determined by subtraction of free from total concentration after acid hydrolysis.

Species (*N*)	Dose/Route	Time	OM		6βOM		6αOM		Total	Total First 24 hr
			Free	Conj	Free	Conj	Free	Conj		
		hr			%				%	%
Human (6)	10 mg (oral)	0–120	1.9	44.1	0.3	2.6	0	0.1	49.0	82
Rat (6)	2.5 mg/kg (sc)	0–48	2.0	12.7	0.1	0.1	0	0	14.9	97
Dog (2)	2.5 mg/kg (sc)	0–48	5.3	56.4	0.4	1.2	0	0	63.3	35
Guinea pig (6)	2.5 mg/kg (sc)	0–48	10.0	81.7	0.3	1.0	0.5	2.3	95.8	94
Rabbit (6)	2.5 mg/kg (sc)	0–48	31.7	11.7	2.0	1.1	0.6	0.2	47.3	99

2.6.4.6 Excretion

In the rats administered 25 mg/kg ^{3}H-oxymorphone orally, 89.5% of the radioactivity was recovered over 5 days. 56.8% ± 5.59% was recovered in the urine and 22.7% ± 7.12% were recovered in the feces. Less then 0.15% was recovered in the expired air up to 48 hours post dose and 9.18% ± 2.31% remained with the carcass and trace amounts were with the cage and cage debris ———, Study # 6052). By comparison, in humans, the terminal half-life of intravenous oxymorphone was 1.3 ± 0.7 hours. The values in the rat are summarized in the sponsor's table below:

Table 6 Quantitative recovery of radioactivity 120 hours following oral dosing of ^{3}H-oxymorphone hydrochloride (mean dose 25.0 mg free base/kg body weight and 8.08 MBq/kg) male rats (Stage 2)

Male rat number	Per cent of radioactive dose in:					Total recovered %
	Urine	Faeces	Expired air#	Carcass	Cage wash*	
22	55.9	25.6	0.041	7.94	0.519	90.0
23	63.9	19.2	0.514	9.45	0.264	93.3
24	50.3	31.0	0.006	7.03	0.157	88.5
25	57.2	14.8	0.037	12.3	1.68	86.1
Mean SD	**56.8 ± 5.59**	**22.7 ± 7.12**	**0.150 ± 0.244**	**9.18 ± 2.31**	**0.655 ± 0.700**	**89.5 ± 3.01**

In the mouse, the following tissue distribution was obtained following oral dosing of ~102 mg free base equivalent of oxymorphone. As noted in the summary table below, 87.2% of the total radioactivity was recovered within 120 hours. A total of 45.3% of that appeared in the urine and 13.4% was recovered in the feces. Overall, the values are comparable to those in the rat.

Table 8 **Quantitative recovery of radioactivity up to 120 hours following oral dosing of ^{3}H-oxymorphone hydrochloride (mean dose 102 mg free base equivalents/kg body weight and 7.10 MBq/kg) male mice (Stage 2)**

Mouse number	Per cent of radioactive dose in:					Total recovered %
	Urine	Faeces	Expired air#	Carcass	Cage wash*	
22	55.2	8.58	2.40	12.8	8.94	88.0
23	28.2	21.6	4.03	16.9	5.90	76.7
24	63.5	8.93	2.94	11.2	3.90	90.5
25	34.1	14.5	6.79	12.4	25.7	93.5
Mean SD	**45.3 ± 16.8**	**13.4 ± 6.10**	**4.04 ± 1.95**	**13.3 ± 2.48**	**11.1 ± 9.94**	**87.2 ± 7.34**

Expired air collected up to 48 hours

* sum of cage washings/debris at 48 and 120 hours

For time course of excretion of radioactivity in urine, faeces and expired air for each animal refer to Table 10

Table 9 **Quantitative recovery of radioactivity following oral dosing of ^{3}H-oxymorphone hydrochloride (mean dose 301 mg free base equivalents/kg body weight and 10.1 MBq/kg) male mice (Stage 2)**

Mouse number	Per cent of radioactive dose in:					Total recovered %
	Urine	Faeces	Expired air#	Carcass	Cage wash*	
22	30.5	3.74	4.27	35.8	8.82	83.1
23	5.00	0.000%	5.58	61.5	6.70	78.8
Mean	**17.8**	**1.87**	**4.93**	**48.7**	**7.76**	**81.0**

Male 22 died between 102 and 111 hours post-dose.

Male 23 died between 31 and 48 hours post-dose

* cage wash at 48 hours for male 23 and 48 hours and 11 hours for male 22

For time course of excretion of radioactivity in urine, faeces and expired air for each animal refer to Table 11

2.6.4.7 Pharmacokinetic drug interactions

The sponsor conducted three in vitro studies designed to characterize the potential for oxymorphone to inhibit or induce cytochrome P450 enzymes as well as to determine what cytochrome P450(s) may be involved in the metabolism of oxymorphone itself. These studies are briefly reviewed below.

The sponsor conducted an initial screen of CYP P450 enzymes via a NovaScreen to determine if either oxymorphone or 6-hydroxyoxymorphone could displace saturating concentrations of specific inhibitors of the P450 isoforms. The percent inhibition was calculated from K_i values generated for the reference compounds. Concentrations of oxymorphone and 6-hydroxyoxymorphone tested were 10 μM and 10 nM. The results indicated that oxymorphone has activity at CYP3A4 and CYP2D6, whereas 6-hydroxyoxymorphone appears to have activity at CYP3A4 and may have activity at CYP2C19. The sponsor's table below summarizes these findings.

Table 30. The Percent Inhibition by Different Concentrations of Oxymorphone or 6-hydroxyoxymorphone for the Major CYP Enzyme Isoforms.

	Concentration of Oxymorphone or 6-Hydroxyoxymorphone	
CYTOCHROME P450 (Human Recombinant)	10 nM	10 μM
OXYMORPHONE	Percent Inhibition[a] (Average; N= 2)	
CYP1A2	5.14%	22.19%
CYP2A6	-22.63%	-24.31%
CYP2C19	13.22%	19.20%
CYP2D6	-14.95%	113.45%[b]
CYP3A4	36.75%	65.50%[b]
6-HYDROXYOXYMORPHONE		
CYP1A2	6.92%	34.29%
CYP2A6	-10. 68%	-8.91%
CYP2C19	2.06%	83.24%[b]
CYP2D6	-17.32%	21.19%
CYP3A4	21.86%	69.55%[b]

[a]Compounds are generally considered inactive in the baseline range of –20 to +20%. Compounds that exhibit inhibition in the range of 20 to 49% are considered to be marginally active and probably not physiologically relevant. Compounds that exhibit inhibition of 50% and greater are considered active and typically have a dose-dependent response profile.
[b] Considered active

Study DCN: 21-172-TC characterized oxymorphone-induced inhibition of cytochrome P450 enzymes in human liver microsomes. The specific isoforms of cytochrome P450 examined were CYP1A2, CYP 2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. As CYP2C9 and CYP3A4 may have independent sites or be subject to allosteric activation, two assays of CYP2C9 enzymatic activity (diclofenac 4′-hydroxylation and tolbutamide hydroxylation) and three assays of CYP3A4 mediated activities (midazolam 1'-hydroxylase, testosterone 6β-hydroxylase and nifedipine dehydrogenase) were completed to examine differential inhibition of these two isoforms. The results indicated that oxymorphone at concentrations up to 200 μM did not inhibit isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4, with the exception of CYP3A4

mediated nifedipine dehydrogenation. An IC_{50} for oxymorphone-inhibition of CYP3A4 mediated nifedipine dehydrogenase inhibition was estimated at 150 μM. As such high concentrations are not attainable in vivo, this finding is not likely physiologically relevant. The results of the study were summarized by the sponsor's table reproduced below:

Table 4. Inhibition Constants Determined in This Study

CYP1A2	NI*
CYP2C9 (TOL)**	NI
CYP2C9 (DIC)**	NI
CYP2C19	NI
CYP2D6	NI
CYP2E1	NI
CYP3A4 (MDZ)**	NI
CYP3A4 (6BT)**	NI
CYP3A4 (NIF)**	150

*NI: No inhibition observed below 50% of control levels at a concentration of 200 μM.

**CYP2C9 (TOL) - Tolbutamide hydroxylation
CYP2C9 (DIC) - Diclofenac 4'-hydroxylation
CYP3A4 (MDZ) - Midazolam 1'-hydroxylation
CYP3A4 (6BT) - Testosterone 6β-hydroxylation
CYP3A4 (NIF) - Nifedipine dehydrogenation

Study 30-173-TK is a non-GLP *in vitro* assessment of the cytochrome P450 isoforms that are involved in the metabolism of oxymorphone to 6-hydroxyoxymorphone. This study was designed to determine the effect of other drugs on the metabolism of oxymorphone. The results suggested that the conversion of oxymorphone to 6-hydroxyoxymorphone occurred in human liver microsomes with a turnover rate of 1.09 nmol/min/nmol and was mediated by both a high affinity component (Km of ~1290 μM) and a lower affinity component (Km ~ 2530 μM). Further studies designed to determine the potential role of the nine major cytochrome P450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) failed to strongly implicate specific isoforms. Based upon modest inhibition of 6-hydroxyoxymorphone formation by ketoconazole and the previous finding that oxymorphone produced slight inhibition of CYP3A4, the sponsor concluded that CYP3A4 may play a role in the metabolism of oxymorphone.

Study DCN: 26-174-TH was a non-GLP *in vitro* study designed to characterize the potential oxymorphone-induced induction of human hepatocyte enzymes. Freshly isolated human hepatocytes were cultured with either oxymorphone hydrochloride at concentrations of 10 and 30 μg/mL or positive controls for 48 hours and 72 hours. Activity levels of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 were determined. The extent of induction was determined using isoforms specific substrates and analyzing for

markers of metabolites. The results suggested that oxymorphone induced CYP3A4 in human hepatocytes by greater than 2-fold. In addition, a significant increase in CYP2C9 metabolites was observed in oxymorphone treated hepatocytes. This effect was 1.2-fold and 1.3-fold for the 10 and 30 μg/mL concentrations of oxymorphone, respectively. The table below summarizes the sponsor's results:

Table SD8: Approximate Change of the Samples Containing Oxymorphone HCl as Compared to the Controls

Isoform	Sample[a]	48-Hour (ng/mL)	Fold Change		72-Hour (ng/mL)	Fold Change	
CYP1A2	Control	442	1.0		576	1.0	
	Oxymorphone HCl 10 μg/mL	368	0.8		513	0.9	
	Oxymorphone HCl 30 μg/mL	388	0.9		495	0.9	
CYP2C9	Control	19.1	1.0		19.4	1.0	
	Oxymorphone HCl 10 μg/mL	15.2	0.8		22.3	1.2	*
	Oxymorphone HCl 30 μg/mL	19.2	1.0		24.9	1.3	*
CYP2D6	Control	22.7	1.0		39.5	1.0	
	Oxymorphone HCl 10 μg/mL	21.2	0.9		34.2	0.9	
	Oxymorphone HCl 30 μg/mL	24.3	1.1		37.8	1.0	
CYP3A4	Control	1090	1.0		960	1.0	
	Oxymorphone HCl 10 μg/mL	1690	1.6		2040	2.1	*
	Oxymorphone HCl 30 μg/mL	2520	2.3	*	3140	3.3	*

[a] Low and high oxymorphone refers to a concentrations of 10 and 30 μg/mL oxymorphone HCl.
*Significantly different from time matched controls; $p<0.05$

Overall the results of the metabolism studies suggest that, depending on plasma concentrations of oxymorphone *in vivo* (C_{max}), there is limited potential for drug-drug interactions when oxymorphone is co-administered with drugs cleared predominantly by cytochrome P450 mediated metabolism. The conversion of oxymorphone to 6-hydroxyoxymorphone appears to be mediated by more than one enzyme. The formation of 6-hydroxyoxymorphone from oxymorphone appears to be completed, in part, by CYP 3A4, however, other enzyme systems may be involved. Collectively, the studies suggest that the cytochrome P450 enzymes do not appear to play a significant role in the phase I metabolism of oxymorphone. However, oxymorphone may be able to induce CYP 2C9 and CYP 3A4 *in vivo* at concentrations around 10 or 30 μM.

2.6.4.8 Other Pharmacokinetic Studies

None submitted

2.6.4.9 Discussion and Conclusions

Oxymorphone has low protein binding to human (12.9) or rat plasma proteins (9.4). The metabolism of oxymorphone shows some differences between humans, rats, dogs, guinea pigs and rabbits, however, all the metabolites observed in human are found in at least one non clinical species tested and qualified in toxicology studies. The results of the metabolism studies suggest that, depending on plasma concentrations of oxymorphone *in vivo* (C_{max}), there is limited potential for drug-drug interactions when oxymorphone is co-administered with drugs cleared predominantly by cytochrome P450 mediated metabolism. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces. Majority of oxymorphone metabolites in human are excreted via urine in human. Absorption of Oxymorphone in rat and mice was found to be biphasic after the single dose administration. In the rat 13-Week repeat dose study, 10 mg/kg, (HED= 59.94 mg/m^2) corresponds to an $AUC_{0\text{-}24h}$ of 47 and 43 ng•h/mL in males and females, respectively. C_{max} values at this dose on day 91 were 8.3 and 6.7 ng/mL in males and females, respectively. In the mice 13-Week repeat dose study at NOAEL dose (300 mg/kg, HED= 888 mg/m^2) corresponds to an $AUC_{0\text{-}24h}$ of 3.59 and 3.9 µg•h/mL in males and females, respectively. C_{max} values at this dose on day 89 were 2.8 and 2.7 µg/mL in males and females, respectively. In the dog 13-Week repeat dos e study at NOAEL dose (10 mg/kg, HED= 200 mg/m^2) corresponds to an $AUC_{0\text{-}24h}$ of 186.72 and 177.62 ng•h/mL in males and females, respectively. C_{max} values at this dose on day 89 were 28.89 and 31.50 ng/mL in males and females, respectively. Tmax in rodents is approximately 0.5 hrs. and non rodent (dog) is approximately 4 hrs. Following tables describes the PK parameter in human.

PK Parameters in Human:

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose[a]	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

2.6.4.10 Tables and figures to include comparative TK summary

Toxicokinetic data was obtained for the mouse, rat and dog during the 13-week repeat dose toxicology studies. The sponsor's summary tables are presented below. As noted in the tables, the toxicology studies produced exposures to oxymorphone that exceeded the exposures obtained following administration of the maximum human daily dose (40 mg q12h).

Table 12. Summary of Oxymorphone Toxicokinetics in Mice (Day 88).

Oxymorphone (mg/kg/day)	Sex	Cmax (ng/ml)	Fold Human Cmax[a]	AUC (ng-h/ml)	Fold Human AUC[a]
50	M	262	58	405	11
	F	255	57	603	16
75	M	544	121	901	24
	F	321	71	682	18
300	M	2797	622	3590	97
	F	2757	613	3957	107
600	M	4493	998	6288	170
	F	3037	675	6557	177

[a]Fold human values = mouse values ÷ steady state values in humans given 40 mg q12h of oxymorphone in Study EN3202-007 (Cmax = 4.5 ng/ml, AUC = 37.0 ng-h/ml)

Table 14. Summary of Oxymorphone Toxicokinetics in Rats (Day 89).

Oxymorphone (mg/kg/day)	Sex	Cmax (ng/ml)	Fold Human Cmax[a]	AUC (ng-h/ml)	Fold Human AUC[a]
10	M	16.1	*4*	106	*3*
	F	18.1	*4*	101	*3*
25	M	46.2	*10*	262	*7*
	F	94.9	*21*	367	*10*
50	M	168	*37*	683	*18*
	F	156	*35*	656	*18*
75	M	271	*60*	1093	*30*
	F	556	*124*	1428	*39*

[a]Fold human values = rat values ÷ steady state values in humans given 40 mg q12h of oxymorphone in Study EN3202-007 (Cmax = 4.5 ng/ml, AUC = 37.0 ng-h/ml).

Table 16. Summary of Oxymorphone Toxicokinetics in Dogs (Day 89).

Oxymorphone (mg/kg/day)	Sex	Cmax (ng/ml)	Fold Human Cmax[a]	AUC (ng-h/ml)	Fold Human AUC[a]
2	F	9.3	*2.1*	33.1	*0.9*
	M	3.7	*0.8*	24.0	*0.6*
10	F	29	*6.4*	187	*5*
	M	32	*7.1*	178	*5*
40	F	159	*35*	993	*27*
	M	138	*31*	643	*17*

[a]Fold human values = dog values ÷ steady state values in humans given 40 mg q12h of oxymorphone in Study EN3202-007 (Cmax = 4.5 ng/ml, AUC = 37.0 ng-h/ml)

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: The key repeat-dose toxicology studies to support the chronic indication were 13-weeks in duration and summarized in the sponsor's table below:

Table 10. Repeat Dose Toxicity Studies of Oxymorphone HCl.

Study Title	Doses (mg/kg/day)	Laboratory Study Number
A 13-Week Oral Study of Oxymorphone Hydrochloride in Mice	0, 50, 75, 300, 600 (Doses were escalated over first 63 days to achieve these final doses)	[redacted]-411012
A 13-Week Oral Study of Oxymorphone Hydrochloride in Rats	0, 10, 25, 50, 75 (Doses were escalated over first 2 weeks to achieve these final doses)	[redacted]-411011
An Oral (Capsule) Escalating Dose Range-Finding Study of Oxymorphone HCl in Dogs	Phase I: Days 0-2: 0, 10 Days 7-9: 0, 40 Days 14-16: 0, 20 Phase II: Days 21-24: 0, 5 Days 25-28: 0, 10 Days 29-32: 0, 20 Days 33-36: 0,40	[redacted]-411002
A 13-Week Oral (Capsule) Study of Oxymorphone Hydrochloride in Dogs	0, 2, 10, 40 (Doses were escalated over first 40 days to achieve these final doses)	[redacted]-411003
[redacted]		

The results of the 13-week repeat-dose toxicology studies demonstrate that oxymorphone produces a toxicity profile consistent with those of a potent opioid. The potential target

organ of toxicity is primarily the CNS. In all species, excessively high doses of oxymorphone, like all full opioid agonists, can produce respiratory depression and death. In rats, the CNS effects include excessive chewing of cage and limbs/tail, hyperactivity, vocalization upon handling and hyperactive to touch. In mice, the CNS effects include the classical Straub tail, hypo- or hyperactivity, unkempt appearance, abnormal stance, muscle rigidity and even tremors. In the dog, oxymorphone produces excessive salivation, injected sclera of the eyes and decreased defecation. Dogs also displayed prostration, slow visual tracking, menace reactions and impaired motor coordination at higher doses. In all species, oxymorphone produced a decrease in body weight and/or body weight gain which correlated with a decrease in food consumption.

In the 13-week repeat-dose rat study, oxymorphone produced mild regenerative anemia which was not associated with any corroborating histological changes. This reduction in red blood cells (maximum of 9%) was not noted in either the mouse or dog studies. The basis for the hematological findings in the rat are not known, however, as they were minimal in nature and did not occur in either the dog or the mouse do not appear to be of toxicological concern. In males, absolute and relative liver weights were reduced; however, there were no corroborating histological changes indicative of toxicity. Likewise, in males, relative adrenal weights were increased at all doses. This is likely do to opioid-induced increases in corticosterone. There were no histological changes in the adrenal gland. Neither tissue was altered in the female rats. However, oxymorphone treatment was associated with decreased uterus weights and increased ovary weights. These changes are likely due to opioid-induced alterations in the estrus cycle.

In the 13-week dog study, ECG data was obtained at week 12 of dosing, 2 hours after drug administration. All electrocardiograms were within normal limits. Microscopic histology detected biliary hyperplasia in 2 of 8 high dose animals (one male and one female). The bile ducts were normal in appearance and were not evident in any of the recovery animals, suggesting that this was an adaptive change.

Genetic toxicology: A standard battery of genetic toxicology studies was completed for oxymorphone HCl. Oxymorphone HCl tested negative in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of 79.1, 211, 632, 1897 and 5270 µg/plate. Oxymorphone HCl also tested negative for the induction of structural and numerical chromosome aberrations in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

Oxymorphone HCl, however, tested positive in the *in vivo* mouse and rat micronucleus assay. Kinetochore analysis indicated that in the mouse, the DNA damage is due to chromosomal breakage rather than loss of the entire chromosome.

[redacted] are impurities in the drug substance that contain a structural alert for mutagenicity. A minimal genetic toxicology screen was completed by the Mallinckrodt (DMF holder) for each of these isolated impurities. All [redacted] compounds tested negative as a mutagen in the *in vitro* bacterial reverse mutation assay. [redacted] was also negative in the in vitro

chromosomal aberrations assay using CHO cells. In contrast, [redacted] tested positive in the *in vitro* chromosomal aberrations assay using CHO cells. As such, these impurities are considered to be clastogenic.

Carcinogenicity: Carcinogenicity assessment for oxymorphone HCl in the mouse and rat were submitted with the NDAs. The studies were determined to be adequate by the Executive Carcinogenicity Assessment Committee (eCAC). The eCAC concurred with the Sponsor's assessment that there was no clear evidence of treatment-related tumor findings in either the mouse or the rat model.

Reproductive toxicology: Reproductive toxicology studies were completed in support of the oxymorphone hydrochloride IR and ER NDAs. The standard battery has been completed. In the segment I study in rats (fertility and embryonic development), oxymorphone was administered to male rats for 28 days prior to mating and continued throughout mating until one day prior to euthanasia. Female rats were treated for a total of 14 days prior to mating, throughout mating and through gestation day 7. The results indicated that reproductive performance in males and females was not altered by oxymorphone treatment under the conditions tested. However, mean estrus cycle length was slightly but significantly increased in the 25 mg/kg/day group. In addition, early embryonic development was significantly altered by oxymorphone treatment. Specifically, the mean number of viable embryos and the mean number of implantation sites were reduced by 14% in the 10 and 25 mg/kg/day group. The mean number of corpora lutea was significantly reduced only in the high dose group (25 mg/kg/day). Overall, due to parental systemic toxicity, the NOAEL for parental toxicity was < 5 mg/kg/day. The NOAEL for reproductive performance in males was > 25 mg/kg/day. The NOAEL for reproductive performance in females was 5 mg/kg/day due to an increase in estrus cycle length.

Segment II (embryo fetal development) studies were completed in both the rat and the rabbit models. Female rats were treated with oxymorphone (5, 10 and 25 mg/kg/day) from gestation day 6-17 in the definitive segment II study. Clinical signs were evident in all treatment groups and were consistent with a high dose opioid and included CNS behavior such as Straub tail, rocking and lurching, hypoactivity and exophthalmus. There was a dose-related and time-related decrease in body weight and food consumption in all dose groups. A NOAEL for maternal toxicity was not established and should be considered to be < 5 mg/kg/day. There was a slight but significant decrease in the mean fetal weights in the mid-dose and high-dose animals (5-6%) compared to control animals. There were no significant malformations (external, soft tissue or skeletal) between treatment groups, indicating that oxymorphone was not teratogenic under the conditions tested. There was a slight increase in the incidence of fetuses with variations (fetuses with unossified pubis, accessory skull bone(s), 27 presacral vertebra and bent ribs, however, these changes were not statistically significant and/or were within the historical control range. Overall the results suggest that the NOAEL for maternal toxicity was < 5 mg/kg based on findings consistent with exaggerated pharmacology associated with the opioid class of compounds. Developmental toxicity was noted at both the mid-dose and

the high-dose groups based upon decreased mean fetal body weights. Therefore the NOAEL for developmental toxicity was 5 mg/kg/day (in agreement with the sponsor).

In the definitive segment II (embryo fetal development) study in the rabbit, female rabbits were treated with oxymorphone from gestation day 7 through gestation day 20. Clinical signs such as hypoactivity and decreased defecation were noted in all treatment groups in a dose-related manner. The mid-dose and high-dose group also demonstrated a few incidences of lacrimation, excessive chewing, exophthalmos and mydriasis. Maternal body weights were decreased in a dose-related manner at all doses tested during the first 3 days of treatment. Body weights of dams treated with 25 or 50 mg/kg/day remained reduced throughout the treatment period, while animals in the low dose group did not demonstrate an overall body weight gain during the treatment period. Food consumption followed a similar pattern. There was a significant decrease in the mean fetal weight of male pups (↓16%) born to the high-dose dams, but this decrease was not noted in the females (↓7%) of the combined fetuses (↓10%). There were no clear increases in the incidence of fetal malformations or variations. Some offspring malformations were noted (mandibular micrognathia, aglossia, lobular agenesis of the lung, sterneabrae fused or forked rib), however, these were either not statistically significant or were within the range of historical controls. The NOAEL for maternal toxicity was < 10 mg/kg based upon the increased incidence of hypoactivity, decreased defecation, body weight and food consumption. Based upon the presence of maternal toxicity, the study is considered to be valid. The NOAEL for fetal development was 25 mg/kg/day based upon a decrease in fetal body weights in males at the high dose (in agreement with the sponsor).

In a segment III (peri- and post-natal development) study in rats, female rats (F_0) were treated with oxymorphone (0, 1, 5, 10 or 25 mg/kg/day) from gestation day 6 to lactation day 20. The results indicated that there were a significantly greater number of gravid females in the high dose group with total litter loss (13/25). Animals that died prior to scheduled necropsy exhibited typical clinical signs produced by high doses of opioids. Clinical signs in surviving F_0 females were noted 1 hour post-dose in all treatment groups, including Straub tail and exophthalmos. Animals in the 5, 10 and 25 mg/kg/day group demonstrated hyperactivity as well as abnormal posture. Higher doses produced whole body tetany, hypoactivity, rales, piloerection and salivation. Mean body weight losses in the F_0 females was significantly reduced early during treatment with the higher doses, however, as the treatment time progressed, a significant reduction in mean body weights were noted in all treatment groups. These effects were noted both during gestation and lactation. In surviving F_0 females, there were not differences between the number of pups born and the number of implantation sites between groups. Mean litter size in the F_1 generation born to the high dose F_0 females was 18% lower than controls (this reduction was not statistically significant, but is likely related to the drug treatment. Post-natal survival of the F_1 pus was reduced in the 25 mg/kg/day treatment group. Offspring mean body weights during the pre-weaning period were significantly reduced in the 25 mg/kg/day treatment groups compared to controls, whereas pups in the low dose group 1 mg/kg/day demonstrated a significantly higher mean offspring weight compared to controls. There were no treatment-related findings on PND 21 pups not selected for further study at necropsy. Developmental landmarks in the F_1 males indicated that

balanopreputial separation in males from the 25 mg/kg/day group was delayed compared to controls, whereas males in the 1 mg/k/day group reached balanopreputial separation earlier than controls. There were no differences in the mean day of acquisition of vaginal patency in F_1 females between treatment groups. There were no treatment-related effects of oxymorphone in behavioral evaluation (acoustic startle, locomotor and Biel Maze Swimming Trials). Reproductive performance in the F_1 generation was not altered by F_0 generation oxymorphone treatment at any dose level tested. Body weights in the F_1 generation during the post-weaning period were significantly reduced in the 25 mg/kg/day groups on PND28, 35, 42, 49, 56, 62 and 70. Mean body weights were reduced in the 10 mg/kg/day groups on PND 49, 56, 63 and 70. Mean body weights in males in the 5 mg/kg/day group were also significantly reduced compared to controls on PND 63. There were no findings in the F_2 fetuses which could be attributed to F_0 maternal treatment with oxymorphone.

Special toxicology: Acute and subacute toxicology studies were conducted with [redacted] a degradation product found exclusively in intravenous preparations of oxymorphone. The studies were designed to determine if the presence of [redacted] altered the toxicity profile of oxymorphone. The results suggested that overall, the [redacted] did not alter the toxicity of oxymorphone. However, there did appear to be an increase in the incidence of thymic necrosis in mice. The sponsor concludes that as [redacted] is a degradation product found exclusively in intravenous preparations of oxymorphone, there are no safety concerns for orally administered dosage forms. However, the drug product appears to contain [redacted] at levels that exceed ICH specifications for qualification.

The potential for dermal sensitization in guinea pigs was assessed via a modified Magnusson-Kligman Guinea Pig Maximization Test. The results suggested that oxymorphone is a dermal sensitizer under the conditions of the test.

Skin irritation studies in rabbits were also conducted to determine if oxymorphone produced skin irritation when administered via parenteral routes including intravenous, subcutaneous, and intramuscular. In these studies 2 rabbits were administered 10 mg (about 4 mg/kg) of oxymorphone by the appropriate route. One animal was sacrificed 24 hours post dose and the other animal was sacrificed 7 days post dose. Histological examination of the injection sites failed to detect any oxymorphone-related irritation.

Study 51062 examined the hemocompatibility and hemolytic potential of oxymorphone. The results indicated that serum is compatible with oxymorphone at 10 mg/mL. The results indicated that a ratio of 1:3 (oxymorphone:plasma) was compatible, but anything greater resulted in precipitation. Regarding hemolytic potential, oxymorphone blood ratios of 1:1, 1:2, and 1:3 did not result in hemolysis.

2.6.6.2 Single-dose toxicity

The following acute and subacute toxicology studies were previously reviewed by Dr. Kathleen Haberny. The following summaries are reproduced verbatim from that review.

Single intravenous exposure in mice: In the single dose intravenous toxicity study in mice, [redacted] of the oxymorphone doses administered at up to 4 mg/kg IV), did not significantly alter mortality and toxicity induced by acute oxymorphone at doses up to 200 mg/kg IV. The highest non-lethal oxymorphone doses in male and female mice were 100 mg/kg without [redacted] and 30 mg/kg in combination with [redacted]. However, mortality was increased in the lower dose by 1 of 10 males and 2 of the 10 females administered oxymorphone + [redacted]. The minimal lethal doses were 200 mg/kg/d in the absence of [redacted], and 100 mg/kg/d oxymorphone in combination with [redacted] in both males and females. The causes of death were not established. Toxicity was measured by mortality, clinical signs, changes in body weights and ophthalmoscopic examination. Necropsy was not performed. Clinical signs characteristic of mu opioid effects were observed at oxymorphone doses at and above 3 mg/kg IV, and included ataxia, increased motor activity and Straub tail. At higher doses, tremors, gasping, loss of righting reflex and deaths were also observed. Corneal opacities were attributed to oxymorphone-induced loss of blinking reflex. There appeared to be an increase in some clinical signs, with [redacted] administration, although these changes were not consistently observed across doses of oxymorphone or across sexes.

Single intravenous exposure in Sprague-Dawley rats: There were no increases in oxymorphone-induced mortality, clinical signs, ophthalmic abnormalities and body weight changes at up to 100 mg/kg IV when combined with [redacted] of the oxymorphone doses at up to 2 mg/kg). The highest non-lethal oxymorphone dose was 30 mg/kg/d in the absence of, and in combination with [redacted] in both male and female rats. The minimal lethal dose with and without [redacted] in both males and females was 100 mg/kg/d. Clinical signs were consistent with known mu-opioid effects and included cloudy eyes, loss of righting reflex, red urine, lacrimation, hair loss, and noisy respiration at doses of 0.3 mg/kg IV and above. At the highest dose (100 mg/kg IV), convulsions, twitching and deaths were observed. Ophthalmic abnormalities were attributed to mu-opioid related depression of the blinking reflex.

Subacute intravenous exposure (2 weeks) in mice: The doses of oxymorphone administered to mice in this study (0.3, 3.0 and 30.0 mg/kg/d) represent approximately 0.5-45 times the human dose (3 mg/d, 0.05 mg/kg IV in a 60 kg patient) on a body surface area basis. There were no treatment-related deaths, differences in body weight changes, or ophthalmic abnormalities in mice administered oxymorphone with or without [redacted] for 14 days. Oxymorphone alone and in combination with [redacted] was associated with increased or decreased motor activity and Straub tail. Motor activity was increased to a greater extent in male mice that received mid- and high-dose oxymorphone with [redacted] than without the degradation product. There were no other differences in the severity of effects of oxymorphone when combined with [redacted] Increased BUN and decreased calcium were

observed in high dose males, but not females co-exposed to [redacted] and these effects were attributed to stress and hyperexcitability. Stress-related thymic necrosis was observed in males and females in the mid- and high-dose oxymorphone + [redacted] groups.

Subacute intravenous exposure (2 weeks) in rats: The oxymorphone doses administered in this study (0.3, 0.9, 3.0 and 30.0 mg/kg/d) represented approximately 1-100 times the human dose (3 mg/d IV, 0.05 mg/kg in a 60 kg patient) on a mg/m^2 basis. There was no effect of [redacted] co-administration when given a[redacted] on oxymorphone-induced mortality, clinical signs, body weight, food consumption, and ophthalmologic toxicity. Oxymorphone-related clinical signs were catalepsy, decreased motor activity, cage biting, salivation, noisy respiration, and cloudy eyes. The cloudy eyes, identified as corneal opacities are attributed to mu-opioid-induced decreased blinking reflex. Hematologic, serum chemistry, urinalysis, and organ weight alterations, gross pathology and histopathology at necropsy were attributed to oxymorphone administration and not related to co-treatment with [redacted]. The oxymorphone-induced changes included elevated serum aspartate aminotransferase activity at 0.9 mg/kg/day and above, reduced serum protein concentrations (male rats at 0.9 mg/kg/d and above), decreased mean serum triglyceride concentrations (male rats only at 30 mg/kg/d), and blood in urine at 0.9 mg/kg/day. Histopathology examination showed corneal mineralization and degeneration of the corneal epithelium at 0.9 mg/kg/day with and without [redacted] resulting from decreased blinking reflex. Drug related atrophy of the uterine horns, reduced thickness of the vaginal mucosa, and decreased thymus weight were observed.

CONCLUSIONS

[redacted] of the oxymorphone doses did not potentiate the acute and subacute (14-day) intravenous toxicity of oxymorphone in mice and rats, with the exception that [redacted] appeared to potentiate oxymorphone-induced necrosis of the thymus in mice. The highest doses tested in the mice and rats were approximately 45 and 100 times respectively the human dose of 3 mg/day on a body surface area basis. The results of these studies suggest that daily exposure, for up to two weeks, to [redacted] in oxymorphone hydrochloride solution for intravenous administration, at therapeutic doses in humans, is reasonably safe from a pharmacology and toxicology viewpoint.

2.6.6.3 Repeat-dose toxicity

Thirteen week repeat-dose toxicology studies were conducted in rats, mice and dogs. In addition, an oral dose-range finding study was conducted in dogs to establish the definitive dosing for the 13-week oral toxicology study in dogs. Only the 13-week oral toxicology study will be reviewed for this NDA review. The 13-week repeat-dose studies

in mice and rats have been previously reviewed by Dr. Kathleen Haberny (January 30, 2002). Her report is basically reproduced verbatim below (fit to the NDA format).

Study title: A 13-Week Oral Study of Oxymorphone Hydrochloride in Rats

Key study findings: Sprague-Dawley rats were treated with gradually escalating doses of oxymorphone (0, 10, 25, 50, 75 mg/kg/day from Day 14-91) via oral gavage. The following key findings were obtained:

1. Possible treatment-related death in a female rat given 75 mg/kg/d on treatment day 48.
2. Subacute liver inflammation, dark red lungs with hemorrhage, thymus hemorrhage observed in female given 75 mg/kg/d that died on day 48.
3. Treatment-related clinical signs typical of opioid-induced effects: GI, behavioral and CNS in nature including self-mutilation.
4. Body weights and body weight gains were significantly decreased in male rats at all doses (10-75 mg/kg/d), to 78%-66% of the control male weight gain; no treatment-related effects on weight or weight gains in female rats.
5. Decreased food consumption in male rats at all doses.
6. Hematology changes indicating mild anemia (↓6-9%).
7. Treatment-related decrease in mean total protein, albumin, calcium, and globulin in male rats, treatment-related decrease in cholesterol in female rats
8. Toxicokinetic evaluation demonstrated dose-related systemic exposure to oxymorphone, T_{max} generally 0.5-1 hour, AUC (0-24h) doubled from day 0 to day 88 in all dose groups, C_{max} and AUC dose-proportional.
9. The MTD was identified as 10 mg/kg/d in the males and 25 mg/kg/d in the females.
10. Based upon clinical signs, decreased body weights and food consumption in males a NOAEL was not obtained in this study (< 10 mg/kg). Although female rats were not as affected by oxymorphone as male rats, a NOAEL for female rats is also below 10 mg/kg/day based upon adverse clinical signs.

Study no.:	[redacted] 411011
Volume #, and page #:	Electronic Document Room
Conducting laboratory and location:	[redacted]
Date of study initiation:	January 28, 2001
GLP compliance:	Yes
QA report:	yes (X) no ( )
Drug, lot #, and % purity:	Oxymorphone, Lot 99193, [redacted] purity

Methods

Doses: The doses were administered in a graduated manner as follows:

Oxymorphone HCl (mg/kg/d)			
Target Dose	Days 0-6	Days 7-13	Days 14-91
0	0	0	0
10	10	10	10
25	25	25	25
50	25	50	50
75	25	50	75

Species/strain: [redacted]CD®(SD)IGS BR rats[redacted]

Number/sex/group or time point (main study): 10/sex/dose group

Route, formulation, volume, and infusion rate: Oral gavage at 10 ml/kg, as a single daily dose

Satellite groups used for toxicokinetics or recovery: 12/sex/dose group

Age: 6 weeks at initiation of dosing

Weight (non-rodents only): 181-247 g males, 141-193 g females

Unique study design or methodology (if any): Dosing was increased over the duration of the study to overcome tolerance and establish adequate toxicity.

Observation times and results

Mortality: Animals were observed for mortality pretest and twice daily. The following deaths were observed.* Only one death, a high-dose female on day 48, is considered to be drug-related.

Dose group (mg/kg/d)	No. of Deaths (dose at time of death)	Study Day	Probable Cause#
0	1 tk M (0 mg/kg/d)	84	Euthanized, urinary obstruction
10	1 tk F (10 mg/kg/d)	42	Euthanized, urinary obstruction
	1 tk M (10 mg/kg/d)	78	Undetermined
25	1 F (25 mg/kg/d)	5	Trapped in food jar, suffocation
50	1 tk M (50 mg/kg/d)	7	Trapped in food jar, suffocation
75	1M (25 mg/kg/d)	6	Trapped in food jar, suffocation
	1 tk M (25 mg/kg/d)	5	Trapped in food jar, suffocation
	1 tk F (25 mg/kg/d)	4	Trapped in food jar, suffocation
	1F (75 mg/kg/d)	48	Possibly Drug Related
	2 tk M (75 mg/kg/d)	14, 21	Mechanical injury during blood collection

*M: male; F: female; tk: toxicokinetic group animal

#Food jars removed after day 7, replaced with solid pellet food from hanging feeders

Clinical signs: Clinical signs were recorded both pretest and twice daily. Clinical signs were observed in all oxymorphone treated groups. The observations were primarily related to gastrointestinal, behavioral and central nervous system changes. Soft feces and vocalization upon handling were observed at a higher incidence at the time of dosing. The incidence of the remaining observed clinical signs was highest at 1 hour after dosing, and higher after the dose adjustments, during weeks 3-13. Inspection of the individual

animal data revealed that the clinical signs persisted throughout the dosing period to week 13. The clinical signs observed during study days 14-91 are presented in the following tables:

Incidence of Clinical Signs at Time of Dosing (Total Occurrence/# Animals)

	Males					Females				
Dose (mg/kg/d)	**0**	**10**	**25**	**50**	**75**	**0**	**10**	**25**	**50**	**75**
Number of Animals	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**9**	**10**	**10**
Soft Feces	0/0	3/3	2/1	12/4	16/5	0/0	0/0	2/2	6/4	9/6
Vocalization upon Handling	0/0	6/2	8/3	13/4	21/4	0/0	8/4	1/1	25/4	3/3
Chewing on Cage Bottom	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0
Hyperactive	0/0	0/0	0/0	2/2	0/0	2/1	0/0	0/0	1/1	0/0
Hyperactive to touch	0/0	1/1	1/1	4/2	5/3	0/0	0/0	0/0	6/1	2/2

Incidence of Clinical Signs at 1-Hour Past Dosing (Total Occurrence/# Animals)

	Males					Females				
Dose (mg/kg/d)	**0**	**10**	**25**	**50**	**75**	**0**	**10**	**25**	**50**	**75**
Number of Animals	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**9**	**10**	**10**
Soft Feces	0/0	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Vocalization upon Handling	0/0	1/1	0/0	0/0	5/2	0/0	1/1	0/0	8/1	0/0
Abnormal Stance	0/0	10/4	13/8	28/9	33/9	0/0	12/5	14/6	25/7	15/6
Excessive Chewing	0/0	20/5	41/7	38/10	44/8	0/0	31/9	31/8	43/9	30/10
Chewing on Forelimb(s)	0/0	45/7	59/10	18/7	22/7	1/1	57/10	67/7	33/8	34/7
Chewing on Cage Bottom	0/0	13/4	32/7	38/8	29/8	0/0	16/6	16/7	48/9	32/8
Chewing on Hindlimb(s)	0/0	0/0	0/0	0/0	0/0	0/0	1/1	1/1	1/1	0/0
Chewing on Tail	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Hyperactive	0/0	23/7	8/4	14/5	21/6	0/0	25/7	14/3	25/8	20/8
Hyperactive to Touch	0/0	0/0	1/1	1/1	6/3	0/0	1/1	0/0	2/1	4/4
Circling	0/0	1/1	0/0	1/1	1/1	0/0	3/2	1/1	0/0	0/0
Licking Cage	0/0	2/2	5/5	25/5	7/4	0/0	0/0	3/2	10/5	11/5
Excessive Grooming	0/0	2/1	1/1	1/1	0/0	1/1	5/3	4/3	1/1	2/2

Body weights: Body weights were recorded both pretest and weekly. The mean body weights and body weight gains at the end of the study are presented in the following table:

Body Weight Observations

	0 mg/kg/d	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d	75 mg/kg/d
			Males		
Weight in g, mean ± SD wk 13 (%control)	553 ± 80.6	481 ± 44.0* (-13%)	446 ± 25.3** (-19%)	440 ± 46.5** (-20%)	438 ± 33.9** (-21%)
Total Body weight gain in g, mean ± SD, wk 0-13 (%control)	338 ± 69.2	265 ± 40.6** (-22%)	230 ± 30.5 (-32%)	223 ± 52.3** (-34%)	225 ± 33.0** (-34%)
% Control bodyweight gain	100	78	68	66	66
			Females		
Weight in g, mean ± SD wk 13 (%control)	307 ± 30.0	305 ± 38.1 (-1%)	288 ± 13.4 (-6%)	304 ± 23.7 (-1%)	289 ± 17.7 (-6%)
Body weight gain in g, mean ± SD wk 0-13 (%control)	136 ± 23.4	134 ± 24.4 (-2%)	118 ± 10.3 (-13%)	133 ± 17.4 (-2%)	118 ± 8.7 (-13%)
% Control bodyweight gain	100	98	87	98	87

*p<0.05; **p<0.01

Body weight gains were decreased by 22%, 32%, 34%, and 34% compared to control body weight gains in the male rats given 10, 25, 50 and 75 mg/kg/d oxymorphone,

respectively, at the end of the study. The mean body weights and body weight gains were comparable to control body weights in the female rats in all groups at the end of the study.

Food consumption: Food consumption was recorded both pretest and weekly. Food consumption was lower in the male rats at all doses, during dosing periods from weeks 0-1, 2-9, and 12-13. There were no treatment-related effects on food consumption in the female rats. The results of food consumption measurements in the male rats are presented in the following table:

Food Consumption (g/animal/d) in Male Rats Given Oral Oxymorphone HCl for 13 Weeks

	0 mg/kg/d	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d	75 mg/kg/d
Mean Food Consumption Baseline	24 ± 2.4	24 ± 1.8	24 ± 1.5	24 ± 1.5	23 ± 1.5
Mean Food Consumption Week 13	33 ± 5.2	30 ± 4.6	29 ± 2.1	27 ± 6.7	28 ± 3.7
Difference from Baseline (Week 13) (%)	+9 (137%)	+6 (125%)	+5 (121%)	+3 (112%)	+5 (122%)
Difference from Controls (Week 13) (%)	0	-9%	-12%	-18%	-15%

Ophthalmoscopy: Ocular exams were conducted both pretest and once during week 12. There were no treatment-related effects.

EKG: Not done.

Hematology: Blood samples were collected during study week 13. Minor changes in red blood cells and red blood cell indices along with larger increases in reticulocytes were observed in all groups of male rats that received oxymorphone, and in the female rat groups that received 50 and 75 mg/kg/day oxymorphone. MCV values were slightly increased at all doses in the male rats, and in the female rats that received 50 and 75 mg/kg/day. The hematology effects suggest mild anemia. The hematology parameters with statistically significant changes are presented in the following table.

Hematology Values: Week 13 (Means ± SD)

	0 mg/kg/d	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d	75 mg/kg/d

Red Cells (mil/uL) (%control) Males	7.95 ± 0.445	7.44 ± 0.671 (-6%)	7.50 ± 0.204 (-6%)	7.32 ± 0.344* (-8%)	7.26 ± 0.720* (-9%)
MCV (fL) (%control) Males	50.6 ± 1.28	53.7 ± 1.79** (+6%)	54.2 ± 1.39** (+7%)	54.1 ± 1.12** (+7%)	54.6 ± 1.97** (+7%)
Females	52.8 ± 1.45	53.9 ± 1.53 (+2%)	54.0 ± 1.61 (+2%)	55.7 ± 3.04** (+5%)	55.1 ± 1.89 (+5%)
MCH (uug) (%control) Males	18.3 ± 0.52	19.7 ± 0.68** (+8%)	19.8 ± 0.55** (+8%)	19.7 ± 0.51** (+8%)	19.9 ± 0.71** (+9%)
Reticulocyte (%) (%control) Males	0.5 ± 0.16	0.8 ± 0.21 (+60%)	1.2 ± 0.16** (+140%)	2.0 ± 0.57** (+300%)	1.4 ± 0.31** (+180%)
Females	1.5 ± 0.25	1.2 ± 0.20* (-20%)	1.0 ± 0.21** (-33%)	1.6 ± 0.24 (+7%)	2.6 ± 0.23** (+73%)
Retic Absolute (mil/uL) (%control) Males	0.039±0.0123	0.058±0.0141 (+49%)	0.087±0.0122** (+123%)	0.149±0.0427** (+280%)	0.104±0.0214** (+167%)
Females	0.108±0.0232	0.088±0.0161 (-29%)	0.073±0.0192** (-32%)	0.109±0.0186 (+1%)	0.182±0.0151** (+68%)

*p<0.05; **p<0.01

Clinical chemistry: Blood samples were obtained during study week 13. Minor treatment-related decreases in mean total protein, albumin, calcium, and globulin levels were observed in the male rats. These parameters were also decreased in the female rats, but the decreases were not statistically significant. Cholesterol was decreased in the female rats given 25, 50 and 75 mg/kg/day oxymorphone, although the decrease was not dose-related. The changes in clinical chemistry values are presented in the following table:

Clinical Chemistry Values: Week 13 (Means ± SD)

	0 mg/kg/d	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d	75 mg/kg/d
Albumin (g/dL) Males	3.9 ± 0.19	3.6 ± 0.26* (-8%)	3.6 ± 0.16* (-8%)	3.5 ± 0.10** (-10%)	3.5 ± 0.23** (-10%)
Females	4.3 ± 0.62	4.3 ± 0.24 No change	4.2 ± 0.22 (-2%)	4.0 ± 0.31 (-7%)	3.9 ± 0.46 (-9%)
Total Protein (g/dL) Males	6.6 ± 0.21	6.1 ± 0.27** (-8%)	5.9 ± 0.29** (-11%)	5.8 ± 0.25** (-12%)	6.0 ± 0.50** (-9%)
Females	7.0 ± 0.69	6.8 ± 0.44 (-3%)	6.6 ± 0.26 (-6%)	6.5 ± 0.37 (-7%)	6.5 ± 0.51 (-7%)
Globulin (g/dL) Males	2.7 ± 0.14	2.5 ± 0.18 (-7%)	2.4 ± 0.26** (-11%)	2.3 ± 0.27** (-15%)	2.5 ± 0.31 (-7%)
Females	2.6 ± 0.45	2.4 ± 0.22 (-8%)	2.4 ± 0.14 (-8%)	2.5 ± 0.22 (-4%)	2.6 ± 0.37 no change
Calcium (mg/dL) Males	10.7 ± 0.35	10.3 ± 0.31* (-4%)	9.9 ± 0.47** (-8%)	10.0 ± 0.48** (-7%)	10.2 ± 0.40* (-5%)
Females	10.8 ± 0.58	10.7 ± 0.42 (-1%)	10.3 ± 0.28 (-5%)	10.3 ± 0.59 (-5%)	10.5 ± 0.70 (--3%)
Cholesterol (mg/dL)					
Females	85 ± 24.6	71 ± 10.0 (-16%)	54 ± 10.1** (-36%)	63 ± 11.6* (-26%)	60 ± 18.3** (-30%)

*p<0.05; **p<0.01

Urinalysis: Urine was collected during study week 13. Urinary pH was increased in the female rats to 6.3, 6.5 and 6.4 at 10, 50 and 75 mg/kg/day, respectively, compared to the control value (5.7). However, the mean pH in the control group was abnormally low.

Gross pathology: All animals found dead, euthanized *in extremis* or at scheduled necropsy (week 13). The macroscopic findings in the animals that died and were euthanized *in extremis* included red fluid contents in duodenum, white areas on liver, raised red area on lung, firm thymus, dark red lungs, clear fluid contents in the pericardial sac, dilated renal pelvis, distended ureter, reddened urethra, enlarged lymph nodes, calculi in the urinary bladder, reddened mucosa of the urinary bladder and thickened urinary bladder. Subacute liver inflammation, dark red lungs with hemorrhage, thymus hemorrhage observed in female given 75 mg/kg/d that died on day 48. There were no treatment-related effects in the macroscopic examination in the rats that were sacrificed at scheduled necropsy.

Organ weights (specify organs weighed if not in histopathology table): The organ weight changes were without relationship to dose and without correlating morphological findings, and were attributed to the changes in final total body weights.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
See histopathology summary table.

Urinary tract calculi were observed in 2 rats that were euthanized *in extremis*. Granulomatous inflammation in the lungs was observed in male rats in all treatment groups and in the females that were given 25, 50, and 75 mg/kg/d oxymorphone, without dose-related differences in severity or incidence. The inflammation was attributed to aspiration of test article. In the high-dose female that died on day 48, subacute liver inflammation, dark red lungs with hemorrhage, and thymus hemorrhage were observed.

Toxicokinetics: 0.5 ml blood collected from 3 rats/sex/group/time point at 0.5, 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours after dosing on study days 0 (10 and 25 mg/kg/d groups), 7 (50 mg/kg/d group), 14 (75 mg/kg/d group), and 88 (all groups). The C_{max} and AUC values increased proportionally to dose, were higher on day 88 than on day 0, and were similar in males and females.

The results of the toxicokinetic evaluation are presented in the following table:

Oxymorphone Toxicokinetic Parameters Following Oral Administration for 89 Days in Rats*

Dose (mg/kg/d)	Study Day	Sex	Cmax (ng/ml)	Tmax (h)	$AUC_{0\text{-}24h}$ (ng.h/ml)
10	0	M	8.34	0.5	47.4 (50.0)[a]
		F	6.68	0.5	41.0 (44.2)[a]
10	88	M	16.1	1	106
		F	18.1	1	101
25	0	M	13.2	0.5	98.2 (130)[a]
		F	9.24	4	113 (152)[a]
25	88	M	46.2	0.5	262
		F	94.9	0.5	367
50	0	M	70.7	2	356
		F	90	1	306
50	88	M	168	0.5	683
		F	156	0.5	656
75	0	M	236	1	703
		F	175	0.5	700
75	88	M	271	0.5	1093
		F	556	0.5	1428

*M:male; F:female

[a]Estimated AUC zero to infinity using terminal half-life of 8.9 h (Kel = 0.0779)

Other: None

Study title: A 13-Week Oral Study of Oxymorphone Hydrochloride in Mice

Key study findings:

1. Treatment-related deaths at 300 mg/kg/d (3M and 1F) and 600 mg/kg/d (1M and 1F).
2. Necroscopic observations in the animals that died: distended stomach and duodenum (1 M at 600); in the 300 mg/kg/d animals that died: enlarged vas deferens and prolapsed penis (all M), swollen green preputial gland (1M), distended/thickened urinary bladder (1M), distended stomach and urinary bladder (1F), impacted caecum (1F), distended gallbladder (1F)
3. Treatment-related clinical signs typical of opioid-induced in rodents and were primarily CNS-related
4. Body weights decreased in all males (-5% to –14% without dose-relationship), body weight gains decreased in all males (–86%, -28%, -88%, and –107% at 300, 600, 50 and 75 mg/kg/d respectively); body weights decreased –6% to –10% in treated females, body weight gains decreased –39% to –51% in all treated females
5. Food consumption decreased in males and females during weeks 1-2 and 6-7
6. Toxicokinetic evaluation demonstrated dose-related exposure to oxymorphone; C_{max} and AUC dose proportional, T_{max} 0.5-1 hour
7. MTD less than 300 mg/kg/day due to deaths observed at doses of 300 mg/kg/day or greater.

Study no.: [redacted]411012
Volume #, and page #: Electronic Document Room
Conducting laboratory and location: [redacted]

[redacted]

Date of study initiation: January 22, 2001
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: Oxymorphone, Lot # 99193, [redacted] purity

Methods

Doses: The doses were administered in a graduated manner as follows:

Oxymorphone HCl (mg/kg/d)						
Target Dose	Days 0-6	Days 7-13	Days 14-41	Days 42-49	Days 50-62	Days 63-91
0	0	0	0	0	0	0
300	10	10	10	150	300	300
600	25	25	25	25	25	600
50	25	50	50	50	50	50
75	25	50	75	75	75	75

The doses were adjusted for body weights weekly, throughout the study.

Species/strain: [redacted] CD-1®(ICR)BR mice
Number/sex/group or time point (main study): 10/sex/group
Route, formulation, volume, and infusion rate: Oral by gavage at 10 ml/kg, once daily for 13 weeks
Satellite groups used for toxicokinetics or recovery: 3/sex/dose/timepoint
Age: 9 weeks
Weight (non-rodents only): 27.0-34.6 g males and 21.3-27.5 g females
Unique study design or methodology (if any):

Observation times and results

Mortality: Mice were monitored both pretest and twice daily during the study. Treatment-related deaths were observed in 3 males (2 found dead in weeks 9 and 12, 1 euthanized week 9) and 1 female (found dead week 9) at 300 mg/kg/day, and in 1 male (found dead week 9) and 1 female (found dead week 9) at 600 mg/kg/day. The deaths occurred after the last increase in dose to the 300 and 600 mg/kg/d levels.

Clinical signs: Clinical signs were recorded pretest and twice daily.

Incidence of Treatment-Related Clinical Signs: Time of Dosing (Total Occurrence/# Mice)

	Males					Females				
Dose (mg/kg/d)	0	10/ 150/ 300	25/ 600	50	75	0	10/ 150/ 300	25/ 600	50	75
Number of Animals	10	10	10	10	10	9	9	9	10	10
Swollen Abdomen	0/0	1/1	6/3	0/0	0/0	0/0	1/1	0/0	0/0	0/0
Unkempt Appearance	0/0	143/5	69/4	32/2	0/0	0/0	0/0	17/3	0/0	0/0
Abnormal Stance	0/0	0/0	4/3	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Hypoactivity	0/0	3/3	3/2	0/0	0/0	0/0	1/1	1/1	0/0	0/0

Straub Tail	0/0	0/0	14/6	0/0	0/0	0/0	0/0	4/3	0/0	0/0
Rigid Muscle Tone	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Tremors	0/0	0/0	1/1	0/0	0/0	0/0	1/1	1/1	0/0	0/0

Incidence of Treatmemt-Related Clinical Signs: 1-H Past Dosing (Total Occurrence/# Mice)

	Males					Females				
Dose (mg/kg/d)	**0**	**10/ 150/ 300**	**25/ 600**	**50**	**75**	**0**	**10/ 150/ 300**	**25/ 600**	**50**	**75**
Number of Animals	**10**	**10**	**10**	**10**	**10**	**9**	**9**	**9**	**10**	**10**
Hypothermia	0/0	2/2	1/1	0/0	0/0	0/0	1/1	0/0	0/0	0/0
Swollen Abdomen	0/0	1/1	8/4	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Unkempt Appearance	0/0	129/5	67/6	33/2	0/0	0/0	3/3	15/3	0/0	0/0
Abnormal Stance	0/0	0/0	9/4	0/0	0/0	0/0	1/1	5/4	0/0	0/0
Hyperactivity	0/0	6/3	9/5	1/1	0/0	0/0	2/2	11/7	3/1	0/0
Hypoactivity	0/0	4/4	4/3	0/0	0/0	0/0	1/1	5/4	1/1	3/3
Straub Tail	0/0	45/8	81/10	41/9	53/8	1/1	46/7	50/9	57/6	50/8
Rigid Muscle Tone	0/0	03/3	7/4	0/0	0/0	0/0	0/0	3/3	0/0	1/1
Tremors	0/0	1/1	3/2	0/0	0/0	0/0	2/2	1/1	0/0	0/0

Body weights: Body weights were recorded pretest and weekly thereafter. The mean body weights and body weight gains at the end of the study are presented in the following table. Although body weight gains were decreased by up to 107%, the overall changes in body weight compared to control animals (3-5 g) is not considered to be significant.

Body Weight Observations

	0 mg/kg/d	10/150/300 mg/kg/d	25/600 mg/kg/d	50 mg/kg/d	75 mg/kg/d
Males					
Weight (g, mean ± SD) wk 13	34.8 ± 3.19	30.5 ± 2.36*	33.0 ± 3.60	31.0 ± 1.63**	29.9 ± 2.16**
Percent control Weight	-	-12%	-5%	-11%	-14%
Total Body weight gain (g, mean ± SD) wk 0-13	4.3 ± 2.64	0.9 ± 1.60	3.1 ± 2.45	0.5 ± 2.41**	-0.3 ± 1.31
Difference in % Control bodyweight gain	100	-86%	-28%	-88%	-107%
Females					
Weight (g, mean ± SD) wk 13	30.0 ± 2.30	28.4 ± 1.47	27.5 ± 1.30	27.1 ± 1.98*	27.0 ± 2.23*
Percent Control Weight	-	-6%	-8%	-10%	-10%
Body weight gain (g, mean ± SD) wk 0-13	5.9 ± 1.11	3.6 ± 1.06*	2.9 ± 0.69	3.2 ± 1.81**	2.9 ± 1.70**
% Control bodyweight gain	100	-39%	-51%	-46%	-51%

*p<0.05; **p<0.01

Food consumption: Food consumption was recorded pretest and weekly. Statistically significant treatment-related decreases in food consumption were observed during weeks 1-2 and 6-7 only.

Changes in Food Consumption (g/animal/d) in Male Mice Given Oral Oxymorphone HCl for 13 Weeks

	0 mg/kg/d	10/150/300 mg/kg/d	25/600 mg/kg/d	50 mg/kg/d	75 mg/kg/d
Baseline Food Consumption	5.9 ± 1.02	5.9 ± 0.46	5.8 ± 0.52	6.8 ± 2.38	5.9 ± 0.70
Food Consumption Week 1-2	5.9 ± 1.47	4.6 ± 0.46**	4.3 ± 0.67**	4.7 ± 0.53**	4.4 ± 0.63**
Change from Baseline (%)	0	-22%	-26%	-31%	-25%

Difference from Control (%)	-	-22%	-27%	-20%	-25%
Food Consumption Week 6-7	5.7 ± 1.27	4.1 ± 0.35**	4.5 ± 0.60**	4.5 ± 0.43**	4.6 ± 0.49**
Change from Baseline (%)	-3%	-31%	-22%	-34%	-22%
Difference from Control (%)	-	-28%	-30%	-21%	-19%

*p<0.05; **p<0.01

Changes in Food Consumption (g/animal/d) in Female Mice Given Oral Oxymorphone HCl for 13 Weeks

	0 mg/kg/d	10/150/300 mg/kg/d	25/600 mg/kg/d	50 mg/kg/d	75 mg/kg/d
Baseline Food Consumption	5.4 ± 0.50	6.2 ± 2.03	7.5 ± 2.38**	5.4 ± 0.71	5.6 ± 0.41
Food Consumption Week 1-2	5.7 ± 1.05	5.7 ± 1.47	5.0 ± 1.26	4.2 ± 0.59*	4.3 ± 0.79*
Change from Baseline	+6%	-8%	-33%	-22%	-23%
Difference from Control	-	0	-12%	-26%	-25%
Food Consumption Week 6-7	6.2 ± 1.73	4.3 ± 0.32**	5.3 ± 1.86	4.6 ± 1.05*	4.6 ± 0.46*
Change from Baseline	+15%	-31%	-29%	-15%	-18%
Difference from Control	-	-31%	-15%	-26%	-26%

Ophthalmoscopy: Ocular exam was conducted both pretest and during study week 12. There were no treatment-related effects noted.

EKG: Not done.

Hematology: Blood samples were collected at the scheduled necropsy (study week 13). There were no treatment-related effects.

Clinical chemistry: Blood samples were collected at the scheduled necropsy (study week 13). There were no treatment-related effects.

Urinalysis: Not done.

Gross pathology: Gross pathological changes were recorded at the scheduled necropsy (study week 13). There were no treatment-related effects.

Necroscopic observations in the animals that died during administration of 600 mg/kg/d included distended stomach (1M) and duodenum (1 M). In the 300 mg/kg/d animals that died, enlarged vas deferens and prolapsed penis (all M), swollen green preputial gland (1M), distended/thickened urinary bladder (1M), distended stomach and urinary bladder (1F), impacted caecum (1F), and distended gallbladder (1F) were observed.

Organ weights (specify organs weighed if not in histopathology table): Organ weights were recorded at scheduled necropsy (study week 13). There were no treatment-related effects.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
At scheduled necropsy (study week 13)

Toxicokinetics: 1.0 ml blood on study days 0, 7, 14, and 88 at 0.5, 1, 2, 3, 4, 8, and 24

hours after dosing. The C_{max} and AUC values increased proportionally to dose, and were similar in male and female mice.

Oxymorphone Toxicokinetic Parameters Following Oral Administration for 13 Weeks in Mice*

Dose (mg/kg/d)	Study Day	Sex	Cmax (ng/ml)	Tmax (h)	AUC_{0-24h} (ng.h/ml)
300	88	M	2797	0.5	3590
		F	2757	0.5	3957
600	88	M	4493	0.5	6288
		F	3037	1	6557
50	7	M	224	0.5	730
		F	279	0.5	698
	88	M	262	0.5	405
		F	255	1	603
75	14	M	438	0.5	895
		F	354	1	886
	88	M	544	0.1	901
		F	351	0.1	682

*M:male; F:female

Other: None

Study title: A 13-Week Oral (Capsule) Study of Oxymorphone hydrochloride in dogs

Key study findings: Oxymorphone (0, 2, 10 or 40 mg/kg/day) was administered via oral gavage to dogs for a total of 13 weeks with the following results:

1. There were no mortalities.
2. Clinical signs were dose-dependent and characteristic of opioids. Animals in the 10 and 40 mg/kg groups demonstrated excessive salivation and foamy/wet material around the mouth. The high dose produced excessive head shaking and decreased mobility in one female and decreased defecation in 2 males and 1 female.
3. Body weight gain and food consumption decreased in the 10 and 40 mg/kg/day groups during the first two weeks of treatment, however, these effects demonstrated tolerance with time.
4. There were no biologically significant changes in hematology or clinical chemistry.
5. Females treated with the high dose had significantly lower spleen weights.
6. Histological analysis indicated that a single male and female animal in the high dose group demonstrated increased bile ducts in the liver with no other histological correlate for toxicity.
7. Based upon the bile duct increases, spleen weight changes and excessive head shaking at the high dose, a NOAEL of 10 mg/kg was proposed by the sponsor for both males and females. The reviewer concurs, as the changes in clinical signs and body weight/food consumption do not indicate safety issues. In the dog, this

dose corresponds to an $AUC_{0\text{-}24h}$ of 186.72 and 177.62 ng•h/mL in males and females, respectively. C_{max} values at this dose on day 89 were 28.89 and 31.50 ng/mL in males and females, respectively.

Study no.: 411003
Volume #, and page #: N/A Electronic Submission
Conducting laboratory and location: [redacted]

Date of study initiation: November 29, 2000
GLP compliance: Yes
QA report: yes ( ) no ( )
Drug, lot #, and % purity: Oxymorphone hydrochloride, Lot A 4297A, purity was between [redacted] via HPLC analysis.

NOTE: Drug substance contained [redacted] as impurities and [redacted] as degradation products. The drug was administered orally via gelatin capsules and doses were individualized based on most recent body weights.

Methods:

Doses: 0, 2, 10 and 40 mg/kg.

Final Dose Levels

Group Number	Test Article	Dose Level (mg/kg/day)	Number of Animals	
			Males	Females
1*	Control	0	6	6
2	Low Dose	2	4	4
3	Mid Dose	10	4	4
4*	High Dose	40	6	6

* = At the end of the dosing period, two dogs/sex/group were assigned to the 28-day recovery period.

Species/strain: Beagle dogs
Number/sex/group or time point (main study): 4/sex/group.
Route, formulation, volume, and infusion rate: Oral gavage, capsule
Satellite groups used for toxicokinetics or recovery: 2/sex in Groups 1 and 4
Age: approximately 6 months
Weight (non-rodents only): Males 7.5-11.2 kg
Females 6.2-9.0 kg

Unique study design or methodology (if any): An escalating dosing regimen was employed for this study with the intention of achieving the maximum dose level for each group within 14 days. The schedule was reproduced from the study report below:

Group Number	Dose Oxymorphone mg/kg				
	Days 0-2	Days 3-6	Days 7-29	Days 30-40	Days 41-91
1	0	0	0	0	0
2	0.1	1	2	2	2
3	0.1	2	10	10	10
4	0.1	2	20	30	40

Observation times and results

Mortality: Mortality was examined twice daily. There were no unscheduled deaths.

Clinical signs: Clinical signs were monitored twice daily (at time of dosing and 1-2 hours post dosing). Detailed physical exams were conducted weekly. Clinical signs were recorded once weekly during the recovery period an on the day of necropsy. Clinical signs were noted at all dose levels.

	Incidence of Clinical Signs							
	Males (mg/kg)				Females (mg/kg)			
Clinical Signs	0	2	10	40	0	2	10	40
Clear discharge left eye	3/1	1/1	4/1	6/3	5/2	3/2	0/0	6/1
Injected Sclera right eye	3/1	0/0	6/1	12/4	0/0	8/2	1/1	1/1
Injected sclera left eye	3/1	0/0	4/1	10/4	0/0	3/3	1/1	1/1
Defecation decreased	0/0	0/0	0/0	4/2	0/0	0/0	0/0	1/1
Wet clear material around mouth	3/2	0/0	17/4	21/6	1/1	5/3	7/2	22/6
Excessive salivation	0/0	0/0	8/2	19/6	0/0	0/0	1/1	39/6
White foamy material round mouth	0/0	0/0	6/2	11/5	0/0	0/0	3/1	12/5
Hypoactive	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Excessive head shaking	0/0	0/0	0/0	0/0	0/0	0/0	0/0	2/1

n/n = total occurrence/number of animals

Body weights: Body weights were recorded twice weekly. There were no significant treatment-related body weight differences in males or females; however, there was a trend toward a decrease in body weights in both sexes at doses of 10 and 40 mg/kg/day. There was a significantly lower body weight gain in male dogs treated with 10 or 40 mg/kg/day during the first two weeks of treatment and on sporadic weeks thereafter. There was a significantly lower body weight gain in female animals treated with 40 mg/kg during weeks 1 and 2. The initial decreases were likely due to drug treatment.

Food consumption: Food consumption was recorded weekly and calculated as g/animal/day. Males treated with 10 mg/kg demonstrated significantly decreased food consumption from weeks 0 to 1. Males treated with 40 mg/kg demonstrated significantly decreased food consumption from weeks 1 to 2. Females treated with the 40 mg/kg/day dose of oxymorphone consumed less food than the other groups (46% reduction).

Ophthalmoscopy: Ophthalmic examinations were conducted prior to randomization and during study week 12. There were no test article related changes in ophthalmic parameters tested.

EKG: A modified lead 1, 2, 3 electrocardiogram for heart rate was conducted prior to randomization and during study week 12 approximately 2 hours after the last dose. All animals fell within the normal limits both pretest and at week 12.

Hematology: Completed during weeks -2, 4, 8 and prior to necropsy (study weeks 12 for main groups and 16 for recovery groups). The following parameters were evaluated:

Total Leukocyte Count (White Cell)
Erythrocyte Count (Red Cells)
Hemoglobin
Hematocrit
Mean Corpuscular Volume (MCV)
Mean Corpuscular Hemoglobin (MCH)
Mean Corpuscular Hemoglobin Concentration (MCHC)
Platelet Count (Platelet)
Prothrombin Time (Pro Time)
Activated Partial Thromboplastin Time (APTT)
Differential Leukocyte Count-Percent and Absolute
-Neutrophil
-Lymphocyte
-Monocyte
-Eosinophil
-Basophil

( ) = Designates tabular abbreviation.

The results indicated some minor changes in hematology parameters when examined as week 12, as summarized in the table below:

Parameter	Percent Change in Hematology (week 12)					
	Males (mg/kg)			Females (mg/kg)		
	2	10	40	2	10	40
Red blood cells	+11	+11	+13*	-4	+4	+10
Platelets	-11	+13	+11	-2	+6	+26
APTT	-7	-6	-3	-1	-5	-11*
% Neutrophils	-3	-2	-2	+13	+32*	+10

There was a slight decrease in lymphocyte numbers in females from weeks 4 and 8, which was no longer significant by week 12. None of these changes should have biological significance. There was a significant increase in neutrophil numbers at weeks 8 and 12 in the 10 mg/kg female animals only and therefore not dose-dependent. Overall, the results indicated that there were no apparent biologically significant test article effects on hematological parameters under the conditions tested.

Clinical chemistry: Completed during weeks -2, 4 and 8 prior to the scheduled necropsy. The following parameters were examined:

Albumin
Total Protein
Globulin [by calculation]
Albumin/Globulin Ratio (A/G Ratio)
Total Bilirubin (Total Bili)
Urea Nitrogen
Creatinine
Alkaline Phosphatase (Alkaline Phos'tse)
Alanine Aminotransferase (Alanine Transfer)
Aspartate Aminotransferase (Aspartat Transfer)
Gamma Glutamyltransferase (Glutamyl Transfer)
Glucose
Total Cholesterol (Cholesterol)
Calcium
Chloride
Phosphorus
Potassium
Sodium
Triglycerides (Triglyceride)

Significant changes noted at the week 12 blood draws are summarized in the table below. There appeared to be a 16% increase in serum potassium in the 10 and 40 mg/kg dose group in males but not females. In contrast, females, but not males, demonstrated an elevation of glucose levels following does of 10 and 40 mg/kg. A significant increase in phosphorus levels in female dogs treated with 40 mg/kg was also noted. These changes do not appear to suggest significant toxicity at the doses tested.

Summary of Clinical Chemistry Changes (Week 12):

	Percent Control Changes in Clinical Chemistry					
	Males (mg/kg)			Females (mg/kg)		
Parameter	2	10	40	2	10	40
Potassium	-5	-16*	-16*	-6	-4	-1
Glucose	+8	+9	+9	+4	+22*	+17*
Phosphorus	-2	-4	--	-10	+4	+22*

-- No change

Urinalysis: Completed during weeks -2, 4 and 8 prior to the scheduled necropsy (weeks 12 and 16). The following parameters were evaluated:

Specific gravity (SG)
pH
Urobilinogen (URO)
Total Volume (TVOL)
Sodium (Urine Sodium)[a]
Potassium (Urine K)[a]
Calcium (Urine Calcium)[a]
Chloride (Urine Chloride)[a]
Phosphorus (Urine Phos)[a]
Color (CLOR)
Appearance (APP)
Protein (PRO)
Glucose (GLU)
Ketones (KET)
Bilirubin (BIL)
Occult blood (BLD)
Leukocytes (LEU)
Nitrites (NIT)
Microscopy of Sediment [Tabular abbreviations appear on individual tables]

Female dogs treated with the 40 mg/kg dose of oxymorphone demonstrated a significant increase in urinary phosphorus at week 12. This effect was not evident in the recovery animals at week 16 or in the male animals treated with oxymorphone, which if anything suggest a dose-dependent decrease in urinary phosphorus levels.

Parameter	Percent Control Changes in Urinalysis Parameters					
	Males (mg/kg)			Females (mg/kg)		
	2	10	40	2	20	40
Phosphorus	-12	-24	-66	+5	-28	+82*

-- No change

Gross pathology: Complete necropsy was performed on all animals. Dogs were euthanized via an intravenous injection of sodium pentobarbital followed by exsanguination. Necropsy consisted of examination of the externals surfaces, all orifices, cranial cavity, external and cut surface of the brain and spinal cord and thoracic and abdominal cavities including contents. Most collected tissues were preserved in 10% neutral buffered formalin. Bone marrow smears were fixed in alcohol, epididymides and testes were fixed in Bouin's solution and eyes with optic nerve were fixed in Davidson's solution. There were no test-article related microscopic findings noted upon necropsy in any animal. Sporadic or isolated changes were noted in some animals; however, there did not appear to be a clear-cut pattern suggesting macroscopic pathology associated with test-article administration (see below).

Parameter	Incidence of Macroscopic Findings (week 12)							
	Males (mg/kg)				Females (mg/kg)			
	0	2	10	40	0	2	20	40
Colon: Depressed area	0/6	0/4	0/4	1/6	0/6	0/4	0/4	0/6
Lymph Node, Med, Reddened	0/6	0/4	1/4	1/6	0/6	2/4	0/4	1/6
Spleen: accessory	0/6	0/4	0/4	1/6	0/6	0/4	0/4	0/6
Stomach: dark red area	0/6	0/4	0/4	0/6	0/6	0/4	0/4	1/6

n/n = total occurrence/number of animals

Organ weights (specify organs weighed if not in histopathology inventory table): See histopathology table.

The sponsor indicates that there were no test-article-related changes in organ weights at any dose tested. Although not present in males, oxymorphone administration significantly and dose-dependently decreased absolute and relative spleen weights in female dogs at the high dose. There were no histological correlates to these changes in the spleen.

Parameter	Percent Control Changes in Organ Weights					
	Males (mg/kg)			Females (mg/kg)		
	2	10	40	2	20	40
Spleen						
Absolute	+31	+3	+9	-22	-29	-46*
Relative to body weight	+20	-1	+11	-13	-22	-43*
Relative to brain weight	+24	-4	-3	-20	-21	-47*

-- No change

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Parameter	Incidence of Microscopic Histological Changes							
	Males (mg/kg)				Females (mg/kg)			
	0	2	10	40	0	2	20	40
Colon								
Mild necrosis	0/6	0/4	0/4	1/6	0/4	0/4	0/4	0/4
Epididymides: Hypospermia								
Mild	0/4	0/4	1/4	1/4	NA	NA	NA	NA
Severe	0/4	1/4	0/4	0/4	NA	NA	NA	NA
Eyes/Optic Nerve								
Mild Retinal dysplasia	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
Esophagus								
Minimal mineralization	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
Gallbladder								
cytoplasmic vacuolization	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
Larynx								
Min-Mild lymphocyte infiltrate	0/4	0/4	0/4	1/4	4/4	2/4	3/4	1/4
Liver								
Increased bile ducts, mild	0/4	0/4	0/4	1/4	0/4	0/4	0/4	1/4
Lung								
Minimal histocytosis alveolar	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
Parathyroid								
Minimal to mild cyst	1/4	0/4	0/4	2/4	1/4	0/4	0/4	0/4
Salivary gland, mandibular								
Infiltrate, lymphocyte, min.	1/4	0/4	1/4	0/4	0/4	1/4	1/4	1/4
Skin								
Inflammation, granulomatous, minimal	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4

n/n = total occurrence/number of animals
NA = not applicable

There were no histological changes noted in the recovery animals.

Toxicokinetics: Blood samples for Groups 2, 3 and 4 were collected for toxicokinetic evaluation at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h post dose on the first day each dose level reached its final dose level (study day 7 and 41 and on study days 30 and 89). The results are presented in the sponsor's table below. Peak plasma levels were generally obtained between 1 and 4 hours. There does not appear to be any differences between males and females. Exposure appears to increase with dose in the range tested. There was no evidence for drug accumulation over time.

Table1: Pharmacokinetic Parameters

Study Day	Dose mg/kg	Sex	T_{max} (hr)	C_{max} (ng/mL)	C_{last} (ng/mL)	AUC_{24} (hr*ng/mL)	k (1/hr)	$t_{1/2}$ (hr)	AUC_{∞} (hr*ng/mL)	AUC_{∞}/D (hr*ng/mL/mg)	Cl/F (L/hr*kg)
7	2	F	1	3.54	0.27	28.85	0.13	5.16	30.86	15.43	64.80
7	2	M	2	4.27	0.75	18.60	0.11	6.59	26.08	13.04	76.67
7	10	F	6	10.63	3.86	141.09	0.02	31.89	318.57	31.86	31.39
7	10	M	1	9.94	1.98	100.62	0.06	11.06	132.29	13.23	75.59
30	2	F	1	4.16	0.57	16.66	0.25	2.78	18.94	9.47	105.58
30	2	M	6	4.07	0.27	23.72	0.25	2.80	24.82	12.41	80.57
30	10	F	2	20.65	1.43	197.56	0.16	4.29	206.40	20.64	48.45
30	10	M	4	13.71	1.39	158.04	0.15	4.49	167.04	16.70	59.87
41	40	F	2	110.84	5.99	710.37	0.15	4.69	750.92	18.77	53.27
41	40	M	2	89.99	4.26	608.11	0.16	4.33	634.72	15.87	63.02
89	2	F	1	9.33	0.26	33.11	0.22	3.22	34.30	17.15	58.31
89	2	M	2	3.73	0.58	24.02	0.13	5.27	28.43	14.22	70.35
89	10	F	2	28.89	1.45	186.72	0.14	5.11	197.39	19.74	50.66
89	10	M	1	31.50	0.82	177.62	0.21	3.37	181.63	18.16	55.06
89	40	F	2	158.88	7.35	992.56	0.12	5.95	1055.65	26.39	37.89
89	40	M	2	138.16	4.34	642.98	0.12	5.69	678.62	16.97	58.94

Histopathology inventory (optional)

Study	[redacted]-411011 13-week PO	[redacted]-411012 13-week, PO	[redacted]-411003 13-week PO	
Species	Rat	Mouse	Dog	
Adrenals	X*	X*	X*	
Aorta	X	X	X	
Bone Marrow smear	X	X	X	
Bone (femur)	X	X	X	
Brain	X*	X*	X*	
Cecum	X	X	X	
Cervix				
Colon	X	X	X	
Duodenum	X	X	X	
Epididymis	X*	X*	X*	
Esophagus	X	X	X	
Eye	X	X	X	
Fallopian tube	X	X		
Gall bladder		X	X	
Gross lesions	X	X	X	
Harderian gland				
Heart	X*	X*	X*	
Ileum	X	X	X	
Injection site				
Jejunum	X	X	X	

Kidneys	X*	X*	X*	
Lachrymal gland			X	
Larynx			X	
Liver	X*	X*	X*	
Lungs	X	X	X	
Lymph nodes, cervical				
Lymph nodes mandibular			X	
Lymph nodes, mesenteric	X	X	X	
Mammary Gland	X	X	X	
Nasal cavity				
Optic nerves	X	X	X	
Ovaries	X*	X*	X*	
Pancreas	X	X	X	
Parathyroid	X*	X*	X*	
Peripheral nerve	X	X	X	
Pharynx				
Pituitary	X	X	X	
Prostate	X*	X*	X*	
Rectum	X	X	X	
Salivary gland	X	X	X	
Sciatic nerve	X	X	X	
Seminal vesicles	X	X		
Skeletal muscle	X	X	X	
Skin	X	X	X	
Spinal cord	X	X	X	
Spleen	X*	X*	X*	
Sternum			X	
Stomach	X	X	X	
Testes	X*	X*	X*	
Thymus	X*	X*	X*	
Thyroid	X*	X*	X*	
Tongue			X	
Trachea	X	X	X	
Urinary bladder	X	X	X	
Uterus	X*	X*	X*	
Vagina	X	X	X	
Zymbal gland				

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

Genetic toxicology studies on oxymorphone were previously reviewed by this reviewer and reproduced below. Additional genetic toxicology studies on the impurity [redacted] were conducted and submitted during the NDA review process. These studies are reviewed following the studies on oxymorphone itself.

Study title: Bacterial Reverse Mutation Assay [for oxymorphone HCl and morphine sulfate]

Key findings: Oxymorphone HCl was tested in the Ames Reverse Mutation Assay at concentrations of 79.1, 211, 632, 1897 and 5270 µg/plate. There was no evidence for cytotoxicity or precipitate at any concentration. Under the conditions of the study, oxymorphone HCl was concluded to be negative in the bacterial reverse mutation assay.

Study no: AA46XC.503.BTL and AA46XD.503.BTL
Study type (if not reflected in title): Bacterial Reverse Mutation Assay (Ames Test)
Volume #, and page #: Volume 2, page 103
Conducting laboratory and location: [redacted]
Date of study initiation: July 19, 2001
GLP compliance: Yes, with some exceptions (analysis of the test article concentrations of oxymorphone and morphine were limited to stock solutions only and the stability of the morphine sulfate and morphine sulfate solutions were not determined by the testing facility).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxymorphone HCl, Mallinckrodt B14802, [redacted]
Morphine Sulfate, [redacted] B05979, [redacted]
Formulation/vehicle: Water was the solvent of choice

Methods: The assay was conducted in two phases using the plate incorporation method. The first phase was the toxicity-mutation assay used to establish the dose-range for the mutagenicity assay and get a preliminary mutagenicity evaluation. The second phase was the mutagenicity assay. Dosing was adjusted to compensate for test article activity. Tester strain TA98 and TA1537 are reverted from histidine dependence to histidine independence by frameshift mutagens. Tester strain TA1535 is reverted by mutagens that cause base pair substitution. Tester strain TA100 is reverted by mutagens that cause both frameshift and base pair substitution mutations. Specificity in *E.coli* is sensitive to base-pair substitution mutations, rather than frameshift.

Strains/species/cell line: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 *uvr*A.
Dose selection criteria: Toxicity and formation of a precipitate.
Basis of dose selection: Doses used in initial toxicity-mutation assay were 2.64, 7.91, 26.4, 79.1, 211, 632, 1897 and 5270 µg/plate for oxymorphone and 2.5, 7.5, 25, 75, 200, 600, 1800 and 5000 µg/plate for morphine. The test article was soluble and clear in water at the highest concentrations tested. Neither precipitate nor appreciable toxicity was observed. No positive mutagenic responses were observed in any tester strains either with or without S9 activation. The definitive study therefore used the maximum recommended concentrations of test article as the basis for dose selection.
Range finding studies: Initial toxicity-mutation assay
Test agent stability: Test agent had an expiration date of November 2, 2010. Stability out to [redacted] days was determined by sponsor. Results indicated that drug solutions of 0.01 mg/mL, 1 mg/mL and 50 mg/mL both in water and pH 4.5 phosphate buffer was stable up to at least [redacted] days under ambient conditions. At [redacted] days, individual known and unknown degradation products as well as total degradation products were less than [redacted] .
Metabolic activation system: Aroclor 1254-induced rat liver S9 (male). Each bulk preparation of S9 was assayed for its ability to metabolize 2-aminoanthracene and 7,12-dimethylbenz(a)anthracene to forms mutagenic to *Salmonella typhimurium* TA100. S9 was tested at 10%.

Controls:
Vehicle: Water
Negative controls: Water
Positive controls:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
All *Salmonella* strains	Rat	2-aminoanthracene	1.0
WP2*uvr*A			10

TA98	None	2-nitrofluorene	1.0
TA100, TA1535		Sodium azide	1.0
TA1537		9-aminoacridine	75
WP2 *uvr*A		Methyl methanesulfonate	1,000

Comments: Controls are acceptable according to current standards.

Exposure conditions:

Incubation and sampling times: 48 to 72 hours at 37°C

Doses used in definitive study: Concentrations of 79.1, 211, 632, 1897 and 5270 µg/plate for oxymorphone were tested. For morphine, concentrations of 75, 200, 600, 1800 and 5000 µg/plate were tested.

Study design: Plate incorporation method as described above.

Analysis:

No. of replicates: 3

Counting method: Either entirely by automated colony counter or entirely by hand (microscope).

Criteria for positive results: Test article was considered positive if it caused a dose-dependent increase in the mean revertants per plate of at least one tester strain over a minimum of two increasing concentrations of test article. For strains TA1535 and TA1537, increase in mean revertants must be equal to or greater than three times the mean vehicle control value. For strains TA98, TA100 and WP2uvrA, increase in mean revertants at peak must be equal to or greater than two times the mean control value.

Summary of individual study findings:

Study validity: The study appears to be valid for the following reasons: 1) the appropriate controls were used, 2) the appropriate strains were tested, 3) the positive control substances produced reliable positive results, 4) the highest concentration of oxymorphone tested reached the maximum recommended concentration was the molar equivalent of 5,000 µg/plate of morphine sulfate and 5) there was no evidence for a dose dependent increase in revertants following drug treatment.

Study outcome: Oxymorphone HCl did not produce any increases in the number of revertants in any tester stain under the conditions tested. Likewise, morphine sulfate did not produce any increase in the number of revertants in any tester strain either (data not shown). This is in concurrence with the Sponsor's conclusions.

Bacterial Mutation Assay
Summary of Results

Table 22

Test Article Id : Oxymorphone HCl
Study Number : AA46XC.503.BTL Experiment No : B2

Average Revertants Per Plate ± Standard Deviation

Liver Microsomes: None

Dose (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
Vehicle	25 ± 3	194 ± 12	34 ± 2	6 ± 2	15 ± 3
79.1	18 ± 7	190 ± 13	24 ± 5	11 ± 3	11 ± 4
211	23 ± 4	209 ± 30	36 ± 4	11 ± 1	13 ± 3
632	26 ± 2	179 ± 8	23 ± 4	10 ± 3	12 ± 3
1897	19 ± 2	173 ± 6	28 ± 3	10 ± 1	11 ± 3
5270	20 ± 1	165 ± 18	22 ± 1	7 ± 2	11 ± 2
Positive	93 ± 6	1083 ± 50	226 ± 14	430 ± 56	141 ± 11

Liver Microsomes: Rat liver S9

Dose (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 uvrA
Vehicle	17 ± 6	154 ± 6	22 ± 4	11 ± 4	10 ± 1
79.1	22 ± 4	193 ± 5	24 ± 6	9 ± 3	12 ± 2
211	20 ± 4	202 ± 14	20 ± 1	8 ± 1	15 ± 1
632	23 ± 6	182 ± 6	24 ± 4	10 ± 6	13 ± 1
1897	26 ± 7	202 ± 19	27 ± 6	9 ± 2	14 ± 1
5270	27 ± 6	185 ± 7	22 ± 3	11 ± 5	13 ± 5
Positive	483 ± 229	468 ± 30	179 ± 20	1189 ± 180	1003 ± 77

Vehicle = Vehicle Control
Positive = Positive Control
Plating aliquot: 100 µL

Study title: ***In vitro*** **mammalian chromosome aberration test [oxymorphone HCl and morphine sulfate]**

Key findings: Both oxymorphone HCl and morphine sulfate were considered to be negative for the induction of structural and numerical chromosome aberrations in the *in vitro* mammalian chromosome aberrations test using human peripheral blood lymphocytes under the conditions tested.

Study no: AA46XC-XD.341-BTL
Study type (if not reflected in title): *in vitro* mammalian chromosomal aberrations test using human peripheral blood lymphocytes
Volume #, and page #: Volume 2, Page 103
Conducting laboratory and location: [redacted]
Date of study initiation: July 17, 2001
GLP compliance: Yes, with some exceptions (analysis of the test article concentrations of oxymorphone and morphine were limited to stock solutions only and the stability of the morphine sulfate and morphine sulfate solutions were not determined by the testing facility).
QA reports: Yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxymorphone HCl, Mallinckrodt B14802, [redacted] Morphine sulfate, [redacted] B05979, [redacted]
Formulation/vehicle: Water

Methods:

Strains/species/cell line: Human peripheral blood lymphocytes (HPBL)

Dose selection criteria: Preliminary toxicology assay and solubility

Basis of dose selection: Test articles were soluble in water at all concentrations tested (maximum concentration was 5,270 µg/mL oxymorphone and 5,000 µg/mL morphine sulfate). The preliminary toxicology test was performed to select final concentrations via test article effects on mitotic index. Cells were incubated with test article with or without S9 for 4 hours and for 20 hours in the absence of S9. The number of cells in mitosis per 500 cells scored was determined.

Range finding studies: HPBL were exposed to a total of 9 concentrations of oxymorphone ranging from 0.527 to 5270 µg/mL with and without S9 for 4 hours and without S9 for 20 hours. Toxicity (mitotic inhibition) in excess of 50% was not observed in any of the concentrations tested in the presence or absence of S9 during the 4 hour exposure. During the 20 hour continuous exposure conditions, the mitotic index in the presence of oxymorphone at 527 µg/mL was 31% below control, whereas the mitotic index at 1581 µg/mL was 93% below control.

Test agent stability: Stability of the test article was determined by the sponsor. Results indicated that drug solutions of 0.01 mg/mL, 1 mg/mL and 50 mg/mL both in water and pH 4.5 phosphate buffer was stable up to at least — days under ambient conditions. At — days, individual known and unknown degradation products as well as total degradation products were less than (—.

Metabolic activation system: Aroclor 1254-induced rat liver S9 was prepared from male Sprague-Dawley rats. Bulk preparations were assayed for their ability to metabolize 2-aminoanthracene and 7,12-dimethyl-benz(α)anthracene to forms mutagenic to *Salmonella typhimurium* TA100. S9 was tested at 20 µl per ml of medium (2%).

Controls:

Vehicle: Water

Negative controls: Water.

Positive controls: Mitomycin C (MMC) was used as a positive control in the non-activated study at a final concentration of 0.3 and 0.6 µg/mL. Cyclophosphamide (CP) was used as the positive control in the S9 activated study at a final concentration of 20 and 40 µg/mL.

Comments: The controls are consistent with OECD recommendations.

Exposure conditions:

Incubation and sampling times: 37°C, 5% CO_2.

Treatment Condition	Treatment Time	Recovery Time	Oxymorphone HCl Concentrations (µg/mL)
Non-activated	4 hr	16 hr	659, 1318*, 2635*, 5270*
	20 hr	0 hr	250*, 500, 700*, 900, 1100*, 1300, 1500
S9-activated	4 hr	16 hr	659, 1318*, 2635*, 5270*

* Concentrations scored for definitive assay.

Doses used in definitive study: See table above. The concentrations scored for the assay were based upon the mitotic index for the cells.

Study design: Chromosomal aberration was assessed via standard procedures by exposing duplicate cultures of human peripheral blood lymphocytes to at least 4 concentrations of test article as well as positive and negative controls. Dividing cells were harvested approximately 20 hours from the initiation of treatment. For chromosome aberration assays, 0.6 ml of heparinized blood was inoculated into 9.4 ml of complete medium supplemented with 1% PHA. The tubes were incubated at 37°C and 5% CO_2 in air for 44-48 hours. Treatment was completed by media replacement with fresh complete media or S9 reaction mixture to which 1 ml of dosing solution of test or control article was added. Cells were then incubated for 4 or 20 hours with in the incubator. For the 4 hour incubation, the treatment media was removed, cells were washed, complete medium containing PHA was added, and returned to the incubator for an additional 16 hours. Two hours prior to the scheduled cell harvest, cells were treated with Colcemed® at a final concentration of 0.1 µg/mL. Following treatment, the cells

Analysis:

No. of replicates: 2

Counting method: Metaphase cells with 46 centromeres were examined under oil immersion. Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations.

Criteria for positive results: A test article was considered to induce a positive response when the percentage of cells with aberrations were increased in a dose-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group. A reproducibly significant increase at the high dose only or one other dose only with no dose-response was considered positive.

Summary of individual study findings:

Study validity: The study appears to be valid for the following reasons: 1) the appropriate positive controls were employed according to OECD guidelines, 2) The appropriate number of cells were evaluated and 3) the conditions of the assay are appropriate based upon OECD guidelines. The dose selection based upon mitotic index was acceptable. The criteria for a positive result should not be based entirely upon statistical analysis; however, the use of these criteria did not affect the validity of the data.

Study outcome: For the 4-hour non-activated group, the highest test article concentration tested (5270 μg/mL) inhibited mitosis by 8% relative to controls. The concentrations selected for analysis were 1318, 2635 and 5270 μg/mL. The percentage of cells with structural or numerical aberrations was not significantly different than controls for any treatment concentration. In contrast, the positive control, Mitomycin C (0.6 μg/mL) significantly increased the percentage of cells with structural aberrations (14%).

For the 4-hour activated group, the highest test article concentration tested, (5270 μg/mL) produced 4% mitotic inhibition relative to controls. The concentrations selected for analysis were 1318, 2635 and 5270 μg/mL. The percentage of cells with structural or numerical aberrations was not significantly different than controls for any treatment concentration. In contrast, the positive control, cyclophosphamide (20 μg/mL) significantly increased the percentage of cells with structural aberrations (8%).

For the 20-hour non-activated group, the highest test article concentration tested (1100 μg/mL) inhibited mitosis by 52% relative to controls. The concentrations selected for analysis were 250, 700 and 1100 μg/mL. Additional concentrations of 500 and 900 were tested, but not scored. The percentage of cells with structural or numerical aberrations was not significantly different than controls for any scored concentration. In contrast, the positive control, Mitomycin C (0.3 μg/mL) significantly increased the percentage of cells with structural aberrations (14%).

The results of the study are summarized in Sponsor's Table 7, reproduced below:

Thus, oxymorphone tested negatively in the *in vitro* chromosome aberration assay under the conditions tested. This is in concurrence with the Sponsor's conclusion. Morphine sulfate also tested negative in this study (Data not shown).

TABLE 7
SUMMARY OF CYTOGENETIC ANALYSIS OF OXYMORPHONE HCl

Treatment (µg/mL)	S9 Activation	Treatment Time (hours)	Mean Mitotic Index	Cells Scored	Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations Numerical (%)	Structural (%)
Water	-	4	6.3	200	0.000	±0.000	0.0	0.0
Oxymorphone HCl								
1318	-	4	6.4	200	0.000	±0.000	0.0	0.0
2635	-	4	5.9	200	0.000	±0.000	0.5	0.0
5270	-	4	5.8	200	0.010	±0.100	0.0	1.0
MMC 0.6	-	4	3.1	200	0.175	±0.496	0.0	14.0**
Water	+	4	4.9	200	0.015	±0.122	0.5	1.5
Oxymorphone HCl								
1318	+	4	5.1	200	0.000	±0.000	0.0	0.0
2635	+	4	5.5	200	0.000	±0.000	0.5	0.0
5270	+	4	4.7	200	0.005	±0.071	0.0	0.5
CP 20	+	4	1.1	200	0.095	±0.341	0.0	8.0**
Water	-	20	6.4	200	0.000	±0.000	0.0	0.0
Oxymorphone HCl								
250	-	20	5.4	200	0.005	±0.071	0.0	0.5
700	-	20	4.8	200	0.000	±0.000	0.0	0.0
1100	-	20	3.1	200	0.005	±0.071	0.5	0.5
MMC 0.3	-	20	3.0	200	0.175	±0.464	0.0	14.0**

Treatment: Cells from all treatment conditions were harvested at 20 hours after the initiation of the treatments.
Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.
Percent Aberrant Cells: *, $p \leq 0.05$; **, $p \leq 0.01$; using the Fisher's exact test.

Study title: Mammalian Erythrocyte Micronucleus Test [oxymorphone HCl and morphine sulfate]

Key findings: A statistically significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed in male and female mice 24 hours after treatment with 500 mg oxymorphone/kg. The results indicate that oxymorphone HCl tested positive in the *in vivo* mouse micronucleus test under the conditions of the assay. In contrast, morphine sulfate was concluded to be negative in the *in vivo* mouse micronucleus test.

Study no: AA46XC.XD.123.BTL
Study type (if not reflected in title): *In vivo* mouse micronucleus assay
Volume #, and page #: Volume 2, page 168
Conducting laboratory and location: [redacted]
Date of study initiation: July 17, 2001
GLP compliance: Yes, with a few exceptions (stability of morphine sulfate and morphine sulfate solutions were not determined by the testing facility. Analysis of the

concentrations of oxymorphone and morphine were limited to the stock solutions, test solutions prepared by serial dilution were not analyzed.

QA reports: yes (X) no ( )

Drug, lot #, radiolabel, and % purity: Oxymorphone HCl, Mallinckrodt B14802, [redacted]
Morphine sulfate, [redacted] B05979, [redacted]

Formulation/vehicle: Water

Methods:

Strains/species/cell line: ICR Mice (Harlan), male and female

Dose selection criteria: Pilot toxicology study

Basis of dose selection: Doses tested were 250, 500, 750 and 1054 mg oxymorphone HCl/kg body weight via oral gavage (20 ml/kg). Doses of morphine sulfate were 250, 500, 700, or 1000 mg/kg. A total of 5 males and 5 females per dose were tested (only 3 animals in the high dose groups).

Range finding studies: For the oxymorphone treatment groups, mortality was noted in3/3 males and 3/3 females in the 1054 mg/kg group and 4/5 males and 3/5 females at the 750 mg/kg group. For the morphine treatment groups, mortality was noted in 1/3 males and 2/3 females in the 1000 mg/kg group. Clinical signs are summarized in the table (below). Based upon these results, the high dose for the oxymorphone in the micronucleus assay was set at 500 mg/kg and the high dose for the morphine was set at 700 mg/kg. These doses correlate with the maximum tolerated non-lethal doses.

Table 1: Pilot Toxicity Study - Clinical Signs Following Dose Administration of Oxymorphone HCl and Morphine Sulfate in ICR Mice

Treatment	Clinical Observation	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Oxymorphone HCL 250 mg/kg	Hyperactivity Erect tails Lethargy	5/5 5/5 1/5	5/5 5/5 0/5	0/5	0/5
500 mg/kg	Hyperactivity Erect tails Convulsions Prostration Lethargy Piloerection	5/5 5/5 1/5 1/5 5/5 5/5	5/5 5/5 1/5 0/5 5/5 0/5	0/5	0/5
750 mg/kg	Hyperactivity Erect tails Aggressiveness	5/5 5/5 0/5	5/5 5/5 1/5	4/5	3/5
1054 mg/kg	Convulsions Erect tails	3/3 3/3	3/3 3/3	3/3	3/3
Morphine Sulfate 250 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
500 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
700 mg/kg	Hyperactivity Erect tails Lethargy Piloerection	5/5 5/5 3/5 1/5	5/5 5/5 0/5 0/5	0/5	0/5
1000 mg/kg	Convulsions Erect tails Lethargy	3/3 3/3 2/3	3/3 3/3 0/3	1/3	2/3

Test agent stability: Expiration data of the oxymorphone powder was November 2, 2010. Stability of the test article was determined by the sponsor. Results indicated that drug solutions of 0.01 mg/mL, 1 mg/mL and 50 mg/mL both in water and pH 4.5 phosphate buffer was stable up to at least [redacted] days under ambient conditions. At [redacted] days, individual known and unknown degradation products as well as total degradation products were less than [redacted]

Metabolic activation system: N/A

Controls:

Vehicle: Water

Negative controls: Water

Positive controls: Cyclophosphamide (40 mg/kg)

Comments: Controls are acceptable in accordance with OECD guidelines.

Exposure conditions:

Incubation and sampling times: Animals were sacrificed either 24 or 48 hours after treatment.

Doses used in definitive study: 125, 250 and 500 mg/kg oxymorphone HCl via oral gavage (20 ml/kg). Morphine sulfate doses were 175, 350 and 700 mg/kg via oral gavage (20 ml/kg).

Study design: A total of 5 male and 5 female mice per treatment group were administered oxymorphone via oral gavage. An additional 5 males and 5 females for the high-dose group

were treated for replacement animals. A satellite group of 5 animals each were dosed for

	Number of Mice Per Sex Dosed	Number of Mice Per Sex Used for Bone Marrow Collection After Dose Administration 24 hr	48 hr
Vehicle Control			
Water	10	5	5
Test Article			
Oxymorphone HCl			
Low test dose (125 mg/kg)	5	5	0
Mid test dose (250 mg/kg)	5	5	0
High test dose (500 mg/kg)	15*	5	5
Test Article			
Morphine Sulfate			
Low test dose (175 mg/kg)	5	5	0
Mid test dose (350 mg/kg)	5	5	0
High test dose (700 mg/kg)	15*	5	5
Positive Control			
Cyclophosphamide	5	5	0

*including 5 replacement animals per sex to ensure the availability of five animals for bone marrow analysis

toxicokinetic analysis to be conducted by the sponsor. The study design was as follows:

At the scheduled time of sacrifice, bone marrow cells were collected 24 and 48 hours after treatment and examined microscopically for micronucleated polychromatic erythrocytes.

Analysis:

No. of replicates: 2000 polychromatic erythrocytes were scored for the presence of micronuclei for each mouse per group. The proportion of polychromatic erythrocytes to total erythrocytes was recorded per 1000 erythrocytes.

Counting method: Microscopy, under an oil immersion lens.

Criteria for positive results: "The test article was considered to produce a positive response if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables) at any sampling time. If a single treatment group was significantly elevated at one sacrifice time with no evidence of a dose-response, the assay was considered a suspect or unconfirmed positive and a repeat assay recommended."

Summary of individual study findings:

Study validity: The study appears to be valid for the following reasons: 1) the positive control, cyclophosphamide produced a statistically significant increase in the number of micronucleated polychromatic erythrocytes compared to controls and 2) the sampling times, positive controls and study design were according to OECD guidelines. However, the highest dose tested for both oxymorphone and morphine appears to be beyond the maximum tolerated non-lethal dose for some animals. Given the use of replacement animals, the dose selection is acceptable as the dose clearly reaches the maximum tolerated dose in surviving animals.

Study outcome: Following dosing, mortality occurred in 2/15 males and 1/15 females treated with 500 mg/kg oxymorphone. Mortality also occurred in 3/15 males and 2/15 females treated with 700 mg/kg morphine sulfate. As extra animals were dosed at the high dose, a total of 5 animals in each group were evaluated for micronuclei. Clinical signs are presented in the sponsor's table 4 (below).

Table 4: Micronucleus Study - Clinical Signs Following Dose Administration of Oxymorphone HCl and Morphine Sulfate in ICR Mice

Treatment	Clinical Observation	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Water 20 mL/kg	*	*/10	*/10	0/10	0/10
Oxymorphone HCl 125 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
250 mg//kg	Hyperactivity Erect tails Lethargy	5/5 5/5 5/5	5/5 5/5 1/5	0/5	0/5
500 mg/kg	Hyperactivity Erect tails Lethargy Piloerection	15/15 15/15 10/15 1/15	15/15 15/15 1/15 0/15	2/15	1/15
Morphine Sulfate 175 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
350 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
700 mg/kg	Hyperactivity Erect tails Lethargy Piloerection	15/15 15/15 11/15 2/15	15/15 15/15 1/15 0/15	3/15	2/15
Cyclophosphamide 40 mg/kg	*	*/5	*/5	0/5	0/5

* No clinical signs observed, all dosed animals appeared normal

Toxicokinetic analysis suggested comparable exposures between males and females (table 2 below).

Table 2. Mean Plasma Concentrations (n=5) and Toxicokinetic Parameters of Oxymorphone in ICR Mice Following Single Oral Administration (QPS Project Number 52-0202PK)

Sex	Male			Female		
Dose, mg/kg	125	250	500	125	250	500
Plasma Conc, ng/mL						
1 h	737.400[a]	2436.408	2621.072	768.408	1746.480	5329.216
4 h	305.805	399.170	2605.552	343.010	574.454	1464.288
24 h	2.192	10.475	10.795	3.885	12.018	62.066
Toxicokinetic Parameter						
Cmax, ng/mL	737.400	2436.408	2621.072	768.408	1746.480	5329.216
Tmax, h	1.0	1.0	1.0	1.0	1.0	1.0
$AUC_{0\text{-}24h}$, ng/mL·h	5013.477	9568.024	35313.950	5520.278	10219.360	28118.400
T1/2, h	2.8	ND	ND	ND	2.8	3.9

[a]n=4
ND=not determined due to insufficient data points.

Results of the micronucleus assay indicated that in females, oxymorphone treatment at doses of 250 mg/kg significantly increased the number of micronucleated polychromatic erythrocytes per polychromatic erythrocytes scored (24 hours). Significant increases were also obtained in both males and females following 500 mg/kg doses. These increases appeared to be dose-related. Cyclophosphamide (50 mg/kg) also produced a significant response. When measured at 48 hours, oxymorphone treatment of 500 mg/kg significantly increased the number of MPCE/PCE scored in males only, although the incidence in drug treated females was increased. The results for oxymorphone are reproduced in sponsor's table 5 below: As noted in the table above, oxymorphone treatment reduced the ratio of polychromatic erythrocytes to total erythrocytes by 19 to 40% relative to controls. This suggests toxicity and that oxymorphone was

Table 5: Summary of Bone Marrow Micronucleus Analysis
Following Dose Administration of Oxymorphone HCl in ICR Mice

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes: Number per 1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored[1]
Water							
20 mL/kg	M	24	5	0.523 ± 0.02	—	0.5 ± 0.00	5 / 10000
	F	24	5	0.505 ± 0.04	—	0.4 ± 0.22	4 / 10000
Oxymorphone HCl							
125 mg/kg	M	24	5	0.413 ± 0.07	-21	0.5 ± 0.35	5 / 10000
	F	24	5	0.353 ± 0.03	-30	0.9 ± 0.22	9 / 10000
250 mg/kg	M	24	5	0.365 ± 0.02	-30	1.2 ± 0.76	12 / 10000
	F	24	5	0.361 ± 0.05	-25	1.3 ± 0.27	**13 / 10000
500 mg/kg	M	24	5	0.343 ± 0.06	-34	5.4 ± 1.29	*54 / 10000
	F	24	5	0.410 ± 0.08	-19	3.8 ± 3.27	*38 / 10000
CP							
50 mg/kg	M	24	5	0.271 ± 0.04	-48	28.8 ± 3.27	*288 / 10000
	F	24	5	0.357 ± 0.08	-29	27.8 ± 5.82	*278 / 10000
Water							
20 mL/kg	M	48	5	0.513 ± 0.05	—	0.4 ± 0.22	4 / 10000
	F	48	5	0.492 ± 0.05	—	0.4 ± 0.22	4 / 10000
Oxymorphone HCl							
500 mg/kg	M	48	5	0.307 ± 0.06	-40	1.4 ± 1.47	**14 / 10000
	F	48	5	0.356 ± 0.07	-28	0.8 ± 0.45	8 / 10000

[1]*, p≤0.05 (Kastenbaum-Bowman Tables)
** Statistically significant but not biologically relevant

bioavailable to the target bone marrow. The increases in MPCE/PCE scored noted above following a dose of 250 mg/kg at 24 hours and a dose of 500 mg/kg at 48 hours were not considered to be biologically relevant as they were within the historical control range for the controls (0-14 in males and 0-18 in females).

Results of the micronucleus assay for morphine indicate that morphine sulfate treatments did not significantly alter the number of micronucleated polychromatic erythrocytes per PCE scored 24 hours after treatment at any dose tested. In contrast, cyclophosphamide (50 mg/kg) produced significant increases. However, at 48 hours, treatment with the high dose morphine sulfate (700 mg/kg produced a significant increase in MPCE/PCE scored in female mice only. The results are reproduced in Sponsor's table 8 below: As noted above, morphine sulfate treatment produced a reduction of 25 to 36% in the ratio of polychromatic erythrocytes to total erythrocytes relative to controls. This indicates toxicity and that the

Table 8: Summary of Bone Marrow Micronucleus Analysis Following Dose Administration of Morphine Sulfate in ICR Mice

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes: Number per 1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored*
Water							
20 mL/kg	M	24	5	0.523 ± 0.02	---	0.5 ± 0.00	5 / 10000
	F	24	5	0.505 ± 0.04	---	0.4 ± 0.22	4 / 10000
Morphine Sulfate							
175 mg/kg	M	24	5	0.388 ± 0.04	-26	0.6 ± 0.55	6 / 10000
	F	24	5	0.380 ± 0.02	-25	0.9 ± 0.74	9 / 10000
350 mg/kg	M	24	5	0.377 ± 0.06	-28	0.8 ± 0.45	8 / 10000
	F	24	5	0.321 ± 0.02	-36	1.1 ± 0.42	11 / 10000
700 mg/kg	M	24	5	0.353 ± 0.06	-33	1.0 ± 0.35	10 / 10000
	F	24	5	0.347 ± 0.04	-31	1.1 ± 0.42	11 / 10000
CP							
50 mg/kg	M	24	5	0.271 ± 0.04	-48	28.8 ± 3.27	*288 / 10000
	F	24	5	0.357 ± 0.08	-29	27.8 ± 5.82	*278 / 10000
Water							
20 mL/kg	M	48	5	0.513 ± 0.05	---	0.4 ± 0.22	4 / 10000
	F	48	5	0.492 ± 0.05	---	0.4 ± 0.22	4 / 10000
Morphine Sulfate							
700 mg/kg	M	48	5	0.331 ± 0.04	-35	0.9 ± 0.42	9 / 10000
	F	48	5	0.340 ± 0.02	-31	1.2 ± 0.84	**12 / 10000

1*, p≤0.05 (Kastenbaum-Bowman Tables)
** Statistically significant but not biologically relevant

morphine sulfate was bioavailable to the target bone marrow. The statistically significant increase in the MPCE/PCE scored in females at 48 hours was not considered to be biologically relevant, as it is within the historical range off the controls (0-18).

Overall, the results indicated that oxymorphone, but not morphine, produced a significant increase in micronucleated polychromatic erythrocytes at a dose of 500 mg/kg under the conditions tested. This conclusion is in concurrence with the sponsor.

Study title: Mammalian erythrocyte micronucleus test [oxymorphone HCl]

Key findings: Oxymorphone at a dose of 20 mg/kg and 40 mg/kg produced a significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow of the rat under the conditions tested. Thus, oxymorphone is considered positive in the rat micronucleus assay, an *in vivo* test for mammalian chromosomal damage.

Study no: AA46XC.125.BTL
Study type (if not reflected in title): *In vivo* rat micronucleus test
Volume #, and page #: Volume 2, Page 250
Conducting laboratory and location: [redacted]
Date of study initiation: October 18, 2001
GLP compliance: Yes, with the exception that analysis of the test article concentration was limited to the stock solution. Test articles prepared by serial dilution from the stock solution were not independently analyzed.
QA reports: Yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxymorphone HCL, Mallinckrodt B14802, [redacted]

Formulation/vehicle: Water

Methods:

Strains/species/cell line: [redacted]CD (SD) IGS BR rats, male and female
Dose selection criteria: Dose range-finding study for toxicity
Basis of dose selection: Tested doses of 50, 75, 100 or 150 mg/kg oxymorphone via oral gavage (10 ml/kg) in preliminary toxicity study (n=5/sex/group).
Range finding studies: Mortality was observed at all doses tested as indicated in the table below. Based on these findings, a dose of 40 mg/kg was set as the high dose for the micronucleus assay as an estimate of the maximum tolerated dose.

Table 1: Toxicity Study - Clinical Signs
Following Dose Administration of Oxymorphone HCl in (—CD® (SD) IGS BR Rats

Treatment	Clinical Observation	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Oxymorphone HCl 50 mg/kg	Lethargy Piloerection	5/5 3/5	5/5 1/5	2/5	2/5
75 mg/kg	Lethargy Piloerection Prostration Irregular breathing Crusty eyes	3/5 2/5 0/5 0/5 0/5	3/5 1/5 1/5 1/5 1/5	3/5	4/5
100 mg/kg	Lethargy Piloerection	5/5 1/5	5/5 2/5	4/5	3/5
150 mg/kg	Lethargy Piloerection	5/5 1/5	5/5 0/5	4/5	5/5

Test agent stability: Expiration date on the powdered drug is November 2, 2010. Stability of the test article was determined by the sponsor. Results indicated that drug solutions of 0.01 mg/mL, 1 mg/mL and 50 mg/mL both in water and pH 4.5 phosphate buffer was stable up to at least ↘ days under ambient conditions. At— days, individual known and unknown degradation products as well as total degradation products were less than —.

Metabolic activation system: N/A

Controls:

Vehicle: Water

Negative controls: Water

Positive controls: Cyclophosphamide

Comments: Positive control is acceptable in accordance with OECD guidelines.

Exposure conditions:

Incubation and sampling times: Animals were sacrificed at 24 and 48 hours.

Doses used in definitive study: 10, 20 and 40 mg/kg oxymorphone/kg via oral gavage (10 ml/kg)

Study design: A total of 5 male and 5 female rats per treatment group were administered oxymorphone via oral gavage. An additional 5 males and 5 females for the high-dose group were treated for replacement animals. A satellite group of 5 animals each were dosed for toxicokinetic analysis to be conducted by the sponsor. The study design was as follows:

	Number of Rats Per Sex Dosed	Number of Rats Per Sex Used for Bone Marrow Collection After Dose Administration	
		24 hr	48 hr
Vehicle Control			
Water	10	5	5
Test Article			
Oxymorphone HCl			
Low test dose (10 mg/kg)	5	5	0
Mid test dose (20 mg/kg)	5	5	0
High test dose (40 mg/kg)	15*	5	5
Positive Control			
CP (40 mg/kg)	5	5	0

*including 5 replacement animals per sex to ensure the availability of five animals for micronucleus analysis

Analysis:

No. of replicates: A total of 2000 polychromatic erythrocytes were scored for the presence of micronuclei. The number of polychromatic erythrocytes to total erythrocytes was recorded per 1000 erythrocytes. 2 slides were prepared for each rat.

Counting method: Slides were analyzed microscopically using an oil immersion lens.

Criteria for positive results: "The test article was considered to induce a positive response if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables) at any sampling time. If a single treatment group was significantly elevated at one sacrifice time with no evidence of a dose-response, the assay was considered a suspect or unconfirmed positive and a repeat assay recommended."

Summary of individual study findings:

Study validity: The study appears to be valid for the following reasons: 1) the positive control, cyclophosphamide produced a statistically significant increase in the number of micronucleated polychromatic erythrocytes compared to controls and 2) the sampling times, positive controls and study design were according to OECD guidelines. Dosing was adequate for the study.

Study outcome: Mortality and clinical signs following oxymorphone administration are presented in the sponsor's table 3 (below). As noted, 2/15 males and 1/15 females in the high dose group died. These animals were replaced for analysis of micronucleated erythrocytes.

Table 3: Definitive Micronucleus Study - Clinical Signs
Following Dose Administration of Oxymorphone HCl in —:CD® (SD) IGS BR Rats

Treatment	Clinical Observation	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Water 10 mL/kg	*	*/10	*/10	0/10	0/10
Oxymorphone HCl 10 mg/kg	Lethargy	5/5	5/5	0/5	0/5
20 mg/kg	Lethargy	5/5	5/5	0/5	0/5
40 mg/kg	Lethargy Piloerection	15/15 14/15	15/15 14/15	2/15	1/15
CP 40 mg/kg	*	*/5	*/5	0/5	0/5

*No clinical signs observed, all animals appeared normal after dose administration

Analysis of the bone marrow cells collected at 24 and 48 hours after treatment indicated that at 24 hours oxymorphone at 20 mg/kg significantly increased the number of micronucleated polychromatic erythrocytes per PCE scored in both males and females. Males treated with the 40 mg/kg dose also demonstrated a significant increase in micronucleated erythrocytes, although MPCE/PCE in females at this dose was not significantly different than controls. At 48 hours, the high dose oxymorphone was not significantly different from controls. Cyclophosphamide treatment produced a significant increase in micronucleated erythrocytes. These results are summarized in sponsor's table 4, reproduced on the following page:

Table 4: Summary of Bone Marrow Micronucleus Analysis After a Single Dose of Oxymorphone HCl in [redacted]:CD® (SD) IGS BR Rats

Treatment	Sex	Time (hr)	Number of Rats	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes: Number per 1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored[1]
Water							
10 ml/kg	M	24	5	0.663 ± 0.06	---	0.7 ± 0.45	7 / 10000
	F	24	5	0.662 ± 0.04	---	0.7 ± 0.67	7 / 10000
Oxymorphone HCl							
10 mg/kg	M	24	5	0.649 ± 0.02	-2	1.4 ± 0.42	14 / 10000
	F	24	5	0.663 ± 0.02	0	0.5 ± 0.61	5 / 10000
20 mg/kg	M	24	5	0.653 ± 0.04	-2	1.7 ± 0.57	*17 / 10000
	F	24	5	0.685 ± 0.05	3	1.6 ± 0.65	*16 / 10000
40 mg/kg	M	24	5	0.664 ± 0.04	0	2.6 ± 0.42	*26 / 10000
	F	24	5	0.693 ± 0.04	5	1.1 ± 0.42	11 / 10000
CP							
40 mg/kg	M	24	5	0.599 ± 0.03	-10	29.8 ± 9.26	*298 / 10000
	F	24	5	0.604 ± 0.03	-9	18.5 ± 6.20	*185 / 10000
Water							
10 ml/kg	M	48	5	0.667 ± 0.08	---	0.4 ± 0.42	4 / 10000
	F	48	5	0.675 ± 0.02	---	0.7 ± 0.76	7 / 10000
Oxymorphone HCl							
40 mg/kg	M	48	5	0.677 ± 0.03	1	0.7 ± 0.45	7 / 10000
	F	48	4**	0.769 ± 0.02	14	0.5 ± 0.41	4 / 8000

[1]*, p≤0.05 (Kastenbaum-Bowman Tables)
**One of the animals was considered to be outlier, number of MPCEs (15) for the animal was not used in statistical analysis

Toxicokinetic analysis indicated that both males and females demonstrated similar exposures (below):

Table 2. **Mean Plasma Concentrations and Toxicokinetic Parameters of Oxymorphone in Sprague-Dawley Rats Following Single Oral Administration (QPS Project Number 52-0201PK)**

Sex	Male			Female		
Dose, mg/kg	10	20	40	10	20	40
Plasma Conc, ng/mL						
1 h	15.675	20.994	26.482	13.646	34.919	22.425
4 h	6.763	9.598	26.410	7.806	14.933	23.777
24 h	0.222	3.993	8.107	1.084	5.128	10.244
Toxicokinetic Parameter						
Cmax, ng/mL	15.675	20.994	33.422	13.646	35.573	28.518
Tmax, h	1.0	1.0	2.8	1.0	1.6	2.2
AUC_{0-24h}, ng/mL-h	111.348	192.293	437.750	127.896	292.844	420.726

As noted in the table above, oxymorphone treatment produced only a slight (2%) reduction in the ratio of polychromatic erythrocytes to normal erythrocytes. This indicates that oxymorphone did not inhibit erythropoiesis in these animals.

Overall, these results suggest that oxymorphone at a dose of 20 mg/kg and 40 mg/kg produces a significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow of the rat. Thus,

oxymorphone is considered positive in the rat micronucleus assay, an *in vivo* test for mammalian chromosomal damage, under the conditions tested. This conclusion is in concurrence with the Sponsor.

Study title: Mammalian erythrocyte micronucleus test with kinetochore analysis [oxymorphone HCl]

Key findings: The results of this study confirm that oxymorphone at doses of 250 and 500 mg/kg produces a significant increase in the incidence of micronucleated polychromatic erythrocytes and therefore is clastogenic. Kinetochore analysis indicated that oxymorphone does not increase the percentage of micronucleated erythrocytes with kinetochores, suggesting that the DNA damage is due to chromosomal breakage rather than loss of the entire chromosome.

Study no: AA46XC.126.BTL
Study type (if not reflected in title): *in vivo* mouse micronucleus test
Volume #, and page #: Volume 2, page 330
Conducting laboratory and location: [redacted]
Date of study initiation: October 18, 2001
GLP compliance: Yes, with the exception that the oxymorphone analysis was limited to the stock solution. Test solutions, prepared via serial dilution of the stock solution, were not analyzed.
QA reports: Yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxymorphone HCl, Mallinckrodt B14802, [redacted],

Formulation/vehicle: Water

Methods:

Strains/species/cell line: ICR mice (male and female)
Dose selection criteria: Previous toxicity results
Basis of dose selection: Doses were based upon results of the previous study AA46XC_XD.123.BTL
Range finding studies: N/A.
Test agent stability: Test article had an expiration date (powder) of November 2, 2010. Stability was tested by the sponsor. Results indicated that drug solutions of 0.01 mg/mL, 1 mg/mL and 50 mg/mL both in water and pH 4.5 phosphate buffer was stable up to at least [redacted] days under ambient conditions. At [redacted] days, individual known and unknown degradation products as well as total degradation products were less than [redacted]
Metabolic activation system: N/A
Controls:
Vehicle: Water
Negative controls: Water
Positive controls: Cyclophosphamide monohydrate as a positive control for MPCE analysis. Vinblastine was used as a positive control for kinetochore analysis (i.p.)
Comments: These controls are adequate.
Exposure conditions:
Incubation and sampling times: 24 hour treatment
Doses used in definitive study: 250 and 500 mg/kg oxymorphone HCl via oral gavage (20 ml/kg).

Study design:

	Number of Mice Per Sex	Number of Mice Per Sex Used for Bone Marrow Collection 24 hours After Dose Administration
Vehicle Control: Water	5	5
Test Article: Oxymorphone HCl		
Mid test dose (250 mg/kg)	5	5
High test dose (500 mg/kg)	10*	5
Positive Control: CP 50 mg/kg	5	5
Positive Control: VB 6 mg/kg	5	5

*including 5 replacement animals per sex to ensure the availability of five animals for micronucleus analysis

Analysis:

No. of replicates: A total of 2000 polychromatic erythrocytes were scored for the presence of micronuclei. The number of polychromatic erythrocytes to total erythrocytes was recorded per 1000 erythrocytes. 2 slides were prepared for each rat. For kinetochore analysis, 25 micronucleated polychromatic erythrocytes per animal were analyzed for the presence or absence of kinetochores.

Counting method: Slides were analyzed microscopically using an oil immersion lens. For kinetochore analysis, a microscope with a blue excitation filter and barrier filter for 520 nm was used with an oil immersion lens.

Criteria for positive results: "The test article was considered to induce a positive response if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables)." "The test article was considered positive for induction of aneuploidy if the frequency of kinetochore-positive micronucleated PCEs in the test article-treated groups was statistically increased (Fisher's exact test, $p \leq 0.05$) above the vehicle (negative) control."

Summary of individual study findings:

Study validity: The study appears to be valid for the following reasons: 1) the positive control, cyclophosphamide, produced a statistically significant increase in the number of micronucleated polychromatic erythrocytes compared to controls and 2) the sampling times, positive controls and study design were according to OECD guidelines. The kinetochore analysis also appears valid as vinblastine produced a clear increase in the number of micronucleated polychromatic erythrocytes with kinetochores.

Study outcome: There was no mortality with either dose tested in this study. Clinical observations are summarized in the sponsor's table 1 reproduced below:

Table 1: Micronucleus Assay with Kinetochore Analyses - Clinical Signs Following Dose Administration of Oxymorphone HCl In ICR Mice

Treatment	Clinical Observation	Number of Animals With Clinical Signs/Total Number of Animals Dosed		Number of Animals Died/Total Number of Animals Dosed	
		Males	Females	Males	Females
Water 20 mL/kg	*	*/5	*/5	0/5	0/5
Oxymorphone HCl 250 mg/kg	Hyperactivity Erect tails	5/5 5/5	5/5 5/5	0/5	0/5
Oxymorphone HCl 500 mg/kg	Hyperactivity Erect tails Lethargy Crusty eyes	10/10 10/10 10/10 0/10	10/10 10/10 10/10 3/10	0/10	0/10
Cyclophosphamide 50 mg/kg	*	*/5	*/5	0/5	0/5
Vinblastine 6 mg/kg	*	*/5	*/5	0/5	0/5

*No clinical signs observed, all animals appeared normal after dose administration

Table 2: Summary of Bone Marrow Micronucleus Analysis After a Single Dose of Oxymorphone HCl In ICR Mice

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes: Number per 1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored[1]
Water							
20 mL/kg	M	24	5	0.458 ± 0.03	—	0.5 ± 0.00	5 / 10000
	F	24	5	0.479 ± 0.05	—	0.6 ± 0.22	6 / 10000
Oxymorphone HCl							
250 mg/kg	M	24	5	0.401 ± 0.02	-12	2.7 ± 0.91	*27 / 10000
	F	24	5	0.354 ± 0.08	-26	3.4 ± 1.29	*34 / 10000
500 mg/kg	M	24	5	0.343 ± 0.07	-25	2.1 ± 1.14	*21 / 10000
	F	24	5	0.348 ± 0.05	-27	3.3 ± 0.76	*33 / 10000
CP	M	24	5	0.276 ± 0.05	-40	29.4 ± 4.76	*294 / 10000
50 mg/kg	F	24	5	0.321 ± 0.01	-33	29.9 ± 2.84	*299 / 10000

[1]*, $p \leq 0.05$ (Kastenbaum-Bowman Tables)

As indicated in the sponsor's table 2 above, both the 250 and 500 mg/kg dose of oxymorphone produced a significant increase in the number of micronucleated polychromatic erythrocytes per number of PCEs scored. Likewise, cyclophosphamide also significantly increased the number of micronucleated polychromatic erythrocytes. Oxymorphone treatments produced a 12 to 27% decrease in the ratio of polychromatic erythrocytes to total erythrocytes, indicating that the drug was bioavailable to the bone marrow target tissue.

As outlined in the table below (data taken from sponsor's table 4), treatment of the animals with vinblastine produced a significant increase in the percentage of micronucleated polychromatic erythrocytes with kinetochores compared to water control. Treatment with either dose of oxymorphone did not significantly

alter the proportion of cells with kinetochores in either males or females treated with 250 mg/kg or males treated with 500 mg/kg. There was a significant increase in the proportion of cells with kinetochores in female animals treated with oxymorphone at 500 mg/kg, however, the sponsor did not interpret this to be biologically significant as it was only a 2 fold increase over the negative control. No historical control data was provided. These data indicate that, for the most part, the effects of oxymorphone on the incidence of micronucleated polychromatic arise primarily from chromosomal breaks rather than loss of whole chromosomes.

Treatment	% of total Micronucleated polychromatic erythrocytes scored			
	Males		Females	
	Without Kinetochores	With Kinetochores	Without Kinetochores	With Kinetochores
Water	89	11	94	6
Oxymorphone HCl 250 mg/kg	88	12	95	5
Oxymorphone HCl 500 mg/kg	87	13	86	14
Vinblastine 6 mg/kg	9	91	10	90

Overall, the results support the previous findings that oxymorphone is a positive clastogen and provide evidence that oxymorphone is a negative aneugen.

Study title: Bacterial Reverse Mutation Study with [redacted]

Key findings: [redacted] was tested in the bacterial reverse mutation assay at concentrations up to 1000 µg/plate with and without metabolic activation. The results indicated that under the conditions of the study, [redacted] was not mutagenic in any strain tested.

Study no.: Endo # SP0002-210-03
Volume #, and page #: Submission N 000 MR
Conducting laboratory and location: [redacted]

Date of study initiation: March 26, 2003
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: [redacted] Lot D14182, [redacted]

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA were tested.

Doses used in definitive study: The concentrations used in the definitive assay (B-1) were 62.5, 125, 250, 500 and 1000 µg/plate. A confirmation assay was also completed (B-2).

Basis of dose selection: Concentrations for the definitive mutation assay were chosen based upon results of a range-finding test using strain TA100 and WP2 uvrA. Seven concentrations of test article ranging from 5 to 5000 µg/plate were evaluated with and

without rat liver S-9. Following 64 hour incubation period, plates with no interfering precipitate were counted by automatic colony counter (plates with precipitate were counted by hand).

Negative controls: As stock solutions of the test article were prepared in 0.16 N HCl, this was used as the solvent control.

Positive controls: The following positive controls were used (sponsor's table). All positive controls were dissolved in DMSO (except NaAz and MMS, which were dissolved in sterile water).

Strain	S-9	Chemical	Concentration (μg/plate)
TA98	-	2-NF (2-Nitrofluorene)	5.0
TA98	+	2-AA (2-Aminoanthracene)	1.25
TA100	-	NaAz (Sodium Azide)	1.0
TA100	+	2-AA (2-Aminoanthracene)	1.25
TA1535	-	NaAz (Sodium Azide)	1.0
TA1535	+	2-AA (2-Aminoanthracene)	1.25
TA1537	-	9-AA (9-Aminoacridine)	50
TA1537	+	2-AA (2-Aminoanthracene)	1.25
WP2 uvrA	-	MMS (Methyl Methanesulfonate)	4000
WP2 uvrA	+	2-AA (2-Aminoanthracene)	10

Incubation and sampling times: For the range finding test, plates were incubated for approximately 64 hours. For the definitive assay, plates were incubated for approximately 68 hours.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The criteria for a valid assay were met. These included mean reversion frequency of the test article solvent control plates falling into pre-specified ranges, the positive controls had a mean reversion frequency 3-times or more greater than the mean reversion frequency of the solvent controls and the tester strains were confirmed for the appropriate growth dependency. The criteria for a negative response are acceptable. Specifically a response was considered to be negative if all strains treated with the test article had a mean reversion frequency that was less than twice the mean reversion frequency of the corresponding solvent control plates in TA98 and TA100 and less than 3-times in TA1535, TA1537 and WP2 uvrA, and there was no evidence of a concentration-dependent response. A response was considered positive if either strain TA98 or TA100 exhibited a mean reversion frequency at least double the mean reversion frequency of the corresponding solvent control in at least one concentration, or if either strain TA1535, TA1537 or WP2 uvrA exhibited a 3-fold increase in mean reversion frequency compared

to solvent control. In addition, the response must be concentration-dependent. A response was considered equivocal if it did not fulfill criteria for a negative or a positive response. The study appears to be valid.

Study outcome: The results of the range-finding assays for strain TA100 and WP2 uvrA are summarized in the table below. Cell viability was expressed as the relative cloning efficiency (number of colonies in test plates divided by the number of colonies in the solvent control plates times 100).

Summary of the Viability of bacterial strains in the presence of [redacted]

Concentration (µg/plate)	TA100		WP2 uvrA	
	- S9	+ S9	-S9	+S9
5.0	125%	103%	112%	103%
10	122%	110%	109%	95%
50	114%	109%	106%	98%
100	101%	107%	106%	101%
500	109%	103%	100%	103%
1000	57%	38%	51%	61%
5000	0%	0%	0%	0%
Solvent control	100%	100%	100%	100%

As noted in the table above, in the absence of S9 5000 µg/plate [redacted] lead to 0% viability, and 1000 µg/plate [redacted] produced 57% viability. For all studies, a greater than 50% decrease in viability was obtained at concentrations of either 500 or 1000 µg/plate. As such, the highest concentration chosen for the definitive assay was 1000 µg/plate.

The results of the definitive assay without metabolic activation are provided in the sponsor's table 3 reproduced below. The results indicate that under the conditions tested, [redacted] did not increase the average revertants per plate.

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