Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): One female in the control group died on gestation day 13. There were no internal observations at necropsy to suggest the cause of death. In the 10 mg/kg group, one female aborted one normally developing implantation. At necropsy, this animal had dark red lungs and five normally developing implantations and two early resorptions *in utero*. All other animals that survive to the scheduled necropsy on gestation day 29 did not show any treatment related internal findings. Additional findings that are common to the laboratory rabbit and not thought to be related to drug treatment included: cystic oviducts, accessory spleens and blood vessel variation in the left carotid artery.

Gestation Day 29 Laparohysterectomy Data. There were no significant changes in the mean fetal data at scheduled necropsy (number of male fetuses, number of female fetuses, viable fetuses, dead fetuses, early resorptions, late resorptions, post implantation loss, implantation sites, corpora lutea, pre-implantation loss or fetal weights). There was a significant decrease in male fetal weights in the high-dose group compared to controls, however, there were no differences in female fetal weights or mean combined fetal weights. These data are expressed below in table format:

| | **Fetal Weights (n=17-21/group) (% of Control, grams)** | | |
|---|---|---|---|
| **Dose (mg/kg) →** | **10** | **25** | **50** |
| Male | -3 | -7 | -16* |
| Female | -1 | -7 | -7 |
| Combined | -2 | -8 | -10 |

Offspring (malformations, variations, etc.): The table below summarizes the results of the analysis of fetuses for malformations:

| | **Percentage of fetuses with malformations (% per liter)** | | | | |
|---|---|---|---|---|---|
| **Parameter Dose (mg/kg) →** | **0** | **10** | **25** | **50** | **Histor. Range** |
| **Number of fetuses (litters) examined** | 127 (22) | 116 (22) | 143 (22) | 113 (22) | |
| **External Malformations** | | | | | |
| Mandibular micrognathia | 0 | 0 | 0 | 0.6 | |
| Aglossia | 0 | 0 | 0 | 0.6 | 0-1 |
| **Visceral Malformations** | | | | | |
| Lungs – lobular agenesis | 0 | 0 | 0 | 0.6 | 0-0.9 |
| **Skeletal Malformations** | | | | | |
| Sternebrae fused | 0 | 0 | 0.6 | 0.6 | 0-1.9 |
| Rib anomaly (forked rib) | 0 | 0 | 0 | 1 | 0-7.1 |

n/n = total occurrences/number of animals

The incidence of aglossia, lung lobular agenesis, fused sternebrae and rib anomaly were within the historical control range for the laboratory and there was no clear dose-dependent relationship noted under the conditions of the assay. There is no evident relationship to the drug treatment. The finding of mandibular micrognathia was not noted in the historical controls; however, this incidence is within the range of the more severe finding of mandibular agnathia (0-1). The low incidence, lack of statistical significance and lack of apparent dose-dependency with this finding (under the conditions tested) suggests that this finding is not clearly related to drug treatment.

## Prenatal and postnatal development

**Study title: Study of the Effects of Oxymorphone Hydrochloride on Pre- and Postnatal Development, Including Maternal Function in the Rat**

**Key study findings**: 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 in a segment III study with the following key findings:

1. $F_0$ female mortality was noted in 5 of 25 in the 10 mg/kg/day group and 1/25 in the 25 mg/kg/day group. 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.
2. 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.
3. 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.
4. In surviving $F_0$ females, there were not differences between the number of pups born and the number of implantation sites between groups.
5. 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.
6. Post-natal survival of the $F_1$ pups was reduced in the 25 mg/kg/day treatment group.
7. 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.

8. There were no treatment-related findings on PND 21 pups not selected for further study at necropsy.
9. 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.
10. There were no treatment-related effects of oxymorphone in behavioral evaluation (acoustic startle, locomotor and Biel Maze Swimming Trials).
11. Reproductive performance in the $F_1$ generation was not altered by $F_0$ generation oxymorphone treatment at any dose level tested.
12. 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.
13. There were no findings in the $F_2$ fetuses which could be attributed to $F_0$ maternal treatment with oxymorphone.

**Study no.:** —-411009
**Volume #, and page #:** Electronic Document Room
**Conducting laboratory and location:** [redacted]

**Date of study initiation:** February 9, 2002
**GLP compliance:** Yes
**QA reports:** yes ( X ) no ( )
**Drug, lot #, and % purity:** Oxymorphone HCl, Lot 0881 A 42771, — purity (dose calculates were corrected based upon the purity of the drug).

**Methods**

Doses: 0, 1, 5, 10 and 25 mg/kg/day. $F_0$ females were dosed from gestation day 6 through lactation day 20.

Species/strain: —:CD(SD)IGS BR female rats

Number/sex/group: 25 females per group as below:

| Group | Test Article | Dosage Level[a] (mg/kg/day) | Dosage Concentration[a] (mg/ml) | Dosage Volume (ml/kg) | Number of Females |
|---|---|---|---|---|---|
| 1 | Vehicle | 0 | 0 | 10 | 25 |
| 2 | Oxymorphone HCl | 1 | 0.1 | 10 | 25 |
| 3 | Oxymorphone HCl | 5 | 0.5 | 10 | 25 |
| 4 | Oxymorphone HCl | 10 | 1.0 | 10 | 25 |
| 5 | Oxymorphone HCl | 25 | 2.5 | 10 | 25 |

[a] = Expressed in terms of the oxymorphone salt

Route, formulation, volume, and infusion rate: Oral gavage as a single dose. Volume was 10 ml/kg in all groups.

Satellite groups used for toxicokinetics: None

Study design: $F_0$ female rats were dosed from gestation day 7 through lactation day 20 with oxymorphone or vehicle. Females were paired with an untreated resident male of the same strain. Once positive identification of mating was obtained (vaginal copulatory plug or presence of sperm in a vaginal smear), the females were transferred to plastic maternity cages. All females were allowed to deliver naturally and rear their young to weaning (PND 21). To reduce variability among the litters, eight pups per litter (4 per sex) were randomly selected on PND 4. Between PND 10 and 16, 25 males and females were randomly chosen for the $F_1$ generation. Offspring ($F_1$) were housed in housed until PND 28 then individually housed until euthanasia (with the exception of the mating period, when each $F_1$ female was cohabitated with $F_1$ makes in the home cage of the male).

Parameters and endpoints evaluated: Animals were observed twice daily for mortality and moribundity. Clinical observations included evaluations of skin and fur appearance, eyes, mucous membranes, respiratory and circulatory systems, autonomic and central nervous systems, somatomotor activity and behavior. In addition, females were observed during the treatment period at the time of dosing and one and three hours following dosing. Body weights were recorded on gestation days 0, 6, 9, 12, 15, 18 and 20 and on lactation days 1, 4, 7, 10, 14, 17 and 21. Food consumption was recorded on the corresponding gestation and lactation body weight days. During parturition, females were observed two times each day for initiation and completion of parturition and for signs of dystocia. The day at which parturition was first observed was designated PND 0. When parturition was complete, the numbers of stillborn and live pups in each litter was recorded. Pups were sexed and examined for gross malformations.

Gross necropsy was performed on $F_0$ animals which died prior to scheduled euthanasia. The number and location of corpora lutea and implantation sites were recorded. Females which failed to deliver were euthanized on post-mating day 25, their abdominal and thoracic cavities were opened, the contents examined and pregnancy status was

determined. Females with total litter loss were examined for the number of former implantation sites. Females that survived to lactation day 21 were euthanized and necropsied. The number of former implantation sites was recorded.

Testing of the F1 litters included daily examination of general appearance, behavior and survival. Any pups that died were necropsied. Litters were examined daily for adverse changes in appearance or behavior. Each pup received a detailed physical examination on PND 1, 4, 7, 10, 14, 17 and 21 and weekly thereafter. Body weights of pups were recorded on PND 1, 4, 7, 10, 14, 17, 21 and weekly thereafter. Pups were sexed individually on PND 0, 4 and 21. A minimum of 1 male and 1 female per litter were selected for assessment of attainment of developmental landmarks, neurobehavioral evaluations and reproductive capacity.

**Results**

$F_0$ in-life:

Mortality: Five $F_0$ females in the 10 mg/kg/day group and 1 female in the 25 mg/kg/day group were found dead. One 10 mg/kg/day female was found dead on lactation day 0, all other deaths were between lactation day 13 and 19.

| Maternal Survival and Pregnancy Status $F_0$ Females | Dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 5 | 10 | 25 |
| **Females in study** | 25 | 25 | 25 | 25 | 25 |
| Females that died early | 0 | 0 | 0 | 5 | 1 |
| Females that were euthanized | 0 | 0 | 0 | 0 | 0 |
| Females Allowed to deliver | 25 | 25 | 25 | 25 | 25 |
| Gravid | 24 | 24 | 25 | 24 | 25 |
| Females with total litter loss | 0 | 1 | 2 | 0 | 13 |
| Females with viable pups | 25 | 24 | 23 | 24 | 12 |
| NonGravid | 0 | 0 | 0 | 1 | 0 |

Clinical Signs: Clinical signs included exophthalmia and Straub tail in the females that died early prior to death. The female in the 25 mg/kg/day group that died early displayed hypoactivity and exhibited whole-body tetany and salivation on gestation day 7. This animal also rocked, lurched and/or swayed while walking on four occasions, the first of which was gestation day 10. Rales and wet material around the nose and mouth were observed in one 10 mg/kg/day female on day 19.

Clinical signs in the animals that survived until scheduled sacrifice that appeared to be related to drug treatment are summarized in the table below:

| Clinical Signs (Daily Examinations) $F_0$ Females | Dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 5 | 10 | 25 |

| | | | | | |
|---|---|---|---|---|---|
| **Cardio-Pulmonary** | | | | | |
| Rales | 0/0 | 0/0 | 0/0 | 1/1 | 4/1 |
| **Eyes/Ears/Nose** | | | | | |
| Dried red material around eyes | 0/0 | 0/0 | 0/0 | 0/0 | 2/1 |
| Dried red material around nose | 0/0 | 0/0 | 1/1 | 0/0 | 3/1 |
| **Excreta** | | | | | |
| Decreased defecation | 0/0 | 1/1 | 1/1 | 1/1 | 4/2 |
| Soft stool | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 |

N/N = Total occurrence / Number of animals

Clinical signs noted 1 hour post-dosing were generally consistent with opioid-mediated effects.

| Clinical Signs (1-hour post-dose) $F_0$ Females | Dose (mg/kg) | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 5 | 10 | 25 |
| **Behavioral/CNS** | | | | | |
| Straub tail | 1/1 | 44/18 | 127/25 | 171/25 | 239/25 |
| Whole body tetany | 0/0 | 0/0 | 0/0 | 1/1 | 4/4 |
| Hypoactive | 0/0 | 0/0 | 0/0 | 1/1 | 10/8 |
| Hyperactive | 0/0 | 0/0 | 2/1 | 1/1 | 1/1 |
| Rocks/lurches, and sways as it walks | 0/0 | 0/0 | 2/2 | 15/12 | 61/21 |
| Piloerection | 0/0 | 0/0 | 1/1 | 1/1 | 8/5 |
| **Cardiopulmonary** | | | | | |
| Rales | 0/0 | 0/0 | 0/0 | 2/1 | 0/0 |
| Shallow respiration | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 |
| **Eyes/Ears/Nose** | | | | | |
| Exophthalmus right eye | 2/2 | 306/25 | 330/25 | 351/25 | 426/25 |
| Exophthalmus left eye | 2/2 | 309/25 | 334/25 | 357/25 | 435/25 |
| Dried red material around nose | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 |
| Lacrimation | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 |
| **Oral/Dental** | | | | | |
| Salivation | 0/0 | 0/0 | 0/0 | 2/1 | 7/6 |

N/n = Total occurrence / Number of animals

Mean body weight losses were observed in the 25 mg/kg/day group from gestation day 6-9 and 9-12. Mean body weight gain in this group was similar to the control group from gestation day 12-20, however, body weights in these animals remained significantly below control animals throughout gestation. Mean body weights in animals treated with the 10 mg/kg/day dose of oxymorphone were significantly lower than the control animals beginning on gestation day 9. Body weights in the 1 and 5 mg/kg/day groups were significantly reduced compared to controls beginning on study day 12. The sponsor's table 6 (reproduced below) represents the mean body weights of the $f_0$ generation.

TABLE 6 (F0)
PROJECT NO.: [redacted]411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

| GROUP : | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| DAY 0 | MEAN | 256. | 254. | 255. | 254. | 254. |
| | S.D./N | 16.3/25 | 15.7/25 | 16.1/25 | 14.5/24 | 11.6/25 |
| DAY 6 | MEAN | 293. | 281. | 290. | 287. | 288. |
| | S.D./N | 20.1/25 | 24.1/25 | 15.8/25 | 16.9/24 | 14.1/25 |
| DAY 9 | MEAN | 304. | 293. | 292. | 286.** | 287.** |
| | S.D./N | 20.5/25 | 19.7/25 | 16.2/25 | 17.0/24 | 16.8/25 |
| DAY 12 | MEAN | 320. | 306.* | 302.** | 290.** | 282.** |
| | S.D./N | 23.2/25 | 21.8/25 | 16.4/25 | 16.6/24 | 15.4/25 |
| DAY 15 | MEAN | 335. | 318.* | 314.** | 304.** | 298.** |
| | S.D./N | 21.4/25 | 23.6/25 | 18.1/25 | 17.0/24 | 18.2/25 |
| DAY 18 | MEAN | 375. | 351.** | 349.** | 342.** | 331.** |
| | S.D./N | 28.2/25 | 30.5/25 | 25.7/25 | 21.8/24 | 24.9/25 |
| DAY 20 | MEAN | 407. | 380.** | 377.** | 371.** | 364.** |
| | S.D./N | 31.3/25 | 35.0/25 | 30.5/25 | 23.0/24 | 31.0/25 |

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Body weight changes during lactation were also still evident in oxymorphone treated animals, as indicated the sponsor's table 8 reproduced below:

Appears This Way
On Original

TABLE 8 (F0)
PROJECT NO. [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN BODY WEIGHTS (GRAMS) DURING LACTATION

| GROUP : | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| DAY 1 | MEAN | 302. | 290. | 280.** | 275.** | 264.** |
| | S.D./N | 24.6/25 | 24.9/25 | 17.4/24 | 16.4/23 | 28.7/23 |
| DAY 4 | MEAN | 318. | 303. | 290.** | 281.** | 265.** |
| | S.D./N | 26.4/25 | 26.9/24 | 18.3/23 | 17.5/23 | 17.5/14 |
| DAY 7 | MEAN | 323. | 305.** | 298.** | 291.** | 290.** |
| | S.D./N | 14.8/25 | 17.3/24 | 22.9/23 | 14.9/23 | 16.6/12 |
| DAY 10 | MEAN | 338. | 324. | 314.** | 307.** | 308.** |
| | S.D./N | 22.2/25 | 24.7/24 | 18.4/23 | 18.7/23 | 14.4/12 |
| DAY 14 | MEAN | 356. | 337.* | 323.** | 315.** | 314.** |
| | S.D./N | 23.3/25 | 25.6/24 | 18.4/23 | 21.8/21 | 19.9/12 |
| DAY 17 | MEAN | 359. | 343.* | 332.** | 322.** | 319.** |
| | S.D./N | 22.1/25 | 25.6/24 | 16.4/23 | 19.1/21 | 16.5/12 |
| DAY 21 | MEAN | 337. | 323. | 320.* | 302.** | 305.** |
| | S.D./N | 23.1/25 | 24.9/24 | 21.1/23 | 16.8/19 | 17.3/11 |

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Food consumption in the $f_0$ animals was reduced by oxymorphone treatment in a dose-dependent manner, consistent with the changes in body weight. The sponsor's table 10 below demonstrates that as early as day 6, food consumption was statistically lower than controls in animals treated with 5 mg/kg/day and above. Animals treated with 1 mg/kg/day consumed statistically lower mass of food on gestation days 12-15. Over the course of the gestational period (day 6-20), all doses of oxycodone produced significantly lower food consumption compared to controls.

TABLE 10 (F0)
PROJECT NO. [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

| GROUP : | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| DAY 0- 6 | MEAN | 22. | 20.* | 22. | 21. | 21. |
| | S.D./N | 2.0/25 | 2.4/25 | 1.6/25 | 1.7/24 | 1.9/25 |
| DAY 6- 9 | MEAN | 23. | 21. | 19.** | 17.** | 14.** |
| | S.D./N | 2.3/25 | 2.0/25 | 1.8/25 | 2.9/24 | 3.3/25 |
| DAY 9- 12 | MEAN | 24. | 22. | 21.** | 19.** | 19.** |
| | S.D./N | 2.3/24 | 2.4/25 | 1.8/25 | 2.1/24 | 3.9/25 |
| DAY 12- 15 | MEAN | 25. | 23.** | 22.** | 21.** | 20.** |
| | S.D./N | 2.6/24 | 2.6/25 | 2.0/25 | 2.1/24 | 2.4/25 |
| DAY 15- 18 | MEAN | 26. | 25. | 24. | 23.** | 21.** |
| | S.D./N | 3.2/25 | 3.2/25 | 2.5/25 | 1.8/24 | 3.6/25 |
| DAY 18- 20 | MEAN | 26. | 24. | 23.* | 23.* | 23.* |
| | S.D./N | 3.2/25 | 3.5/25 | 3.9/25 | 4.2/24 | 4.4/25 |
| DAY 6- 20 | MEAN | 25. | 23.** | 22.** | 21.** | 19.** |
| | S.D./N | 2.1/25 | 2.3/25 | 1.8/25 | 2.0/24 | 2.7/25 |
| DAY 0- 20 | MEAN | 24. | 22.** | 22.** | 21.** | 20.** |
| | S.D./N | 2.1/25 | 2.1/25 | 1.4/25 | 1.6/24 | 2.2/25 |

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Mean food consumption was also reduced by oxymorphone treatment during lactation, as indicated in the sponsor's table 12 below:

TABLE 12 (F0)
PROJECT NO. [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN FOOD CONSUMPTION DURING LACTATION (GRAMS/ANIMAL/DAY)

| GROUP : | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| DAY 1- 4 MEAN | 37. | 36. | 35. | 34. | 26.** |
| S.D./N | 5.3/25 | 5.4/24 | 8.9/23 | 5.2/23 | 4.8/14 |
| DAY 4- 7 MEAN | 42. | 42. | 39. | 41. | 37. |
| S.D./N | 7.3/25 | 7.2/24 | 7.4/23 | 3.6/23 | 4.6/12 |
| DAY 7- 10 MEAN | 52. | 55. | 47. | 49. | 44.** |
| S.D./N | 6.2/25 | 5.9/24 | 10.6/23 | 5.6/23 | 5.7/12 |
| DAY 10- 14 MEAN | 62. | 63. | 56.* | 59. | 53.** |
| S.D./N | 6.2/25 | 7.3/24 | 13.9/23 | 6.5/21 | 7.5/12 |
| DAY 14- 17 MEAN | 68. | 68. | 61. | 64. | 57.** |
| S.D./N | 5.4/25 | 5.8/24 | 16.5/23 | 5.9/21 | 10.2/12 |
| DAY 17- 21 MEAN | 68. | 68. | 61. | 73. | 72. |
| S.D./N | 5.8/24 | 7.3/24 | 17.0/23 | 9.4/19 | 8.9/11 |
| DAY 1- 21 MEAN | 56. | 56. | 51.* | 55. | 49.* |
| S.D./N | 3.3/24 | 4.6/24 | 11.6/23 | 2.9/19 | 5.1/11 |

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

The effects of oxymorphone on food consumption during lactation was significant primarily in the animals dosed with 25 mg/kg/day.

Gestation length. Oxymorphone treatment produced a slight (maximum of 2.3% or less than one day) but statistically significant increase in the mean gestation length. The gestational lengths noted in oxymorphone treated rats were, however, within the historical control data for the laboratory (21.6 to 22.3 days). Therefore, the clinical significance of this observation appears to be minimal.

$F_0$ necropsy: The female animal in the 25 mg/kg/day treatment group that was found dead on lactation day 18 had enlarged adrenal glands and a dark red pituitary. The female in the 10 mg/kg/day group that died early had a distended stomach and intestine at necropsy. The pathology report indicated that these findings were not considered to be test article related.

One, two and 13 females in the 1, 5 and 25 mg/kg/day group had total litter loss. One animal in the high dose group had a mass in the renal cortex and medulla. There were no other observations noted upon necropsy in these animals.

Female animals that survived to the scheduled sacrifice on lactation day 21 did not show any treatment-related findings on necropsy. There were no differences between the number of pups born and the number of implantation sites between groups.

$F_1$ physical development: There were no significant differences in the mean number of pups born, % males at birth or the mean litter size between groups. Mean litter size in the high dose oxymorphone treatment group (12.4) was 18% lower than the mean litter size in control animals (15.2). Although this effect was not statistically significant, the reduction is likely attributed to the administration of the test article.

Post-natal survival was reduced in the 25 mg/kg/day treatment group throughout the pre-weaning period (PND 0, 0-1, 1-4, birth-PND 4 and PND 4-21). This is consistent with 13 of 25 animals in the high dose group demonstrating total litter loss. In addition, there was significantly lower survival in the 5 and 10 mg/kg/day groups from PND 0-1. Although these effects were not dose-related, they are likely related to the treatment administration. In the 1 mg/kg/day group, post-natal survival

| | Summary of Postnatal Survival ($F_1$) % per litter | | | | |
|---|---|---|---|---|---|
| **Parameter (mean)** **Dose (mg/kg) →** | **0** | **1** | **5** | **10** | **25** |
| PND 0 | 97.4 | 96.9 | 92.1 | 97.5 | 79.9* |
| PND 0-1 | 99.8 | 94.8 | 86.2* | 92.9* | 45.6* |
| PND 1-4 | 99.0 | 99.7 | 96.7 | 99.1 | 79.6 |
| PND 4-7 | 99.5 | 100 | 98.4 | 100 | 84.5 |
| PND 7-14 | 100 | 99.5 | 97.4 | 100 | 100 |
| PND 14-21 | 100 | 100 | 100 | 100 | 98.9 |
| Birth to PND 4 | 96.2 | 91.6 | 80.7 | 87.5 | 35* |
| PND 4 to PND 21 | 99.5 | 99.5 | 96.7 | 100 | 82.4* |

* $p < 0.05$ compared to control group

The general physical condition of the surviving pups in the oxymorphone treated groups were overall similar to the control group during the pre-weaning period.

Offspring mean body weights during the pre-weaning period were significantly reduced in the 25 mg/kg/day treatment group compared to controls on PND 1, 4 (pre-selection), 7, 10, 14, 17 and 21. In general, pups in the 1 mg/kg/day treatment group demonstrated higher mean offspring weights compared to control animals.

PROJECT NO.: [redacted]411009
SPONSOR:ENDO PHARM., INC.

TABLE 23 (F1 - PRE-WEANING)
STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SUMMARY OF MEAN OFFSPRING WEIGHTS (GRAMS)

(LITTER AS EXPERIMENTAL UNIT)

| DOSE GROUP: | | 0 MG/KG/DAY | 1 MG/KG/DAY | 5 MG/KG/DAY | 10 MG/KG/DAY | 25 MG/KG/DAY |
|---|---|---|---|---|---|---|
| PND 1 | | | | | | |
| MALES | MEAN | 7.0 | 7.4 | 7.0 | 6.8 | 5.8** |
| | S.D. | 0.69 | 0.49 | 0.84 | 0.47 | 0.37 |
| | N | 25 | 24 | 23 | 23 | 15 |
| FEMALES | MEAN | 6.6 | 7.0 | 6.7 | 6.3 | 5.4** |
| | S.D. | 0.61 | 0.49 | 0.62 | 0.47 | 0.56 |
| | N | 25 | 24 | 21 | 23 | 16 |
| PND 4 (BEFORE SELECTION) | | | | | | |
| MALES | MEAN | 9.7 | 10.6* | 9.5 | 9.4 | 7.0** |
| | S.D. | 1.09 | 1.04 | 1.19 | 0.75 | 1.57 |
| | N | 25 | 24 | 23 | 23 | 14 |
| FEMALES | MEAN | 9.1 | 10.1** | 9.2 | 8.8 | 7.0** |
| | S.D. | 0.93 | 0.99 | 1.01 | 0.65 | 1.61 |
| | N | 25 | 24 | 21 | 23 | 13 |
| PND 7 | | | | | | |
| MALES | MEAN | 15.4 | 16.9* | 14.5 | 14.9 | 11.3** |
| | S.D. | 2.15 | 1.86 | 2.66 | 1.30 | 1.71 |
| | N | 25 | 24 | 23 | 23 | 12 |
| FEMALES | MEAN | 14.4 | 16.3** | 14.1 | 13.9 | 11.3** |
| | S.D. | 1.66 | 1.57 | 2.06 | 1.28 | 2.07 |
| | N | 25 | 24 | 21 | 23 | 12 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PND 10 | | | | | | |
| MALES | MEAN | 22.2 | 24.5* | 20.8 | 21.3 | 16.6** |
| | S.D. | 3.02 | 2.34 | 4.41 | 2.02 | 2.31 |
| | N | 25 | 24 | 23 | 23 | 12 |
| FEMALES | MEAN | 21.0 | 23.6** | 20.7 | 20.2 | 16.4** |
| | S.D. | 2.51 | 2.10 | 2.98 | 1.62 | 2.84 |
| | N | 25 | 24 | 21 | 23 | 12 |
| PND 14 | | | | | | |
| MALES | MEAN | 32.4 | 34.7 | 29.5 | 30.7 | 24.9** |
| | S.D. | 4.19 | 3.07 | 6.83 | 2.73 | 2.63 |
| | N | 24 | 24 | 23 | 22 | 12 |
| FEMALES | MEAN | 30.9 | 33.7* | 29.7 | 29.2 | 24.2** |
| | S.D. | 3.28 | 2.78 | 3.81 | 2.46 | 3.36 |
| | N | 24 | 24 | 21 | 23 | 12 |
| PND 17 | | | | | | |
| MALES | MEAN | 39.7 | 41.5 | 35.1* | 37.4 | 30.8** |
| | S.D. | 4.64 | 3.55 | 8.62 | 3.00 | 2.95 |
| | N | 25 | 24 | 23 | 21 | 12 |
| FEMALES | MEAN | 37.9 | 40.3 | 35.7 | 35.4 | 29.3** |
| | S.D. | 3.66 | 3.30 | 4.88 | 3.02 | 4.69 |
| | N | 25 | 24 | 21 | 21 | 12 |
| PND 21 | | | | | | |
| MALES | MEAN | 50.0 | 53.1 | 44.9* | 49.2 | 39.6** |
| | S.D. | 5.81 | 4.42 | 10.98 | 3.89 | 3.12 |
| | N | 25 | 24 | 23 | 19 | 11 |
| FEMALES | MEAN | 47.3 | 51.4* | 46.8 | 46.9 | 38.0** |
| | S.D. | 4.54 | 4.41 | 6.23 | 3.74 | 4.78 |
| | N | 25 | 24 | 21 | 19 | 11 |

PND - POSTNATAL DAY
* - Significantly different from the control group at 0.05 using Dunnett's test
** - Significantly different from the control group at 0.01 using Dunnett's test

Necropsies were completed on pups that were found dead and on pups that were not selected for further study. There were no remarkable findings in the pups that were found dead that could be attributed to maternal treatment with the test article. One pup in the 25 mg/kg/day treatment group had an absent right kidney and ureter. At scheduled necropsy (PND 21) for pups not selective for further, there were no internal findings that could be attributed to maternal care.

Developmental landmarks in the $F_1$ pups were examined. Balanopreputial separation in males in the 25 mg/kg/day group was delayed compared to the control group. As this delay was also longer than the historical control mean, this finding may be attributable to the drug treatment. This delay is likely due to the reduction in body weight. Pups in the 1 mg/kg/day treatment group reached balanopreputial separation earlier than controls.

| **Developmental Landmarks** | **Day of acquisition and body weights ($F_1$)** | | | | |
|---|---|---|---|---|---|
| **Parameter (mean) Dose (mg/kg) →** | **0** | **1** | **5** | **10** | **25** |
| **Balanopreputial Separation (males)** | | | | | |
| Day (PND) | 44.4 | 42.8* | 44.3 | 44.2 | 46.1* |
| Body Weight (grams) | 231.8 | 229.1 | 222.0 | 223.0 | 211.0* |

* $p < 0.05$ compared to control group

There was no difference in the mean day of acquisition of vaginal patency in females between treatment groups.

$F_1$ behavioral evaluation: Behavioral evaluations included the acoustic startle test (PND 20 and 60), locomotor activity (PND 21 and 61), or the Biel Maze Swimming Trials (PND 22 and 62). There were no treatment-related findings in the oxymorphone treated animals that were significantly different from control values.

There were no treatment-related effects of oxymorphone on either clinical observations or survival of the $F_1$ generation males or females.

$F_1$ reproduction: Reproductive performance in the $F_1$ generation was not altered by $F_0$ maternal treatment. There were no differences in female or male mating indices or fertility indices. Likewise, there were no differences in the pre-coital interval or estrous cycle duration.

Body weights in the $F_1$ generation during the post-weaning period were significantly reduced in the 25 mg/kg/day groups on PND 28, 35, 42, 49, 56, 62 and 70. Mean body weights in the 10 mg/kg/day group were significantly reduced compared to controls 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.

TABLE 39 (F1 - POST-WEANING)
PROJECT NO. [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. SUMMARY OF MEAN OFFSPRING WEIGHTS (GRAMS)

(LITTER AS EXPERIMENTAL UNIT)

| DOSE GROUP: | | 0 MG/KG/DAY | 1 MG/KG/DAY | 5 MG/KG/DAY | 10 MG/KG/DAY | 25 MG/KG/DAY |
|---|---|---|---|---|---|---|
| PND 28 | | | | | | |
| MALES | MEAN | 87.8 | 94.8 | 83.3 | 85.5 | 71.5** |
| | S.D. | 11.40 | 9.19 | 13.15 | 6.01 | 6.50 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 82.1 | 85.9 | 79.8 | 79.4 | 67.3** |
| | S.D. | 9.22 | 5.25 | 7.84 | 6.55 | 10.52 |
| | N | 25 | 24 | 21 | 19 | 11 |
| PND 35 | | | | | | |
| MALES | MEAN | 148.9 | 157.6 | 140.4 | 143.1 | 123.0** |
| | S.D. | 17.91 | 17.11 | 20.61 | 7.68 | 9.32 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 130.8 | 134.9 | 127.3 | 125.4 | 109.9** |
| | S.D. | 11.19 | 8.27 | 9.25 | 9.49 | 15.14 |
| | N | 25 | 24 | 21 | 19 | 11 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PND 42 | | | | | | |
| MALES | MEAN | 212.1 | 221.5 | 201.6 | 204.7 | 180.6** |
| | S.D. | 22.34 | 23.61 | 25.67 | 12.07 | 12.78 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 166.7 | 167.4 | 161.6 | 157.9 | 144.3** |
| | S.D. | 11.97 | 11.06 | 10.63 | 11.25 | 14.61 |
| | N | 25 | 24 | 21 | 19 | 11 |
| PND 49 | | | | | | |
| MALES | MEAN | 273.7 | 283.7 | 258.2 | 258.2 | 235.6** |
| | S.D. | 27.15 | 29.81 | 30.54 | 14.96 | 17.16 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 195.0 | 191.3 | 186.8 | 183.6* | 168.9** |
| | S.D. | 15.00 | 15.23 | 13.43 | 12.39 | 16.52 |
| | N | 25 | 24 | 21 | 19 | 11 |
| PND 56 | | | | | | |
| MALES | MEAN | 335.8 | 344.8 | 317.0 | 315.3 | 294.9** |
| | S.D. | 30.44 | 34.83 | 33.01 | 19.55 | 21.52 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 220.4 | 212.2 | 211.4 | 204.8* | 188.8** |
| | S.D. | 18.32 | 19.22 | 16.24 | 17.11 | 13.20 |
| | N | 25 | 24 | 21 | 19 | 11 |
| PND 63 | | | | | | |
| MALES | MEAN | 382.3 | 385.5 | 357.2* | 352.6* | 336.1** |
| | S.D. | 40.59 | 36.92 | 37.18 | 19.80 | 24.27 |
| | N | 25 | 24 | 22 | 19 | 11 |
| FEMALES | MEAN | 236.1 | 229.4 | 225.6 | 220.7* | 206.3** |
| | S.D. | 20.47 | 18.30 | 18.04 | 19.51 | 13.66 |
| | N | 25 | 24 | 21 | 19 | 11 |
| PND 70 | | | | | | |
| MALES | MEAN | 410.8 | 422.3 | 392.0 | 385.5 | 368.1** |
| | S.D. | 38.55 | 40.25 | 43.00 | 27.39 | 24.68 |
| | N | 25 | 24 | 22 | 18 | 11 |
| FEMALES | MEAN | 254.7 | 246.3 | 241.6 | 238.3* | 223.4** |
| | S.D. | 20.01 | 21.26 | 17.83 | 20.99 | 14.36 |
| | N | 25 | 24 | 21 | 19 | 11 |

PND - POSTNATAL DAY
* - Significantly different from the control group at 0.05 using Dunnett's test
** - Significantly different from the control group at 0.01 using Dunnett's test

The table below summarizes the overall differences in mean body weight of the offspring during the post-weaning period.

| | | Summary of Mean Offspring Weight ($F_1$) Changes ($F_1$) % Δ of Control | | | | |
|---|---|---|---|---|---|---|
| **Interval** | **Dose (mg/kg) →** | **0** | **1** | **5** | **10** | **25** |
| **PND 21 to 70** | | | | | | |
| Males | | | +2 | -4 | -7 | -9* |
| Females | | | -6 | -5 | -7* | -11* |

* $p < 0.05$ compared to control group

Mean material body weights were reduced for the females in the 25 mg/kg/day treatment group throughout gestation. These changes were statistically significant days 0-16 and on day 20. Mean maternal body weight gains in the group were not affected by $F_0$ test article administration. Mean gravid uterine weights and net body weight gains in the 1, 5, 10 and 25 mg/kg/day groups were similar to controls.

| | | Summary of Mean Gravid Uterine Weights and Net Body Weight Changes ($F_1$) % Δ of Control | | | | |
|---|---|---|---|---|---|---|
| **Parameter (mean)** | **Dose (mg/kg) →** | **0** | **1** | **5** | **10** | **25** |

| | | | | | |
|---|---|---|---|---|---|
| Initial body weight | | -1 | -4 | -6 | -12* |
| Terminal body weight | | 0 | -0.5 | -2 | -7* |
| Gravid uterine weights | | +3 | +4 | +3 | +2 |
| Net body weights | | +0 | -1 | -3 | -8* |
| Net body weight changes | | +4 | +9 | +7 | +8 |

* $p < 0.05$ compared to control group

Necropsy of the dams and $F_1$ males failed to detect any treatment-related findings that could be attributed to treatment of the $F_0$ generation.

$F_2$ findings: Intrauterine growth and survival of the $F_2$ fetuses were not altered by $F_0$ maternal treatment at any dose level tested. Parameters evaluated included postimplantation loss, viable fetuses, fetal body weights and fetal sex ratios. The numbers of corpora lutea and implantation sites were similar among all groups, including the control group. Morphologically, there were no external malformations or developmental variations in the fetuses in this study.

**2.6.6.7 Local tolerance**

There were no local tolerance studies submitted with these NDA applications.

**2.6.6.8 Special toxicology studies:**

**Study title: Dermal Sensitization Study in Guinea Pigs/Maximization Procedure Using Oxymorphone**

**Key study findings**: The ability for oxymorphone to induce skin sensitization was tested in the guinea pig maximization test in rabbits with the following results:

1. Oxymorphone and the positive control DNCB induced clear erythema and edema in the rabbit and should be considered to be dermal irritants.
2. The guinea pig maximization test is currently accepted by CDER to identify the sensitization potential of drugs intended for topical use.
3. The study suggests that oxymorphone may have the potential to produce a hypersensitivity reaction when applied topically.

**Study no.:** 410-1964
**Volume #, and page #:** Electronic Document Room
**Conducting laboratory and location:**

**Date of study initiation:** Unspecified, report dated April 3, 1986.
**GLP compliance:** Yes
**QA reports:** yes ( X ) no ( )
**Drug, lot #, and % purity:** Oxymorphone base, Lot R84-188, purity unspecified.
**Formulation/vehicle:** The vehicle control was propylene glycol (lot 417620) . The sensitization control was DNCB (1-chloro-2,4-dinitrobenzene). The adjuvant used was Complete H37 RA from

**Methods**
Young adult male and female Hartley guinea pigs were used to test the dermal sensitization potential of oxymorphone. The back of each animal was clipped free of hair 24 hours prior to the initiation of treatment. The induction phase consisted of an intradermal injection into the right flank

Doses: Induction with 5% oxymorphone and challenged with 30% oxymorphone.

Study design: The basic study design is depicted below:

| | | Induction Phase | | Treatment Challenge Phase |
|---|---|---|---|---|
| Group | Number of Animals | Intradermal Injection Sites 1,2,3 | Topical Application | Topical Application |
| Vehicle Control | 10M/10F | 1 FCA<br>2 Vehicle<br>3 FCA/Vehicle | Vehicle | Vehicle |
| Irritation Control | 10M/10F | 1 FCA<br>2 FCA<br>3 FCA | None | Test article |
| Positive Control | 10M/10F | 1 FCA<br>2 PC Article<br>3 FCA/PC Article | PC Article | PC Article |
| Test Article | 10M/10F | 1 FCA<br>2 Test Article<br>3 FCA/Test Article | Test Article | Test Article |

FCA denotes 50% FCA/50% deionized water emulsion
Vehicle denotes the test article carrier (propylene glycol)
PC Article denotes DNCB
FCA denotes Freund's Adjuvant, complete

The following groups were employed for the Induction Phase (Day 1):

| Group (n=10/sex/group) | Paired Injection Sites[1] | Article Administered |
|---|---|---|
| Vehicle Control | 1<br>2<br>3 | Adjuvant emulsion<br>Propylene glycol (vehicle)<br>5% propylene glycol in adjuvant emulsion |
| Irritation Control | 1, 2 and 3 | Adjuvant emulsion |
| Sensitization Control | 1<br>2<br>3 | Sensitization control adjuvant emulsion<br>0.1% DNCB suspension<br>0.1% DNCB in sensitization control adjuvant emulsion |
| Test | 1<br>2<br>3 | Adjuvant emulsion<br>Oxymorphone in propylene glycol (5%)<br>Oxymorphone in adjuvant emulsion (5%) |

[1] There were six intradermal injection sites on each animal within a 2 x 4 cm area. Paired injection sites 1 and 2 were closest to the head and injection sites 3 were posterior to 1 and 2.

Two 0.1 ml of each of the article listed above were administered intradermally to each animal of the appropriate group. Seven days after the intradermal injections, the topical induction applications (see table below) were applied to 2 x 4 cm [redacted] patches attached to [redacted] tape to the induction area. The entire trunk was wrapped with an impervious binder consisting of a plastic wrap, adhesive tape and masking tape.

| Group (n=10/sex/group) | Article Applied | Volume or weight/animal |
|---|---|---|
| Vehicle Control | Propylene glycol | 0.2 ml |
| Irritation Control | None | -- |
| Sensitization Control | 0.1% DNCB suspension | 0.2 ml |
| Test | Oxymorphone | 200 mg (moistened) |

After 48 hours of topical induction exposure the impervious binders and patches were removed and the application sites were gently cleaned with gauze moistened with propylene glycol for vehicle control or reagent grade water for sensitization control animals.
Fourteen days after the topical induction, surviving animals were challenged as follows:

| Group (n=10/sex/group) | Article Applied | Volume or weight/animal |
|---|---|---|
| Vehicle Control | Propylene glycol | 0.1 ml |
| Irritation Control | 30% (w/w) oxymorphone | 100 mg |
| Sensitization Control | 30% (w/w) oxymorphone | 100 mg |
| Test | 0.1% DNCB suspension | 0.1 ml |

The articles above were applied to a 2 x 2 cm [redacted] patch attached to [redacted] tape and applied to the right flank of the appropriate animal (clipped free of hair). The trunk was wrapped with an impervious binder as previously described. After 24 hours of topical challenge exposure, the wrapping was removed, the sites were gently cleaned and the challenge sites were evaluated for erythema and edema according to the method of Draize (see below) at 24 and 48 hours after the removal of the challenge articles.

| The Draize Grading Scale for Evaluation of Dermal Reactions | |
|---|---|
| Erythema and Eschar Formation | |
| No erythema | 0 |
| Very slight erythema (barely perceptible) | 1 |
| Well defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema (beet redness) to slight eschar formation (injuries in depth) | 4 |
| **Total Possible Erythema Score** | **4** |
| Edema Formation | |
| No edema | 0 |
| Very slight edema (barely perceptible) | 1 |
| Slight edema (edges of area well defined by definite raising) | 2 |
| Moderate edema (raised approximately 1 mm) | 3 |
| Severe edema (raised more than 1 mm and extending beyond area of exposure) | 4 |
| **Total Possible Edema Score** | **4** |

Sensitizers were graded and classified using the following allergenicity rating (Magnusson and Kligman, 1969).

| Allergenicity Rating | | |
|---|---|---|
| **Sensitization Rate (%)** | **Grade** | **Classification** |
| 0 to 8 | I | Weak |
| 9 to 28 | II | Mild |
| 29 to 64 | III | Moderate |
| 65 to 80 | IV | Strong |
| 81 to 100 | V | Extreme |

**Results:**

Mortality: One male in the oxymorphone test group was found in a moribund condition and was sacrificed in extremis on day 10. Two other animals in the oxymorphone test group were found dead during the study (one male and one female, both on day 11). Abnormalities noted in these animals were as follows:

| Animal Number | Sex | Area or Organ | Abnormality |
|---|---|---|---|
| AG6826 | M | External Surface | Multiple ulcerative dermatitis |
| | | Intestine | Hyperemia, Gaseous distension |
| | | Liver | Mottled, white |
| | | Urinary Bladder | Distended by red fluid |
| AG6827 | M | Treated Skin | Ulceration, multiple, focal, red tan |
| | | Urinary Bladder | Distended with amber fluid |
| AG6873 | F | External Surface | 2 $cm^2$ area of deep dermal necrosis |
| | | Liver | Mottle, white |
| | | Intestine | Hyperemia |

Clinical signs: Clinical signs in the oxymorphone treated group included cowering and rigid/strained body, lacrimation, muscle tremors, squinting, slow respiration, lethargy and ataxia. No clinical signs were noted in other groups.

Skin reaction: A summary of the incidences of erythema and edema observed for the test and sensitization control groups is reproduced below:

| | | Incidence of Challenge Dermal Reactions (number affected/number evaluated) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Test Group[1] | | | | Sensitization Control Group[2] | | | |
| | | Males | | Females | | Males | | Females | |
| | Grade | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr |
| **Erythema** | 1 | 5/8 | 3/8 | 1/9 | -- | 3/10 | 1/10 | -- | -- |
| | 2 | 3/8 | 4/8 | 5/9 | 2/9 | 6/10 | 2/10 | 1/10 | 1/10 |
| | 3 | -- | -- | 1/9 | 1/9 | -- | 3/10 | 2/10 | 2/10 |
| | 4 | -- | 1/8 | 2/9 | 6/9 | 1/10 | 4/10 | 7/10 | 7/10 |
| **Edema** | 1 | 2/8 | 1/8 | -- | -- | 3/10 | 1/10 | -- | -- |
| | 2 | 6/8 | 5/8 | 4/9 | -- | 5/10 | -- | 5/10 | -- |
| | 3 | -- | 2/8 | 5/9 | 5/9 | 2/10 | 7/10 | 5/10 | 7/10 |
| | 4 | -- | -- | -- | 4/9 | -- | 2/10 | -- | 3/10 |

[1] Test group was induced with oxymorphone and challenged with oxymorphone.
[2] Sensitization group was induced with DNCB and challenged with DNCB.

Based upon the results presented above, both oxymorphone and DNCB were characterized as extreme sensitizers (Grade 5) based upon the allergenicity rating of Magnusson and Kligman.

Histological examination of sections of treated and untreated skin indicates that the test article produced changes such as acanthosis, hyperkeratosis, lymphocytic infiltrate and superficial epidermitis. The incidence of these findings and severity were generally higher in female guinea pigs than males. A summary of these changes were provided by the pathology report reproduced below:

MALE GUINEA PIGS

| GROUP: | POSITIVE CONTROL | VEHICLE CONTROL | IRRITATION CONTROL | TEST ARTICLE |
|---|---|---|---|---|
| UNTREATED SKIN | | | | |
| Number Examined | (10) | (10) | (10) | (8) |
| Acanthosis | 8 | 2 | 3 | 6 |
| Acantholysis | 0 | 0 | 0 | 1 |
| Acute Dermatitis | 1 | 0 | 0 | 0 |
| Hyperkeratosis | 1 | 2 | 2 | 6 |
| Lymphocytic Infiltrate | 3 | 0 | 0 | 3 |
| Panniculitis | 1 | 3 | 0 | 1 |
| Superficial Epidermitis | 1 | 1 | 0 | 1 |
| | | | | |
| TREATED SKIN | | | | |
| Number Examined | (10) | (10) | (10) | (8) |
| Acanthosis | 10 | 3 | 0 | 8 |
| Acantholysis | 0 | 0 | 0 | 3 |
| Acute Dermatitis | 2 | 0 | 0 | 0 |
| Hyperkeratosis | 6 | 2 | 0 | 7 |
| Lymphocytic Infiltrate | 4 | 0 | 0 | 2 |
| Panniculitis | 3 | 0 | 1 | 0 |
| Superficial Epidermitis | 5 | 0 | 0 | 3 |

FEMALE GUINEA PIGS

| GROUP: | POSITIVE CONTROL | VEHICLE CONTROL | IRRITATION CONTROL | TEST ARTICLE |
|---|---|---|---|---|
| UNTREATED SKIN | | | | |
| Number Examined | (10) | (10) | (10) | (9) |
| Acanthosis | 10 | 6 | 3 | 7 |
| Acantholysis | 1 | 1 | 0 | 1 |
| Acute Dermatitis | 0 | 0 | 0 | 0 |
| Hyperkeratosis | 9 | 4 | 1 | 4 |
| Lymphocytic Infiltrate | 6 | 5 | 3 | 6 |
| Panniculitis | 1 | 3 | 2 | 3 |
| Superficial Epidermitis | 1 | 2 | 0 | 1 |
| | | | | |
| TREATED SKIN | | | | |
| Number Examined | ( 10) | (10) | (10) | (9) |
| Acanthosis | 10 | 6 | 6 | 9 |
| Acantholysis | 0 | 1 | 0 | 1 |
| Acute Dermatitis | 6 | 0 | 0 | 0 |
| Hyperkeratosis | 9 | 4 | 1 | 7 |
| Lymphocytic Infiltrate | 4 | 5 | 4 | 9 |
| Panniculitis | 5 | 4 | 3 | 4 |
| Superficial Epidermitis | 8 | 1 | 0 | 7 |

In the first cycle review of this NDA, the reviewer (Dr. R. Daniel Mellon) observed that the oxymorphone induced significant increase in the incidence of micronucleated polychromatic erythrocytes (MPCE) in bone marrow of the rat and mouse in the micronucleus assay indicating mammalian chromosomal damage. Genetic toxicology studies for morphine reported in the published literature also report positive findings in the in vivo micronucleus assay. Mechanistic studies in the morphine model suggest that the positive findings with morphine in the in vivo micronucleus assay may be mediated through opioid-induced increases in glucocorticoid levels in that species. These mechanistic data, reported in the literature and included in the FDA approved drug label for oxycodone for morphine, did not exist for oxymorphone. Dr. Mellon concluded that the positive result *in vivo* with oxymorphone could also be mediated by an opioid-receptor/adrenal-dependent mechanism, like morphine, or it could be due to a mutagenic metabolite of oxymorphone. In the original NDA submission, the sponsor provided no data to support either assumption for oxymorphone, it was recommended that the sponsor should determine the mechanism of oxymorphone-induced *in vivo* clastogenicity and define the relevance of these findings to humans.

The mechanistic studies were completed by the sponsor, and were submitted to the Division for review. Followings are review of the mechanistic studies conducted by the Sponsor to analyze the oxymorphone induced increase in the MPCEs observed in the in the mammalian erythrocyte micronucleus test. Rather than explore the potential role of

the HPA axis, the sponsor hypothesized that the positive in vivo findings were related to the effects of opioids on core body temperature.

**Study Number /Study Title: EN3202-251-03 Monitoring of Rat Body Temperature Following Oxymorphone Administration**

The objective of this study was to determine the effect of the antipyretic drugs sodium salicylate and acetaminophen on the oxymorphone HCl induced increase in the body temperature in rats. This initial study was completed to understand whether the increase in the body temperature observed after oxymorphone administration is due to prostaglandin release at the level of the hypothalamus.
The study was done following SOP, and a quality assurance document is provided by the Sponsor. The study completion date was November 3, 2003.

**METHODS:** Five male Sprague Dawley rats were administered 20 or 40 mg/kg oxymorphone HCl by oral gavage. Either sodium salicylate or acetaminophens was administered (300 mg/kg) prior to the oxymorphone HCl administration. The antipyretic drugs were given intraperitoneally 15 mins prior to the oxymorphone HCl administration. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The following table depicts the study design:

| | Group | Treatment (10 mL/kg) | Dose (mg/kg) | Dose Administration | Number of Animals Dosed |
|---|---|---|---|---|---|
| First | 1 | Water (vehicle) | 0.0 | Oral gavage | 5 |
| Phase | 2 | Oxymorphone | 20 | Oral gavage | 5 |
| | 3 | Oxymorphone | 40 | Oral gavage | 10[a] |
| Second | 4 | Water (vehicle) | 0.0 | Oral gavage | 5 |
| Phase | 5 | Oxymorphone | 40 | Oral gavage | 5 |
| | 6 | Acetaminophen[b]<br>Oxymorphone | 300<br>40 | Intraperitoneal<br>Oral gavage | 5 |
| | 7 | Sodium Salicylate[b]<br>Oxymorphone | 300<br>40 | Intraperitoneal<br>Oral gavage | 5 |

[a] Including 5 replacement animals to ensure the availability of five animals for body temperature analysis
[b] Administered 15 minutes prior to oxymorphone

RESULTS: Under this experimental condition oxymorphone HCL was shown to induce an increase in body temperature (see tables below) with a maximal increase of about 2 degrees Celsius produced by 40 mg/kg oxymorphone. Pretreatment with sodium salicylate effectively blocked the effect of oxymorphone HCl induced increase in the body temperature in rats; the effect of acetaminophen varied widely, suggesting that pretreatment with acetaminophen was not completely effective.

**Effect of Oxymorphone HCl on Body Temperature in Rat:**

| | Predose | 0.5 Hour Postdose | 1 Hour Postdose | 2 Hours Postdose | 3 Hours Postdose | 4 Hours Postdose | 6 Hours Postdose | 8 Hours Postdose | 24 Hours Postdose |
|---|---|---|---|---|---|---|---|---|---|
| Animal # | | | | Water | | | | | |
| MEAN | 37.0 | 37.5 | 37.4 | 37.2 | 37.3 | 37.2 | 37.1 | 37.1 | 37.0 |
| SD | 0.2 | 0.3 | 0.6 | 0.4 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 |
| Animal # | | | | Oxymorphone (20 mg/kg) | | | | | |
| MEAN | 37.0 | 37.7 | 38.7 | 38.5 | 38.6 | 38.5 | 38.1 | 37.6 | 36.7 |
| SD | 0.6 | 0.6 | 0.6 | 0.3 | 0.2 | 0.3 | 0.3 | 0.4 | 0.6 |
| Animal # | | | | Oxymorphone (40 mg/kg) | | | | | |
| MEAN | 37.0 | 38.1 | 39.0 | 38.8 | 38.9 | 38.5 | 37.4 | 37.6 | 37.0 |
| SD | 0.2 | 0.1 | 0.2 | 0.1 | 0.2 | 0.3 | 1.7 | 0.4 | 0.2 |
| Animal # | | | | Oxymorphone (40 mg/kg)** | | | | | |
| MEAN | 36.9 | 38.1 | 38.8 | 38.9 | 39.0 | 38.0 | 38.3 | 38.1 | 37.4 |
| SD | 0.2 | 0.4 | 0.4 | 0.2 | 0.3 | 1.2 | 0.5 | 0.1 | 0.4 |

*No data due to mortality
**Replacement group of animals

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

The objective of this study was to determine the effect of the antipyretic drug naproxen on the oxymorphone HCl induced increase in the body temperature in rats.
The study was done following SOP, and the quality assurance document was provided by the Sponsor. The study completion date was February 24, 2004.

METHODS: Six male Sprague Dawley rats were administered with 40 mg/kg dose of oxymorphone (this dose was previously shown to induce MPCEs in rat); naproxen was administered (oral) simultaneously at different doses (10, 20, 40, 80, and 120 mg/kg). The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The following table depicts the study design:

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| Group | Treatment (10 mL/kg) | Dosage (mg/kg) | Concentration (mg/mL) | Route of Administration | Number of Animals |
|---|---|---|---|---|---|
| 1 | Vehicle: Water | 0.0 | 0.0 | Oral gavage | 6 |
| 2 | Test Article: Oxymorphone | 40 | 4 | Oral gavage | 6 |
| 3 | Antipyretic: Naproxen | 120 | 12 | Oral gavage | 6 |
| 4 | Oxymorphone<br>Naproxen | 40<br>10 | 4<br>1 | Oral gavage | 6 |
| 5 | Oxymorphone<br>Naproxen | 40<br>20 | 4<br>2 | Oral gavage | 6 |
| 6 | Oxymorphone<br>Naproxen | 40<br>40 | 4<br>4 | Oral gavage | 6 |
| 7 | Oxymorphone<br>Naproxen | 40<br>80 | 4<br>8 | Oral gavage | 6 |
| 8 | Oxymorphone<br>Naproxen | 40<br>120 | 4<br>12 | Oral gavage | 6 |

RESULTS: Under the experimental conditions, oxymorphone (40 mg/kg) induced rapid increase in the animal body temperature (37.3-37.9°C). Administration of naproxen did not block oxymorphone induced increase in the body temperature in rats.

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

The objective of this study was to determine the effect of the antipyretic drug sodium salicylate on the oxymorphone HCl induced increase in the body temperature in rats. The study was done following SOP, and a quality assurance document was provided by the Sponsor. The study completion date was February 27, 2004.

METHODS: Six male Sprague Dawley rats were administered 40 mg/kg oxymorphone (this dose was previously shown to induce MPCEs in rat); sodium salicylate was administered orally at different doses (100, 200, and 300 mg/kg), 30 mins prior to the oxymorphone administration. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The table below depicts the study design:

| Group | Treatment (10 mL/kg) | Dosage (mg/kg) | Concentration (mg/mL) | Dose Administration | Number of Animals Dosed |
|---|---|---|---|---|---|
| 1 | Oxymorphone | 40 | 4 | Oral gavage | 5 |
| 2 | Sodium Salicylate[a]<br>Oxymorphone | 100<br>40 | 10<br>4 | Oral Gavage | 5 |
| 3 | Sodium Salicylate[a]<br>Oxymorphone | 200<br>40 | 20<br>4 | Oral Gavage | 5 |
| 4 | Sodium Salicylate[a]<br>Oxymorphone | 300<br>40 | 30<br>4 | Oral Gavage | 5 |

[a]Administered 30 minutes prior to oxymorphone

**RESULTS:** Under this experimental conditions employed, oxymorphone induced rapid increase in the animal body temperature (37.4-37.6°C). Sodium salicylate pretreatment did not block oxymorphone HCl induced increase in the body temperature in rats.

**Study Number/Study Title: 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**

The objective of this study was to determine the effect of the antipyretic drug sodium salicylate on the oxymorphone HCl induced increase in the body temperature in rats. The study was done following SOP, and a quality assurance document was provided by the Sponsor. The study completion date was February 27, 2004.

METHODS: Six male Sprague Dawley rats were administered 40 mg/kg dose of oxymorphone (this dose was previously shown to induce MPCEs in the rat model); sodium salicylate was administered orally at different doses (300 and 500 mg/kg), 60, 90, and 120 mins prior to the oxymorphone administration. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The following table depicts the study design:



| Group | Treatment (10 mL/kg) | Dosage (mg/kg) | Concentration (mg/mL) | Timepoints for Sodium Salicylate Administration (before oxymorphone; min) | Number of Animals |
|---|---|---|---|---|---|
| 1 | Oxymorphone | 40 | 4 | - | 6 |
| 2 | Sodium salicylate | 500 | 50 | - | 6 |
| 3 | Oxymorphone<br>Sodium salicylate | 40<br>300 | 4<br>30 | 60 | 6 |
| 4 | Oxymorphone<br>Sodium salicylate | 40<br>300 | 4<br>30 | 90 | 6 |
| 5 | Oxymorphone<br>Sodium salicylate | 40<br>300 | 4<br>30 | 120 | 6 |
| 6 | Oxymorphone<br>Sodium salicylate | 40<br>500 | 4<br>30 | 30 | 6 |
| 7 | Oxymorphone<br>Sodium salicylate | 40<br>500 | 4<br>50 | 60 | 6 |
| 8 | Oxymorphone<br>Sodium salicylate | 40<br>500 | 4<br>50 | 90 | 6 |
| 9 | Oxymorphone<br>Sodium salicylate | 40<br>500 | 4<br>50 | 120 | 6 |

**RESULTS:** Under this experimental condition oxymorphone induced rapid increase in the animal body temperature (37.0-37.9° C). Sodium salicylate pretreatment for 30 and 60

mins did block oxymorphone HCl induced increase in the body temperature in rats. However, there was huge variation in the individual animal response (see table below).

**Effect of Sodium Salicylate on Oxymorphone HCl Induced Body Temperature in Rat:**

| Animal # | Predose | 0.25 Hr Postdose | 0.5 Hr Postdose | 1 Hr Postdose | 2 hrs Postdose | 3 hrs Postdose | 4 hrs Postdose | 6 hrs Postdose | 8 hrs Postdose | 24 hrs Postdose |
|---|---|---|---|---|---|---|---|---|---|---|
| Oxymorphone (40 mg/kg) | | | | | | | | | | |
| MEAN | 37.9 | 37.6 | 38.5 | 39.0 | 39.1 | 39.0 | 38.8 | 38.3 | 37.8 | 37.4 |
| SD | 0.3 | 0.1 | 0.3 | 0.8 | 0.2 | 0.3 | 0.2 | 0.3 | 0.4 | 0.3 |
| Sodium salicylate (500 mg/kg) | | | | | | | | | | |
| MEAN | 37.6 | 37.3 | 37.5 | 36.9 | 36.7 | 36.7 | 36.8 | 36.7 | 36.8 | 36.8 |
| SD | 0.5 | 0.4 | 0.4 | 0.3 | 0.5 | 0.5 | 0.4 | 0.3 | 0.6 | 0.3 |
| Sodium salicylate (300 mg/kg) 60 min. before Oxymorphone (40 mg/kg) | | | | | | | | | | |
| MEAN | 37.3 | 37.5 | 38.0 | 38.4 | 38.1 | 38.0 | 37.9 | 37.9 | 37.5 | 38.1 |
| SD | 0.3 | 0.3 | 0.4 | 0.4 | 0.5 | 0.4 | 0.4 | 0.4 | 0.2 | 0.3 |
| Sodium salicylate (300 mg/kg) 90 min. before Oxymorphone (40 mg/kg) | | | | | | | | | | |
| MEAN | 37.2 | 37.2 | 37.9 | 38.7 | 38.6 | 38.2 | 37.9 | 37.7 | 37.3 | 38.1 |
| SD | 0.3 | 0.2 | 0.4 | 0.7 | 0.3 | 0.4 | 0.3 | 0.3 | 0.3 | 0.5 |
| Sodium salicylate (300 mg/kg) 120 min. before Oxymorphone (40 mg/kg) | | | | | | | | | | |
| MEAN | 37.0 | 37.2 | 37.6 | 38.1 | 38.1 | 38.4 | 37.8 | 37.8 | 37.5 | 38.3 |
| SD | 0.4 | 0.4 | 0.3 | 0.4 | 0.4 | 0.6 | 0.3 | 0.1 | 0.4 | 0.2 |

*No data due to mortality

Study Number/Study Title: EN3202-261-03 Relationship between Micronuclei Formation and Animal Body Temperature Changes Following Oxymorphone HCl Administration in Rats

**Key findings:**

- There was an increase in the body temperature and MPCEs in the animals treated with oxymorphone HCl. The increase in MPCEs was not statistically significant compared to the vehicle. Thus the positive response observed might not be valid. Therefore, MPCE increase by hypothermia induced by oxymorphone is not confirmed.
- A decrease in the oxymorphone-induced increase in body temperature and MPCEs was noted in the animals pretreated with the sodium salicylate.
- The sponsor repeated the assay due to the lack of validity of the positive response.

**Study no (CRO):** AA46XC.125 B.BTL
**Study type** (if not reflected in title): *In vivo* rat micronucleus test
**Volume #, and page #:** EDR, 1-64
**Conducting laboratory and location:** [redacted]
**Date of study initiation:** July 31, 2003
**GLP compliance:** Yes
**QA reports:** Yes ( X ) no ( )
**Drug, lot #, radiolabel, and % purity:** Oxymorphone HCl, Mallinckrodt D13462, [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:** A preliminary study tested doses 20 and 40 mg/kg oxymorphone via oral gavage (10 mL/kg; n=5/sex/group) and showed increase MPCE formation.

**Range finding studies:** No range finding study was submitted under the current study title; however mortality was observed at higher doses tested > 40 mg/kg . Based on those 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.

**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 [redacted] days under ambient conditions. At [redacted] days, individual known and unknown impurities and known degradation products were less than [redacted] respectively.

**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 hours.

**Doses used in definitive study:** 40 mg/kg oxymorphone/kg via oral gavage (10 ml/kg).

**Study design:** This study was designed to investigate the relationship between hypothermia and micronuclei formation following oxymorphone HCl administration. A total of 5 male rats per treatment group were administered oxymorphone via oral gavage. 300 mg/kg sodium salicylate (an antipyretic agent) was administered intraperitoneally 15 mins prior to the oxymorphone HCl administration. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The study design was as follows:

| Group | Treatment | Dose (mg/kg) | Route of Administration | Number of Animals[a] |
|---|---|---|---|---|
| 1 | Water (vehicle control) | 0 | Oral gavage | 5 |
| 2 | Oxymorphone | 40 | Oral gavage | 5 |
| 3 | Oxymorphone + Sodium Salicylate (15 minutes before oxymorphone) | 40<br>300 | Oral gavage<br>Intraperitoneal injection | 5 |
| 4 | Sodium Salicylate | 300 | Intraperitoneal injection | 5 |
| 5 | Cyclophosphamide monohydrate (Positive control) | 40 | Oral gavage | 5 |

[a]Male — CD® (SD) IGS BR rats



Six additional animals were used for toxicokinetics. Blood was colleted at 0.5, 1, 2, 4, 8, and 24 hrs for analyzing the plasma concentration of the oxymorphone at different time points from the animals.

**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. Two 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 positive if a statistically significant increase in MPCEs were noted compared to that of the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables).

**Summary of individual study findings:**

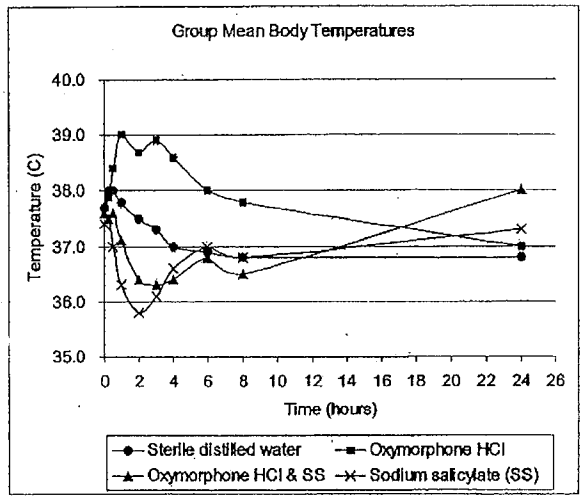
**Study validity:** The study appears to be valid for the following reasons: 1) the positive control, cyclophosphamide produced a statistically significant increase in the number of micronucleated polychromatic erythrocytes compared to controls and 2) the sampling times, positive controls and study design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

**Study outcome:** Clinical signs following oxymorphone HCl administration are presented in the sponsor's table (below). All treated animals showed clinical signs of lethargy. An increase in body temperature was observed with the oxymorphone HCl treated animals. As indicated in the figure below administration of oxymorphone HCl was observed to increase the body temperature in the rats (male) up to 6 hrs post dose. There was an increase in MPCEs with the administration of oxymorphone alone at 24 hrs (11/1000, 18/1000, 278/1000 in control, oxymorphone HCl, and CP respectively). There was no increase in the number of MPCEs from the animals pretreated with sodium salicylate. The increase in MPCEs after oxymorphone HCl administration was, however, not statistically significant compared to vehicle. Therefore, the assay can not be considered positive and recommended that the study should be repeated.

Effect of Sodium Salicylate in the Oxymorphone HCl induced Clinical Signs:

| | | Number of Animals With Clinical Signs/Total Number of Animals Dosed | Number of Animals Died/Total Number of Animals Dosed |
|---|---|---|---|
| Treatment (10 mL/kg) | Observation | Males | Males |
| Water | Normal | 5/5 | 0/5 |
| Oxymorphone (40 mg/kg) | Lethargy | 5/5 | 0/5 |
| Sodium salicylate (300 mg/kg)/ Oxymorphone (40 mg/kg) | Lethargy | 5/5 | 0/5 |
| Sodium salicylate (300 mg/kg) | Lethargy | 5/5 | 0/5 |
| CP (40 mg/kg) | Normal | 5/5 | 0/5 |

Effect of Sodium Salicylate in the Oxymorphone HCl induced Body Temperature:






Effect of Sodium Salicylate in the Oxymorphone HCl induced MPCE at 24 hrs:

**24 hrs postdose**

| Treatment (10 mL/kg) | Sex | Time (hr) | Number of Rats | PCE/Total Erythrocytes (Mean +/- SD) | Change from Control (%) | Micronucleated Polychromatic Erythrocytes: Number/1000 PCEs (Mean +/- SD) | Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored[1] |
|---|---|---|---|---|---|---|---|
| Water | M | 24 | 5 | 0.690 ± 0.05 | --- | 1.1 ± 0.82 | 11 / 10000 |
| Oxymorphone 40 mg/kg | M | 24 | 5 | 0.720 ± 0.05 | 4 | 1.8 ± 0.76 | 18 / 10000 |
| Sodium salicylate (300 mg/kg)/ Oxymorphone (40 mg/kg) | M | 24 | 5 | 0.723 ± 0.06 | 5 | 0.7 ± 0.45 | 7 / 10000 |
| Sodium salicylate 300 mg/kg | M | 24 | 5 | 0.749 ± 0.04 | 9 | 0.6 ± 0.65 | 6 / 10000 |
| CP 40 mg/kg | M | 24 | 5 | 0.727 ± 0.05 | 5 | 29.8 ± 13.21 | *298 / 10000 |

[1]*Statistically significant, p≤0.05 (Kastenbaum-Bowman Tables)

Study Number/Study Title: EN3202-261a-03 Relationship between Micronuclei Formation and Animal Body Temperature Changes Following Oxymorphone HCl and Sodium Salicylate (Antipyretic) Administration

Key findings:

- There was an increase in body temperature in male rats after the administration of oxymorphone HCl. Pretreatment with sodium salicylate reduced the amplitude

and the duration of the body temperature increase compared to the animals treated with oxymorphone alone but not up to the level of the control animals.

- The increase in body temperature can not be directly related to the plasma level of the oxymorphone since the body temperature in the animals treated with oxymorphone alone remains high up to 8 hrs, but the plasma concentration of the oxymorphone decreased significantly after 2 hrs.
- There was a significant increase in the MPCEs in animals treated with the oxymorphone alone, animals pretreated with sodium salicylate did not show any increase in the MPCEs.

**Study no (CRO):** AA46XC.125.BTL
**Study type** (if not reflected in title): *In vivo* rat micronucleus test
**Volume #, and page #:** EDR, 1-151
**Conducting laboratory and location:** [redacted]
**Date of study initiation:** September 17, 2003
**GLP compliance:** Yes
**QA reports:** Yes ( X ) no ( )
**Drug, lot #, radiolabel, and % purity:** Oxymorphone HCl, Mallinckrodt D13462, [redacted]

**Formulation/vehicle:** Water

**Methods:**

**Strains/species/cell line:** [redacted] CD (SD) IGS BR rats, male
**Dose selection criteria:** Dose range-finding study for toxicity
**Basis of dose selection:** In a previous study tested doses 20 and 40 mg/kg oxymorphone via oral gavage (10 mL/kg; n=5/sex/group) which showed increase MPCE formation.
**Range finding studies:** No range finding study was submitted under the current study title; however mortality was observed at higher doses tested > 40 mg/kg, therefore, a dose of 40 mg/kg was set as the high dose for the micronucleus assay as an estimate of the maximum tolerated dose.

**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 [redacted] days under ambient conditions. At [redacted] days, individual known and unknown degradation products were less than [redacted] respectively.

**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 hours.
**Doses used in definitive study:** 40 mg/kg oxymorphone/kg via oral gavage (10 ml/kg).

**Study design:** This study was designed to investigate the relationship between hypothermia and micronuclei formation following oxymorphone HCl administration. A total of 7 male rats per treatment group were administered oxymorphone via oral gavage. 300 mg/kg sodium salicylate (an antipyretic agent) was administered intraperitoneally 15 mins prior to the oxymorphone HCl administration. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The study design was as follows:

| Group | Treatment | Dosage (mg/kg) | Route of Administration | Number of Animals[a] Micronucleus | TK[b] |
|---|---|---|---|---|---|
| 1 | Water (vehicle) | 0 | Oral gavage | 7 | 0 |
| 2 | Oxymorphone | 40 | Oral gavage | 7 | 6 |
| 3 | Oxymorphone + Sodium Salicylate (15 minutes before oxymorphone) | 40<br>300 | Oral gavage<br>Intraperitoneal injection | 7 | 6 |

[a]Male —CD® (SD) IGS BR rats
[b]Plasma samples were collected from 3 animals at 0.5, 2 and 8 hr after dosing and from 3 animals at 1, 4 and 24 hr after dosing for determination of plasma oxymorphone concentration. Timepoints were relative to administration of oxymorphone.

Six additional animals were used for toxicokinetics. Blood was colleted at 0.5, 1, 2, 4, 8, and 24 hrs for analyzing the plasma concentration of the oxymorphone. .

**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. Two 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 positive if a statistically significant increase in MPCEs were noted compared to that of the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables).

**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.

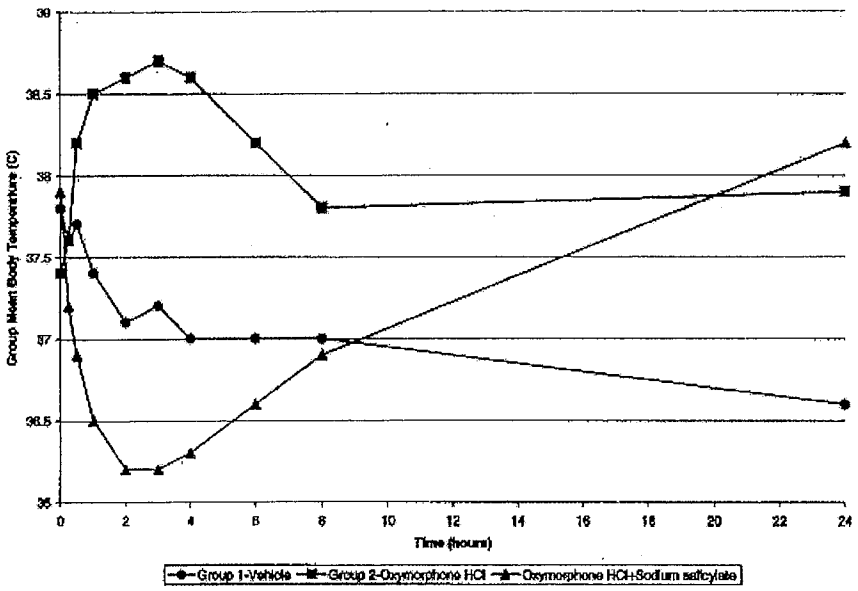
**Study outcome:** Clinical signs following oxymorphone HCl administration are presented in the sponsor's table (below). All treated animals showed clinical signs of lethargy. As indicated in the figure below, administration of oxymorphone HCl increased the body temperature in the rats (male) up to 8 hrs post dose. Mean body temperature increase from 1-4 hr post dose was 38.2-38.7°C. There was a statistically significant increase in MPCEs (refer to sponsor's table below) with the administration of oxymorphone alone at 24 hrs (5/14,000, 26/12,000, 278/14,000 in control, oxymorphone HCl, and CP respectively). Pretreatment with sodium salicylate in animals still show an increase in body temperature up to 4 hrs. The amplitude of body temperature increase in the group of animals pretreated with this antipyretic drug; however, smaller than that of the group treated with oxymorphone alone. There was no increase in the number of MPCEs from the animals pretreated with sodium salicylates. The number of MPCEs in animals pretreated with sodium salicylate was equivalent to the vehicle control group. There was a rapid increase of plasma oxymorphone HCl concentration from 0.5 (75 ng/mL)-2 (338 ng/mL) hrs post dose. The body temperature was markedly high at 4 hrs. The plasma concentration of oxymorphone HCl at 4 hrs was however, very low (16 ng/mL). Therefore, the increase in the plasma concentration can not be directly co related with the body temperature. Sponsor repeated the experiment to determine the relationship of the body temperature and the micronucleus formation after oxymorphone HCl administration.

**Effect of Sodium Salicylate in the Oxymorphone HCl induced Change in Body Temperature:**

| | | Number of Animals With Observed Signs/Total Number of Animals Dosed | Number of Animals Died/Total Number of Animals Dosed |
|---|---|---|---|
| Treatment (10 mL/kg) | Observation* | Males | Males |
| Water | Normal | 7/7 | 0/7 |
| Oxymorphone (40 mg/kg) | Lethargy | 7/7 | 1/7 |
| Sodium salicylate (300 mg/kg )/ Oxymorphone (40 mg/kg) | Lethargy | 7/7 | 0/7 |

*Observations do not include animals used for the toxicokinetic portion of the assay.

**Effect of Sodium Salicylate in the Oxymorphone HCl -Induced Body Temperature:**






Effect of Sodium Salicylate in the Oxymorphone HCl induced MPCEs

| Treatment (10 mL/kg) | 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 | M | 24 | 7 | 0.577 ± 0.04 | --- | 0.4 ± 0.24 | 5 / 14000 |
| Oxymorphone (40 mg/kg) | M | 24 | 6 | 0.515 ± 0.05 | -11 | 2.2 ± 0.88 | *26 / 12000 |
| Sodium salicylate (300 mg/kg)/ Oxymorphone (40 mg/kg) | M | 24 | 7 | 0.498 ± 0.10 | -14 | 0.6 ± 0.38 | 9 / 14000 |

[1] *Statistically significant, p≤0.05 (Kastenbaum-Bowman Tables)

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Effect of Sodium Salicylate in the Oxymorphone HCl induced Toxicokinetics

**Table 6.2.A: Group II - Summary of Oxymorphone Concentrations (ng/mL) in Male Rats After Oral Administration of 40 mg/kg Oxymorphone HCl**

Endo Study Number: EN3202-261A-03
Study Number: 37-6306

| Time, h | Mean | SD | CV, % |
|---|---|---|---|
| 0.5 | 75.33 | 68.79 | 91.3 |
| 1 | 267.4 | 409.0 | 153.0 |
| 2 | 365.7 | 606.9 | 166.0 |
| 4 | 16.64 | 7.74 | 46.5 |
| 8 | 10.24 | 2.82 | 27.5 |
| 24 | 23.41 | NC | NC |

NC: Not Calculated
Run Numbers: 030925-501 and 031015-502

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

Key findings:

- Under the current experimental condition oxymorphone alone induce micronucleus formation in rats. Sodium salicylate pretreatment, 15 and 30 mins prior to the oxymorphone administration did not show any induction of micronucleus in these animals.
- Hypothermia was observed in rats with the oxymorphone alone, sodium salicylate pretreatment partially blocked oxymorphone induced hyperthermia. Plasma concentration of oxymorphone was not related to the hyperthermia observed; therefore, hyperthermic effect of oxymorphone might not be a direct effect.

| | |
|---|---|
| **Study no (CRO):** | AA46XC.125 D.BTL |
| **Study type** (if not reflected in title): | *In vivo* rat micronucleus test |
| **Volume #, and page #:** | EDR, 1-112 |
| **Conducting laboratory and location:** | [redacted] |
| **Date of study initiation:** | January 23, 2004 |

**GLP compliance:** Yes
**QA reports:** Yes ( X ) no ( )
**Drug, lot #, radiolabel, and % purity:** Oxymorphone HCl, Mallinckrodt, E06575; [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:** In a previous study tested doses 20 and 40 mg/kg oxymorphone via oral gavage (10 mL/kg) in preliminary toxicity study (n=5/sex/group) showed increase MPCE formation.

**Range finding studies:** No range finding study was submitted under the current study title, however mortality was observed at higher doses tested ≥ in the previous studies reviewed under this submission. Based on those 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.

**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 [redacted] days under ambient conditions. At [redacted] days, individual known and unknown and known degradation products were less than [redacted] .

**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 hours.
**Doses used in definitive study:** 40 mg/kg oxymorphone/kg via oral gavage (10 ml/kg).

**Study design:** This study was designed to investigate the relationship between hypothermia and micronuclei formation following oxymorphone HCl administration. A total of seven male rats per treatment group were administered oxymorphone via oral gavage. The doses of either 300 or 500 mg/kg sodium salicylate (an antipyretic agent) were administered intraperitoneally 60 and 30 mins prior to the oxymorphone HCl administration. The subcutaneous body temperature was monitored at 0.25,

0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The study design was as follows:

| Treatment (10 mL/kg) | Number of Animals Micronucleus Analysis | Number of Animals Toxicokinetic Evaluation (TK) [a] |
|---|---|---|
| Group 1. Vehicle Control: Water | 7 | 0 |
| Group 2. Test Article: Oxymorphone (40 mg/kg) | 7 | 6 |
| Antipyretic+Test Article: Group 3. Sodium salicylate (300 mg/kg) 60 minutes before Oxymorphone (40 mg/kg) | 7 | 6 |
| Group 4. Sodium salicylate (500 mg/kg) 30 minutes before Oxymorphone (40 mg/kg) | 7 | 6 |
| Antipyretic: Group 5. Sodium salicylate (300 mg/kg) | 7 | 0 |
| Group 6. Sodium salicylate (500 mg/kg) | 7 | 0 |

[a] Plasma samples were collected from 3 animals at 0.5, 2 and 8 hr after dosing and from 3 animals at 1, 4 and 24 hr after dosing for determination of plasma oxymorphone concentration. Timepoints were relative to administration of oxymorphone.

Six additional animals were used for toxicokinetics. Blood was colleted at 0.5, 1, 2, 4, 8, and 24 hrs for analyzing the plasma concentration of the oxymorphone at different time points from the animals.

**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. Two 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 positive if a statistically significant increase in MPCEs were noted compared to that of the vehicle control ($p \leq 0.05$, Kastenbaum-Bowman Tables).

**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.

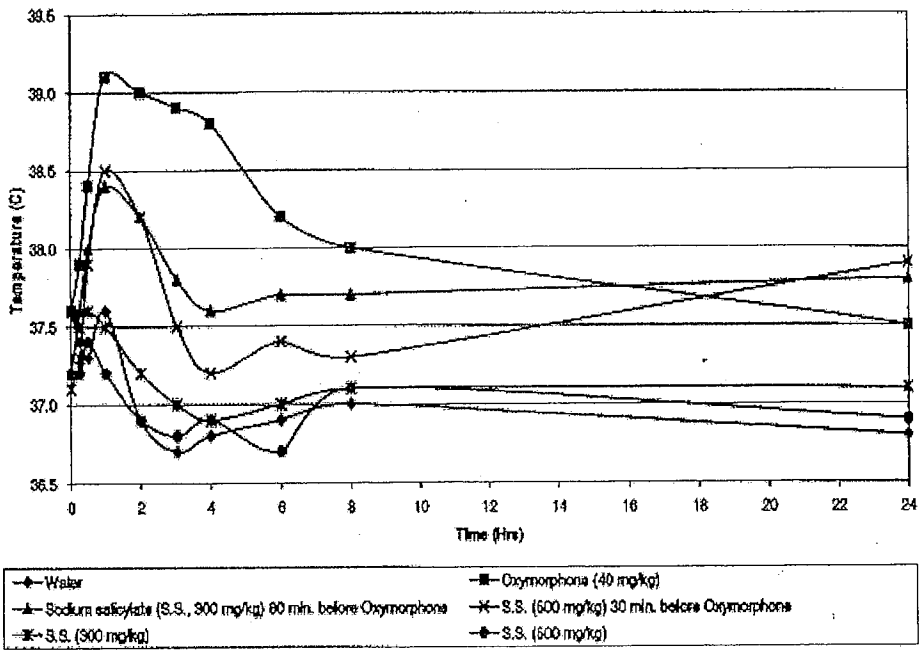
**Study outcome:** Clinical signs following oxymorphone HCl administration are presented in the sponsor's table (below). All treated animals showed clinical signs of lethargy. An increase in body temperature was observed with the oxymorphone HCl treated animals. As indicated in the figure below, administration of oxymorphone HCl increased the body temperature in the rats (male) up to 4 hrs post dose. Mean body temperature increased at 0.5-2 hrs post dose was 37.9.2-38.5°C. The mean body temperature in animals pretreated with sodium salicylate (300 mg and 500 mg) was lower than that of the group treated with oxymorphone alone but higher than the vehicle control. This indicates that the hyperthermia induced by oxymorphone might not be mediated entirely through the prostaglandin mediated events and therefore might not be completely controlled by the application sodium salicylate. There was a statistically significant increase in MPCEs (refer to sponsor's table below) with the administration of oxymorphone alone at 24 hrs (6/14,000, 51/12,000, 6/12,000, and 5/12,000 in control, oxymorphone HCl, 300 mg/kg sodium salicylate pretreatment and 500 mg/kg sodium salicylate pretreatment respectively). Toxicokinetics varied widely in animals from individual groups and there was no correlation between the plasma concentrations of oxymorphone with hypothermia observed in rats. However, the purpose of the experiment was to find out whether the pretreatment of the antipyretic drug prevents MPCE formation after oxymorphone administration. The present study demonstrated that MPCE formation after administration of oxymorphone and sodium salicylate is similar to that of the controls.

## Effect of Sodium Salicylate in the Oxymorphone HCl induced Clinical Signs

| Treatment (10 mL/kg) | Observation | Number of Animals With Clinical Signs/Total Number of Animals Dosed | Number of Animals Died/Total Number of Animals Dosed |
|---|---|---|---|
| Water | Normal | 7/7 | 0/7 |
| Oxymorphone (40 mg/kg) | Lethargy | 7/7 | 0/7 |
| Sodium salicylate (300 mg/kg) 60 min. before Oxymorphone (40 mg/kg) | Lethargy | 7/7 | 1/7 |
| Sodium salicylate (500 mg/kg) 30 min. before Oxymorphone (40 mg/kg) | Lethargy | 7/7 | 1/7 |
| Sodium salicylate (300 mg/kg) | Lethargy | 7/7 | 0/7 |
| Sodium salicylate (500 mg/kg) | Normal | 7/7 | 0/7 |

*Observations do not include animals used for the toxicokinetic evaluation

## Effect of Sodium Salicylate in the Oxymorphone HCl induced Body temperatures

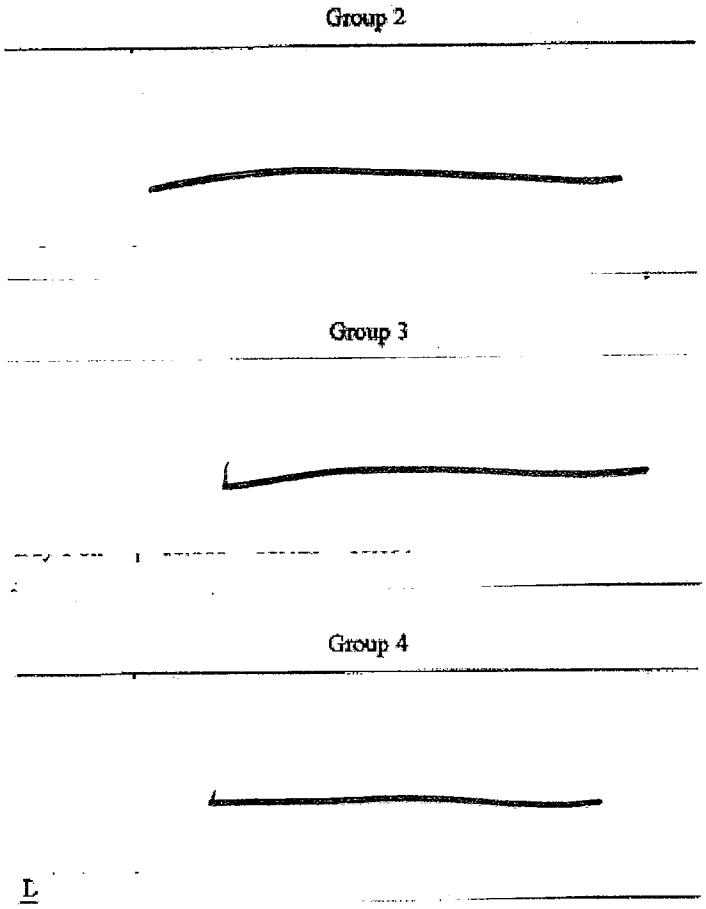


## Effect of Sodium Salicylate in the Oxymorphone HCl induced MPCEs

| Treatment (10 mL/kg) | Sex | Time (hr) | Number of Rats | PCE/Total Erythrocytes (Mean +/- SD) | Change from Control (%) | MPCEs/1000 PCEs (Mean +/- SD) | MPCEs/ PCEs Scored[1] |
|---|---|---|---|---|---|---|---|
| Water | M | 24 | 7 | 0.624 ± 0.05 | --- | 0.4 ± 0.35 | 6 / 14000 |
| Oxymorphone (40 mg/kg) | M | 24 | 7 | 0.642 ± 0.04 | 3 | 3.6 ± 1.65 | *51 / 14000 |
| Sodium Salicylate (300 mg/kg) 60 min. before Oxymorphone (40 mg/kg) | M | 24 | 6 | 0.625 ± 0.05 | 0 | 0.5 ± 0.45 | 6 / 12000 |
| Sodium Salicylate (500 mg/kg) 30 min. before Oxymorphone (40 mg/kg) | M | 24 | 6 | 0.638 ± 0.04 | 2 | 0.4 ± 0.49 | 5 / 12000 |
| Sodium Salicylate (300 mg/kg) | M | 24 | 7 | 0.623 ± 0.02 | 0 | 0.4 ± 0.35 | 6 / 14000 |
| Sodium Salicylate (500 mg/kg) | M | 24 | 7 | 0.637 ± 0.03 | 2 | 0.5 ± 0.29 | 7 / 14000 |

[1]*Statistically significant, p≤0.05 (Kastenbaum-Bowman Tables)
MPCEs: Micronucleated Polychromatic Erythrocytes
PCEs: Polychromatic Erythrocytes

**Effect of Sodium Salicylate in the Oxymorphone HCl induced Toxicokinetics**




**Study Number/Study Title: EN3202-252-03 Monitoring of Mouse Body Temperature Following Oxymorphone Administration**

The objective of this study was to determine the effect of oxymorphone HCl on the body temperature in mice. The study was done following SOP, quality assurance document is provided by the Sponsor. The study completion date was April 4th, 2004.

METHODS: Five male ICR mice were administered with 250 and 5000 mg/kg doses of oxymorphone HCl by oral gavage. The subcutaneous body temperature was monitored at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose using an implantable programmable temperature transponder. The following table summarizes the study design:

**Best Possible Copy**

| | Group | Treatment (20 mL/kg) | Dosage (mg/kg) | Route of Administration | Number of Animals Dosed |
|---|---|---|---|---|---|
| First | 1 | Water (vehicle) | 0.0 | Oral gavage | 5 |
| Phase | 2 | Oxymorphone | 250 | Oral gavage | 5 |
| | 3 | Oxymorphone | 500 | Oral gavage | 10[a] |

[a] Including 5 replacement animals to ensure the availability of five animals for body temperature analysis

RESULTS: Under this experimental condition oxymorphone HCl was shown to induce an increase in body temperature (see tables below).

Effect of Oxymorphone HCl on Body Temperature in Mice:

Following Dose Administration of Vehicle and Oxymorphone in Male ICR Mice

| Animal # | Predose | 0.25 hour Postdose | 0.5 Hour Postdose | 1 Hour Postdose | 2 Hours Post Dose | 3 Hours Post Dose | 4 Hours Postdose | 6 Hours Postdose | 8 Hours Postdose | 24 Hours Postdose |
|---|---|---|---|---|---|---|---|---|---|---|
| Water | | | | | | | | | | |
| MEAN | 37.5 | 38.6 | 38.4 | 38.0 | 36.9 | 37.3 | 36.8 | 37.3 | 37.6 | 37.4 |
| SD | 0.4 | 0.4 | 0.7 | 0.4 | 0.6 | 0.4 | 0.5 | 0.7 | 0.5 | 0.7 |
| Oxymorphone (250 mg/kg) | | | | | | | | | | |
| MEAN | 36.3 | 37.5 | 36.6 | 36.9 | 37.5 | 38.1 | 38.1 | 37.9 | 38.2 | 37.4 |
| SD | 0.4 | 0.6 | 1.8 | 1.0 | 0.9 | 0.4 | 0.2 | 0.3 | 0.4 | 0.7 |
| Oxymorphone (500 mg/kg) | | | | | | | | | | |
| MEAN | 36.7 | 38.0 | 37.6 | 37.8 | 38.5 | 38.3 | 38.0 | 37.9 | 37.7 | 37.7 |
| SD | 0.4 | 0.6 | 1.0 | 1.1 | 1.0 | 0.7 | 0.6 | 0.7 | 1.1 | 1.5 |

*No data due to mortality

## 2.6.6.9 Discussion and Conclusions:

The sponsor has provided repeat-dose toxicology studies in the rodent and non-rodent, a full battery of genetic toxicology studies and reproductive and developmental toxicology studies in support of their NDAs for oxymorphone ER (21-610) and IR (21-611). The non-clinical data is the same for both drug products and therefore the NDAs were reviewed together. Overall, oxymorphone produced characteristic opioid toxicities. The Sponsor obtained the Executive Carcinogenicity Assessment Committee's concurrence on the design of the protocols prior initiation of the studies. 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 sponsor that the study was negative for the drug related neoplasms.

There was a greater incidence of malignant lymphoma in the low-mid dose and high-mid dose treatment groups compared to controls. However, the incidence in the high-dose group was below that of the control group, and therefore not dose-dependent or statistically significant. The historical control data from the [redacted] laboratories for male and female mice showed incidence of spontaneous malignant lymphoma is high 62/805 (7%) in males and 175/805 (21%) in females. In contrast, the historical control data from [redacted] laboratories show incidence of malignant lymphoma in males and females of 3/2874 (0.1%) and 317/3192 (9%) respectively.

Neoplastic lesion findings include malignant lymphoma in male rat (1/100 in control vs. 4/65 in 10 mg/kg), kidney tubular cell adenoma in males rats (0/100 in control vs. 2/65 at high dose), all body leiomyoma in female rats (0/100 in control vs. 3/65 at high dose) and all body squamous cell carcinoma in males (2/100 in control, 4/65, 2/65, and 4/65 at low, mid, and high dose respectively) and females (0/100, 2/65, 2/65, and 3/65 in control, low, mid, and high dose respectively), and all body leiomyoma in females (0/100 in control vs. 3/65 at high dose). The incidence of tumors in rat and mice carcinogenicity studies was not statistically significant.

In the 2-year rat carcinogenicity assay, nonneoplastic findings include increase in eye lesions, described as corneal inflammation and retinal degeneration in all doses in females and mid and high dose in males. The cause of the ocular damage is not clear. Reduced 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 may play a role in the retinal degeneration. Pupil dilation or mydriasis is widely reported in literature following morphine administration which might contribute to the retinal degeneration. The clinical significance of any of these potential contributing factors is not known.

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 is often associated with the presence of foreign material (bedding) in the bronchi, bronchioles and/or alveoli. These changes were graded minimal to severe. The findings in the animal model are consistent with a reduced respiratory drive due to opioids and may suggest reduced mucociliary clearance (Wang, et al., 2003), which are known complications of opioid therapy and can be monitored clinically.

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 might be correlated with the primary pharmacodynamic effects of opioids on the urinary system.

Oxymorphone 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.

During the first review cycle of the NDAs, the sponsor proposed that the positive *in vivo* genotoxicity data in the rat and mouse are not biologically relevant. They provide the following arguments for this position:

1. The "apparent clastogenic activity of oxymorphone seen in the mouse and rat micronucleus studies is a class-related phenomenon that is of no demonstrated clinical significance and does not pose a health threat to human." This statement is based upon the following:

   A. The effect is indirect and mediated through glucocorticoids and/or opioid receptor binding.
   B. The effect resolves rapidly following repeated daily dosing.
   C. There are no corroborative findings in the chronic toxicology or reproductive/developmental studies suggesting evidence for pre-neoplastic changes or mutagenic activity.
   D. Codeine, a structurally related compound, did not increase incidence of tumors in rats or mice (NTP).

2. Humans have been exposed to oxymorphone directly and indirectly (oxymorphone is a major metabolite of oxycodone).

## Followings were FDA's response to the Sponsor's argument:

FDA Response to Point 1.

a. The Sponsor concludes that the response is due to a class-effect and is indirect based upon previously published results with morphine sulfate (Swain, et al., 1980; Das and Swain, 1982; Sawant and Couch, 1995; Couch and Sawant, 1995; Sawant, et al., 2001). These reports suggest that the *in vivo* effects of morphine sulfate are mediated by opioid receptors and adrenal-dependent factors. Although these results suggest that opioid-induced alterations in *in vivo* mutagenicity testing

is due to activation of the HPA axis, the authors note several observations that suggest that the effect of morphine is more complex. Specifically, N-methylmorphine, a quaternary opioid agonist that does not readily cross the blood brain barrier, also produces an increase in the frequency of micronucleated cells. Second, metyrapone, an inhibitor of glucocorticoid biosynthesis, did not alter morphine-induced clastogenicity. Third, the concentrations of dexamethasone that induce micronuclei *in vitro* are approximately 5-fold higher than the concentrations of corticosterone obtained at clastogenic doses of morphine sulfate. Fourth, intravenous β-endorphin, which should not readily cross the blood brain barrier, also produces a clastogenic response *in vivo*. Fifth, 5 consecutive treatments with codeine, which is structurally similar to morphine and oxymorphone, did not produce alterations in the mouse *in vivo* micronucleus test (Bruce and Heddle, 1979). Overall, the evidence suggests that opioids may make cells more susceptible to genetic damage via depressed DNA repair capacity (Madden, et al., 1979), however, the exact mechanism of morphine-induced alterations in the frequency of micronuclei is not known.

The Sponsor's data from the *in vitro* mutagenicity studies were negative, while the data in the *in vivo* studies were positive. As such, this reviewer agrees that the mechanism of oxymorphone-induced mutagenicity appears to be indirect. However, this alone does not support the conclusion that the findings have no relevance to humans. The positive result *in vivo* could be mediated by an opioid-receptor/adrenal-dependent mechanism, like morphine, or it could be due to a mutagenic metabolite of oxymorphone. The sponsor has provided no data to support either assumption for oxymorphone.

b. The Sponsor claims that the effect is transient and resolves following repeated administration. This conclusion is based upon a literature reference for morphine (Swain, et al., 1980), but has not been demonstrated for oxymorphone. Therefore, the sponsor has not provided evidence that this is true for their product.

c. The Sponsor claims that there are no corroborative findings in either the 13-week repeat-dose toxicity studies or the reproductive/developmental studies to suggest mutagenic or pre-neoplastic changes following oxymorphone treatment. Although this appears to be a true statement, the studies did not administer oxymorphone for a sufficient duration to be of use for accurate assessment of carcinogenic potential. It is also not likely that pre-neoplastic changes will be detected in studies of these durations.

d. The Sponsor claims that codeine, a structurally similar compound has been evaluated for carcinogenic potential by the NTP and found negative. This is true. However, in contrast to oxymorphone, codeine was negative in the *in vivo* micronucleus test, questioning the claim for a class-effect in this test. In addition, the results of the carcinogenicity assessment for codeine cannot be extrapolated to oxymorphone.

FDA Response to Point 2.

Although humans have been exposed to oxymorphone, there are no epidemiological studies available that can demonstrate any assessment of increases or decreases in tumor incidence in patients which receive oxymorphone. As a result, there is no human data to support the claim made by the sponsor.

**Evaluation of mechanism of oxymorphone-induced micronuclei formation**

The positive result for oxymorphone in the *in vivo* micronucleus test indicates that oxymorphone has the potential to cause DNA damage when administered to both rats and mice. The mechanism mediating this effect is not clear.

Aside for the requirement to characterize the [redacted] degradation products in the drug products [redacted]) the primary pharmacology toxicology issues complicating these NDAs is the positive *in vivo* micronucleus assays with oxymorphone and the positive in vitro genetic toxicology result with the impurity [redacted]. These NDAs are also complicated by the discovery of [redacted] which has not been characterized to date and contains the same structural alert for mutagenicity as [redacted].

There are no formal FDA guidance documents that describe the Agency's position on acceptable levels of genotoxicity impurities in drug products. The European Agency for the Evaluation of Medicinal Products (EMEA) published a draft position paper on the limits of genotoxic impurities in December 2002. This document proposes that there are two classes of genotoxic impurities: 1) genotoxic compounds with sufficient evidence for a threshold-related mechanism, and 2) genotoxic compounds without sufficient evidence for a threshold-related mechanism. The EMEA document maintains that in some circumstances, there may be a threshold for genotoxicity with some compounds. EMEA notes that this is particularly true for potential mutagens that are rapidly detoxified, and as such, a NOEL level can be established for risk assessment. The position paper also recommends that if there is no clear evidence for a threshold mechanism, there sponsor should evaluate their manufacturing process to determine if the impurity can be eliminated by changing the synthetic pathway or in the formulation. If you cannot eliminate the impurity, the EMEA document recommends that the sponsor explore alternative synthetic schemes or formulations to eliminate the genotoxic impurity or justify why the impurity is unavoidable. If the impurity is unavoidable, technical efforts to reduce the content of the impurity to levels as low as technically feasible should be undertaken. They refer to this approach as the pharmaceutical (quality) assessment. Should the presence of the impurity be sufficiently justified, a critical assessment of the toxicological acceptability should be provided. This could be a quantitative risk assessment based on mathematical models or a determination of a no effect level of carcinogen response modified by uncertainly factors in order to establish an acceptable safety margin.

The Genetic Toxicology Subcommittee of PTCC at FDA has commented upon the draft guidance proposed by EMEA. The Genetic Toxicology Subcommittee acknowledges that position that a threshold mechanism for some genotoxic effects exist has begun to gain acceptability. They note that current practice is to assume that there is no threshold for the genotoxic effect. Further, they conclude that at this time, methods to demonstrate that a threshold-related mechanism for a genotoxic response is not well established. Although the approach is commendable, it is not feasible at this time due to the difficulties in extrapolating a NOEL in the currently accepted genetic toxicology tests to a human dose. A NOEL cannot be extrapolated from an in vitro study. The existing in vivo test in the standard batter (in vivo micronucleus test) detects clastogenic events, but not mutagenic ones. Further this test only monitors one target tissue and does not take into account the potential accumulation of the impurity into specific tissues. This reviewer concurs with CDER's Genetic Toxicology Subcommittee. Further the sponsor has provided no data demonstrating that a threshold for the oxymorphone or [redacted] effects exists.

The determination of an acceptable specification for this impurity has been discussed extensively in the division. The specification of NMT [redacted] for the [redacted] in the drug products is based, in part, upon the acceptable levels of benzene (known human carcinogen) in drinking water, as defined by the EPA (maximum contaminant level for drinking water is 5 ppb). EPA's qualitative risk estimate of carcinogenic risk from oral exposure to benzene is 1 in 1,000,000 with a concentration in drinking water of 1-10 μg/L (assuming 2 L/day = 20 μg/day). For a person taking a daily dose of 1000 mg/day of oxymorphone, a maximum of 20 μg/day would require the [redacted] to be at a level of [redacted]. A specification of NMT [redacted] for [redacted] corresponds to a maximum daily dose of 10 μg/day.

The impurities [redacted] have been identified and contain a structural alert for mutagenicity. A minimal genetic toxicology screen for [redacted] have been completed and the results indicate that this impurity tests positive in the *in vitro* chromosome aberrations assay. The sponsor should either reduce the levels of each impurity to NMT [redacted] or further qualify each impurity via carcinogenicity assessment in a single species.

**Deficiencies from the first review cycle**

During the first cycle of the review, [redacted] additional impurities were identified which exceed ICH Q3B thresholds for qualification [redacted]. The approvable letter dated October 15, 2003 contained the following deficiency:

> 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.

During the post-action meeting, the Division clarified that the 14-day repeat-dose toxicology study would be required for safety qualification; however, if the sponsor elected to reduce the levels of the impurities to below the ICH thresholds for qualification, the 14-day study was not required. ENDO revised the specification with the current submission. The specification for the above mentioned impurities is labeled as [redacted] which is acceptable according to the ICH Q3B Guidance.

The impurities [redacted] have been identified and contain a structural alert for mutagenicity. Minimal genetic toxicology screens for [redacted] were completed and the results indicate that these impurities test positive in the *in vitro* chromosome aberrations assay. The sponsor should either reduce the levels of each impurity to NMT [redacted] or further qualify each impurity via carcinogenicity assessment in a single species. The DMF holder has been working toward reducing the levels [redacted] of these impurities in the drug substance since the time of the original NDA submission in 2002. The Agency and the DMF holder have agreed upon a time line for the reduction of these impurities in the drug substance. Based upon this agreement, the requirement for these impurities to be reduced below the current specifications may be completed post-approval.

## 2.6.7 TOXICOLOGY TABULATED SUMMARY

Not provided

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** The Sponsor has addressed all of the outstanding pharmacology toxicology issues that were raised during the first cycle review of these NDAs.

**Unresolved toxicology issues (if any):** None.

**Recommendations:** From a pharmacology/toxicology perspective, based upon review of the non-clinical data, NDA 21-611 (oxymorphone IR) and NDA 21-610 (oxymorphone ER) may be approved.

**Suggested 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):

[redacted]

# 2 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Pharm/Tox-_____*

## APPENDIX/ATTACHMENTS

Reference List

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/s/

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Mamata De
6/19/2006 09:32:26 AM
PHARMACOLOGIST

R. Daniel Mellon
6/19/2006 09:55:36 AM
PHARMACOLOGIST
I concur with Dr. De's recommendation that, from the nonclinical pharmacology toxicology perspective, NDA 21-610 may be approved.

1ST 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 12/20/2002** |
| DRUG NAME: | **Oxymorphone Hydrochloride Extended Release (21-610)** |
| | **Oxymorphone Hydrochloride Immediate Release (21-611)** |
| INDICATION: | **Moderate to severe pain** |
| SPONSOR: | **ENDO Pharmaceuticals** |
| DOCUMENTS REVIEWED: | **Electronic Submissions** |
| REVIEW DIVISION: | **Division of Anesthetic, Critical Care & Addiction Drug Products (HFD-170)** |
| PHARM/TOX REVIEWER: | **R. Daniel Mellon, Ph.D.** |
| PHARM/TOX SUPERVISOR: | **R. Daniel Mellon, Ph.D.** |
| PROJECT MANAGER: | **Lisa Basham-Cruz** |

Date of review submission to Division File System (DFS): October 15, 2003

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# *EXECUTIVE SUMMARY*

## 1. Recommendations

1.1 Recommendation on approvability:

From the non-clinical pharmacology and toxicology perspective, NDAs 21-610 and 21-611 are considered to be approvable.

1.2 Recommendation for nonclinical studies:

The following non-clinical studies should be completed by the sponsor:

1. The ongoing carcinogenicity assessments of oxymorphone in the rat and mouse models should be submitted upon completion.

2. Oxymorphone tested positive in the *in vivo* micronucleus assay in both the rat and the mouse. Although the sponsor has hypothesized that oxymorphone produces this result in a manner similar to that reported for morphine in the literature, this hypothesis has not been tested for oxymorphone. The sponsor should determine the mechanism of oxymorphone-induced positive finding in the *in vivo* micronucleus assay and determine the relevance of these findings to humans. These studies should be submitted at the time of resubmission of the NDA. The Division is willing to review proposed study protocols.

3. The sponsor should adequately qualify the impurities [redacted] via a minimal genetic toxicology screen (one *in vitro* gene mutation and one *in vitro* chromosomal aberration assay) or reduce the specifications for each of these impurities to NMT [redacted] prior to resubmission of the NDA. In addition, a 14-day repeat-dose toxicology study for each compound should be completed in a single species.

4. Carcinogenicity assessment of the impurity [redacted] in a single species should be completed if the sponsor can not reduce the levels of this drug impurity to not more than [redacted]

5. A minimal genetic toxicology screen (one *in vitro* mutagenicity and one *in vitro* chromosome aberrations assay) should be completed for the impurity [redacted] if the sponsor can not reduce the levels of this drug impurity to not more than [redacted]. Should this compound test positive in either assay, the sponsor should either reduce the levels of each impurity to NMT [redacted] or further qualify [redacted] via carcinogenicity assessment in a single species.

1.3 Recommendations on labeling:

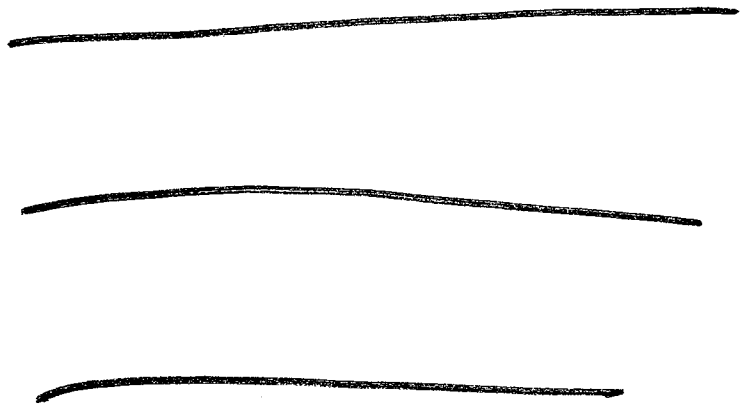
1 Page(s) Withheld

____ Trade Secret / Confidential

6 Draft Labeling

____ Deliberative Process

*Withheld Track Number: Pharm/Tox-_____*



## 2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings:

In support of the NDA's for Oxymorphone ER and IR, the sponsor conducted 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. In addition, the sponsor has initiated carcinogenicity assessment in two species that are planned for submission 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.

Additional genetic toxicology studies have been conducted on the impurity [redacted] which contains a structural alert for mutagenicity [redacted] tested negative in the *in vitro* bacterial reverse mutation assay either with or without metabolic activation. In contrast, [redacted] tested positive in the *in vitro* chromosome aberrations assay at concentrations that did not produce significant cytotoxicity and therefore should be considered a clastogen. The sponsor is currently conducting a minimal genetic toxicology screen on a [redacted] impurity containing the [redacted] structural alert, [redacted]. A consult was requested from the Genetic Toxicology Subcommittee of PTCC and Dr. David Jacobson-Kram (Associate Director for Pharmacology and Toxicology at CDER). The committee members concurred with both the sponsor's and this reviewer's interpretation of the assay as positive.

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 (embryofetal 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 (embryofetal 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, exophthalamus 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 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 exophthalamus. 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-weening 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-weening 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 protocols for carcinogenicity assessment of oxymorphone were submitted to the CAC and found to be acceptable. The studies were initiated in the fall of 2002 and will be submitted to the NDA as a phase 4 commitment.

2.2 Pharmacologic activity:

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 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, 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 □-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.

2.3 Nonclinical 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 not been further qualified via carcinogenicity assessment as of the submission of the NDA. Carcinogenicity for oxymorphone is being conducted by the sponsor. Until that data is available, patients should be advised of the positive clastogenic effect of oxymorphone via the labeling. The results of the *in vivo* micronucleus assay are stated in the labeling/package insert.

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

[redacted]. The molecule contains an [redacted] moiety, which is a structural alert for mutagenicity. During the NDA review process, the sponsor tested the [redacted] in a minimal genetic toxicology screen. The results indicated that the impurity tests positive in the *in vitro* chromosomal aberrations assay.

# *PHARMACOLOGY/TOXICOLOGY REVIEW*

## 3.1 INTRODUCTION AND DRUG HISTORY

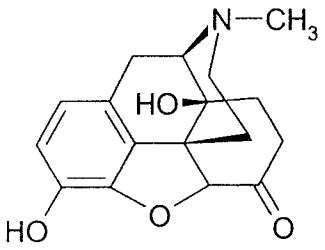
| | |
|---|---|
| **NDA number**: | 21-610 (oxymorphone HCl ER)<br>21-611 (oxymorphone HCl IR) |
| **Review number**: | 1 |
| **Sequence number/date/type of submission**: | N 000 / December 19, 2002 / NDA<br>N 000 / December 20, 2002 / NDA |
| **Information to sponsor**: | Yes ( X ) No ( ) |
| **Sponsor and/or agent**: | ENDO Pharmaceuticals<br>100 Painters Drive<br>Chadds Ford, PA 19317 |
| **Manufacturer for drug substance**: | Mallinckrodt Chemical Company<br>St. Louis, Missouri 63134 |

| | |
|---|---|
| **Reviewer name**: | R. Daniel Mellon |
| **Division name**: | Anesthetics, Critical Care & Addiction Drug Products |
| **HFD #**: | 170 |
| **Review completion date**: | October 15, 2003 |

**Drug**:

| | |
|---|---|
| Trade name: | To be determined |
| Generic name: | Oxymorphone hydrochloride |
| Code name: | None |
| Chemical name: | (5alpha)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride |
| CAS registry number: | 357-07-3 |
| Molecular formula/molecular weight: | $C_{17}H_{19}NO_4 \bullet HCl$ / 337.80 |

Structure: (freebase)




**Relevant INDs/NDAs/DMFs**:

IND 56,919 oxymorphone HCl Controlled Release (ENDO; active 9/10/1998)
IND 58,602 oxymorphone HCl Immediate Release (ENDO; active 7/8/1999)

NDA 11-707 Numorphan® Injection (ENDO, approved 4/02/1959)
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.

**Indication**: 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, | | | | | |
| Methylparaben, | | | | | |
| **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 | | |
| 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 TIMERx-N. Based upon the specifications, that would be 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.

# 1 Page(s) Withheld

2 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Pharm/Tox-_____*

[redacted]

Based upon a structural alert for mutagenicity, the impurity [redacted] should be adequately qualified or reduced to NMT [redacted] prior to approval.

[redacted]

[redacted]

The degradation products [redacted] exceed ICH Q3B thresholds for qualification. Adequate qualification of these impurities should be provided or the levels of each of these compounds should be reduced to NMT [redacted] prior to approval.

**Route of administration**: Oral

**Proposed use**: Analgesic

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

**Studies reviewed within this submission:**

**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

**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)

**Studies not reviewed within this submission:**

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]

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.

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

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

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

## 3.2 PHARMACOLOGY

**3.2.1 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.

**3.2.2 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.

**3.2.3 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.

### 3.2.4 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.

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).

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).

### 3.2.5. Pharmacodynamic drug interactions

According to the current labeling:

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.

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.

## 3.3 PHARMACOKINETICS/TOXICOKINETICS

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### 3.3.1 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 (——— 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. After being treated with oxymorphone, the rat plasma was incubated with

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

3.3.3 **Absorption:** Oxymorphone is absorbed following oral, intramuscular, rectal and subcutaneous administration. Quantitative bioavailability has not been reported in the literature. In——— 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:

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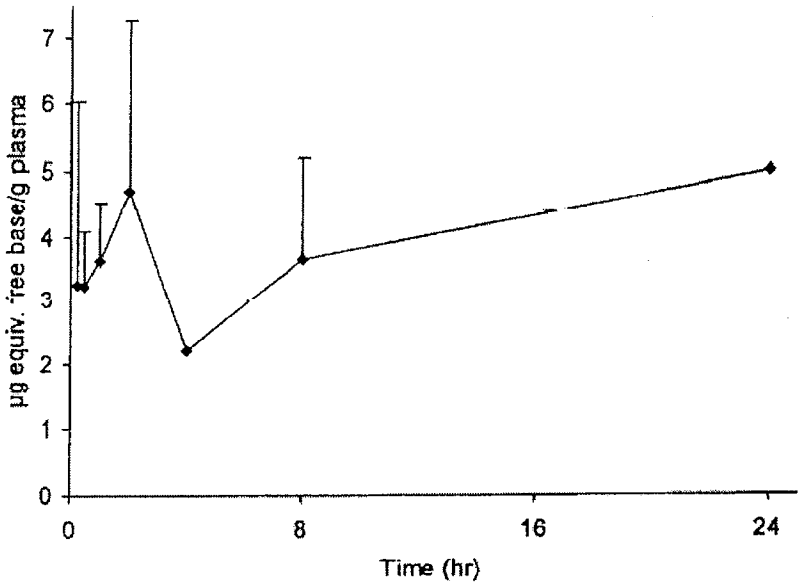
**Figure 2. Concentration of radioactivity (expressed as µg equiv. of $^{3}$H-oxymorphone) in plasma following oral administration of $^{3}$H-oxymorphone (mean dose 25.0 mg/kg body weight and 8.08 MBq/kg) to male rats.**

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 ( ——— 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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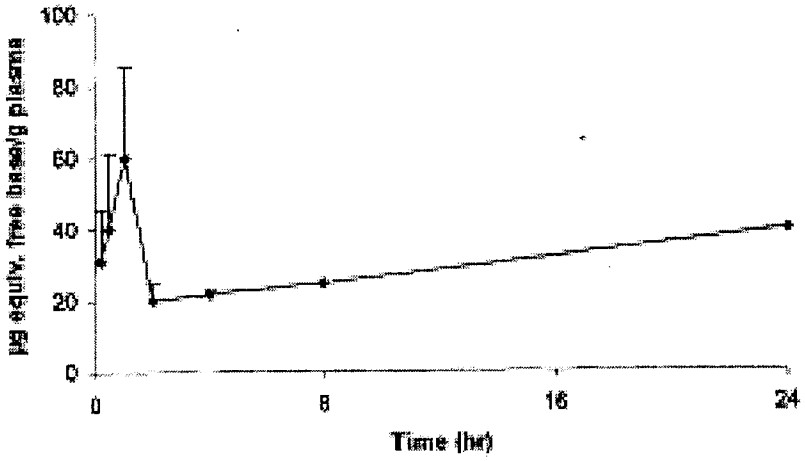


**3.3.4 Distribution:** Specific tissue distribution studies have not been completed for oxymorphone. A study conducted by ——— for Endo Pharmaceuticals ——— Study #UK6052) examined the pharmacokinetics, excretion/balance and metabolite identification in the adult male rat following $^{3}$H-oxymorphone (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 in healthy males and females. Oxymorphone has low protein binding to human or rat plasma proteins (see sponsor's table below from ——— Study #6052):

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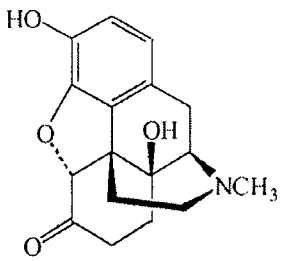
**Table 8 Summary of binding of $^3H$ to plasma proteins following incubation of $^3H$-oxymorphone hydrochloride (0.05, 0.5 and 5 µM free base) with rat and human plasma at 37 °C for 10 minutes**

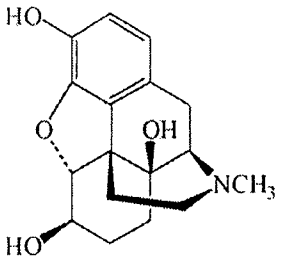
| $^3H$-oxymorphone µM | % radioactivity binding to: Rat plasma proteins* | Human plasma proteins* |
|---|---|---|
| 5.0 | 9.4 | 12.9 |
| 0.5 | 8.4 | 4.5 |
| 0.05 | 11.7 | 0.1 |

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

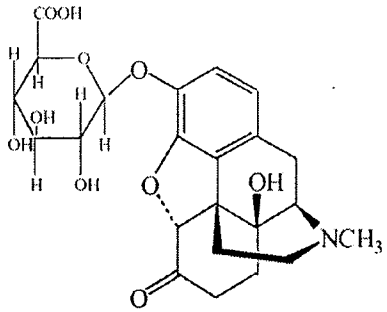
3.3.5 **Metabolism:** In the rat, a total of 4 putative metabolites of oxymorphone were detected in the urine and three in the plasma following oral administration. The major metabolite found in both urine and plasma is 3β-oxymorphone-glucuronide. The other possible metabolites are 6-OH-oxymorphone; 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:



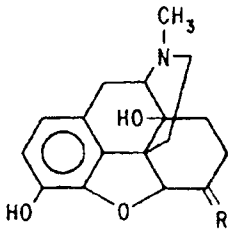

Oxymorphone
MW = 301
M+1 = 302




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 |

**3.3.6 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:

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**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.

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**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

## 3.3.6. 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**

| Isoform | Oxymorphone IC50 Estimate (μM) |
|---|---|
| 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- 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.

### 3.3.10 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)

## 3.4 TOXICOLOGY

### 3.4.1 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<br>(Doses were escalated over first 63 days to achieve these final doses) | -411012 |
| A 13-Week Oral Study of Oxymorphone Hydrochloride in Rats | 0, 10, 25, 50, 75<br>(Doses were escalated over first 2 weeks to achieve these final doses) | -411011 |
| An Oral (Capsule) Escalating Dose Range-Finding Study of Oxymorphone HCl in Dogs | Phase I:<br>Days 0-2: 0, 10<br>Days 7-9: 0, 40<br>Days 14-16: 0, 20<br>Phase II:<br>Days 21-24: 0, 5<br>Days 25-28: 0, 10<br>Days 29-32: 0, 20<br>Days 33-36: 0,40 | -411002 |
| A 13-Week Oral (Capsule) Study of Oxymorphone Hydrochloride in Dogs | 0, 2, 10, 40<br>(Doses were escalated over first 40 days to achieve these final doses) | -411003 |

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] an impurity in the drug substance that contains a structural alert for mutagenicity, tested negative as a mutagen in the *in vitro* bacterial reverse mutation assay. This impurity, however, tested positive in the *in vitro* chromosomal aberrations assay using CHO cells. As such, the impurity, [redacted] is considered to be a clastogen.

[redacted] a recently identified impurity in the drug product also contains a structural alert for mutagenicity [redacted]. The sponsor is currently conducting a minimal genetic toxicology screen on this compound as well.

Carcinogenicity: Carcinogenicity assessment for oxymorphone HCl in the mouse and rat are currently underway. The division has previously informed the sponsor that these studies may be submitted as a Phase 4 commitment.

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 (embryofetal 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 (embryofetal 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, exophthalamus 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 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 exophthalamus. 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-weening 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-weening 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