CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

PHARMACOLOGY REVIEW(S)

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:	**21-378**
SERIAL NUMBER:	**000/12.1-12.11**
DATE RECEIVED BY CENTER:	**05/27/04**
PRODUCT:	**Combunox™ (Oxycodone HCl/Ibuprofen 5/400 mg tablets)**
INTENDED CLINICAL POPULATION:	**For the management of short term (up to 7 days) moderate to severe pain**
SPONSOR:	**Forest Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Vol. 1, 2 and 11**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Mamata De, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham-Cruz**

Date of review submission to Division File System (DFS): November 12, 2004

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the nonclinical pharmacology and toxicology perspective, NDA 21-378 can be approved, if the sponsor commits to completing the Segment I and Segment III reproductive toxicology studies previously agreed to. In addition, the sponsor should continue to work with the Division and the DMF holder to clarify the potential risks associated with the impurity — and any other detected impurity with a structural alert for mutagenicity, or reduce the levels of this and any other potentially genotoxic impurity to acceptable levels.

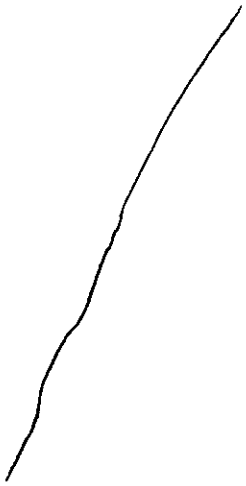
B. Recommendation for nonclinical studies

As previously agreed, the sponsor should commit to conducting Segment I and Segment III reproductive toxicology studies as a phase 4 commitment.

C. Recommendations on labeling

NOTE: The following labeling recommendations reflect only the pharmacology toxicology review team recommendations and thus may not represent the final labeling for this drug product. The sponsor's proposed labeling appears in black text, suggested addition appear red and suggested deletions appear blue with strikeout.

Carcinogenicity, Mutagenicity and Impairment of Fertility



7 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

II. Summary of nonclinical findings

A. Brief overview of non clinical findings:

Combunex™ is a — combination oxycodone to ibuprofen has been tested via single-dose toxicology studies in the rat, repeat-dose toxicology studies in the rat and the dog, and Segment II reproductive toxicology studies in the rat and rabbit. Toxicity is consistent with the known toxic effects of NSAIDs and opioids. The single-dose toxicology studies demonstrate a maximum non-lethal dose of 5 mg/kg oxycodone: 400 mg/kg ibuprofen in females and 6.25 mg/kg oxycodone: 500 mg/kg ibuprofen in males. Toxicity was characterized as immediate CNS depression followed by delayed general deterioration associated with the ulcerogenic potential of the drug product. Deaths were considered to be due to circulatory collapse secondary to CNS depression. Administration of the combination of oxycodone:ibuprofen (1.25:100 mg/kg/day) to the rat for 28-days produced decreased red blood cells, hemoglobin and hematocrit and in increase in platelet counts. Histologically, red or black foci on the gastrointestinal mucosa were suggestive of NSAID-induced alterations in the gastric-mucosa. These changes in the gastric mucosa were not altered significantly via the presence of the opioid.

Administration of the combination of oxycodone:ibuprofen (1:80) to the dog for 28-days produced clinical signs of dark tar-like loose stools and fecal occult blood as the highest dose (0.25:20 mg/kg/day oxycodone: ibuprofen). Although these changes were consistent with gastrointestinal irritation, there was no histological evidence for ulceration in this study. The study was repeated with a 1:40 ratio of oxycodone: ibuprofen. The highest dose tested was 0.5:20 mg/kg oxycodone: ibuprofen. The results of the study demonstrated that the combination product can lead to unformed or liquid stools and positive findings of fecal occult blood. The incidence of fecal occult blood with the combination of the two drugs was far greater than with ibuprofen or oxycodone alone. In addition, the combination of the two drugs produced a significant decrease in red blood cells, hemoglobin and hematocrit which were significantly greater then that produced by ibuprofen alone and consistent with mild blood loss. However, these changes were not correlated with microscopic evidence of GI toxicity. Neither dog study reached a maximum tolerated dose and therefore may not fully predict the potential toxicity to humans.

Segment II reproductive toxicology studies have been completed in both the rat and the rabbit models. The results of the rat study demonstrated no evidence of developmental toxicity at doses that were maternally toxic. The developmental study in the rabbit also indicated that the combination of oxycodone:ibuprofen was maternally toxic at lower

doses than those which produced signs of developmental toxicity. The potential for developmental toxicity of the drug combination was manifested as a non-significant increase in the number of resorptions at the highest dose tested and a trend toward an increase in retarded development and fetal variations (delayed skeletal ossification).

B. Pharmacologic Activity:

Pain is a multi-modal process that involves both central and peripheral mechanisms and a host of chemical mediators and receptors that are involved in the transmission of pain signals to the CNS. As such, treatment of pain with combination products which act via different mechanisms can be more effective while reducing the potential for side effects associated with each compound alone.

Combinations of an opioid analgesic with a non-steroidal anti-inflammatory drug (NSAIDs) have proven to be an effective analgesic combination. The FDA has approved combinations of codeine, oxycodone or hydrocodone with acetaminophen, aspirin and/or ibuprofen. This NDA is the first to test the combination of oxycodone with ibuprofen. Oxycodone is an opioid receptor agonist that acts via interaction primarily with the μ-opioid receptor subtype within the central nervous system. Specifically, oxycodone is though to activate of opioid receptors located on the terminals of sensory afferents inhibit substance P release and activation of opioid receptors located on interneurons inhibit 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. In contrast to the opioid, ibuprofen is a well-characterized NSAID. As such, this compound is thought to produce analgesia primarily via the nonselective, reversible, competitive inhibition of cyclooxygenase enzymes. Cyclooxygenase converts arachidonic acid to the unstable intermediates prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2). Prostaglandins can sensitize pain receptors to mechanical and chemical stimulation and thereby lowering their firing threshold. Therefore, the combination of oxycodone and ibuprofen can act at multiple sites within the pain perception pathways to therefore produce significantly greater analgesia than either compound administered alone at the same dose.

C. Nonclinical Safety Issues Relevant to Clinical Use:

The potential toxicity of opioids has been well characterized and includes respiratory depression, circulatory depression, constipation, nausea, vomiting and physical dependence. The potential toxicity of ibuprofen is also well characterized and includes renal failure in conditions of low intravascular volume of low cardiac output, gastrointestinal bleeding and/or ulceration and hypersensitivity reactions in sensitive individuals. Repeat dose toxicology studies of the combination of oxycodone and ibuprofen in the dog suggest an increased risk of gastrointestinal toxicity with the combination of oxycodone and ibuprofen compared to ibuprofen alone. A description of this increased gastrointestinal toxicity should be considered for the product label.

Additionally, the sponsor should perform Segment I and III reproductive toxicology studies as these components of the reproductive toxicology battery have not been adequately addressed. Assessment of the carcinogenic potential should be performed unless the sponsor stated that the product would not be used chronically.

The sponsor provided two genetic toxicology studies on —, an impurity — that contains a structural alert for mutagenicity, specifically, an — Under the present experimental condition the test articles was negative in the mutagenicity assay. The in vivo clastogenicity assay results were negative under the present experimental condition. MTD was not reached in the assay and bone marrow toxicity with the high dose at 24 hrs (indicating exposure of the bone marrow to test article at this time point) was not observed. However, considering that the test article is an impurity — mg in human for the present indication, the test article can be predicted to have only minimal genotoxicity potential in human at this time. The sponsor currently agreed to limit the impurity at —. Clastogenicity has been shown in an in vitro chromosomal aberration assay done by the — with —, the sponsor indicated that they were aware of the result in April 2nd, 2004 meeting. The equivocal results in different assays with the same test article should be reviewed and analyzed in depth as more data arrive.

APPEARS THIS WAY
ON ORIGINAL

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-378
Review number: 2
Sequence number/date/type of submission: N000 resubmission, 5-27-04
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Forest Laboratories
Manufacturer for drug substance: Mallinckrodt Inc.
Reviewer name: Mamata De, Ph.D.
Division name: Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD #: 170
Review completion date: Sept 20th 2004

Drug:

Trade name: Combunox™

Generic name List alphabetically): Oxycodone HCl and ibuprofen in combination

Code name: DuP 604 (combination product)

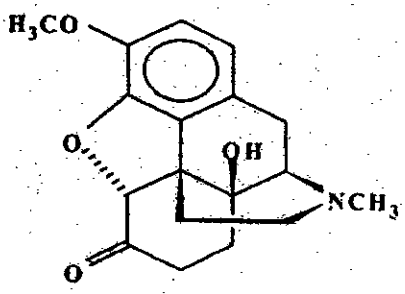
Chemical name: 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and (±)-2-(p-isobutylphenyl)propionic acid

CAS registry number: 76-42-6 (Oxycodone hydrochloride) 15687-27-1 (ibuprofen)

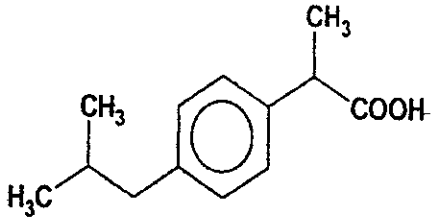
Mole file number: N/A

Molecular formula/molecular weight.$C_{18}H_{21}NO_4$•HCl/ 351.83 (Oxycodone HCl) $C_{13}H_{18}O_2$/ 206.29 (ibuprofen)

Structure:



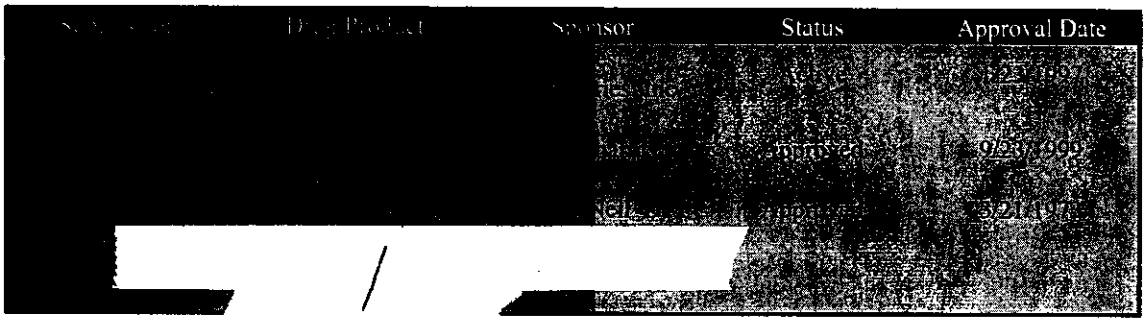
Oxycodone



Ibuprofen

Relevant INDs/NDAs/DMFs:

As a 505(b)(2) NDA submission, Forest Laboratories relies upon the Agency's evaluation of the Safety and Efficacy on Motrin® and Roxicodone™. The NDAs for these drugs are as follows:



Drug class: Opioid/NSAID combination.

Intended clinical population: Short term management of moderate to severe pain

Clinical formulation:

Components and Composition of Oxycodone HCl/Ibuprofen Tablets, 5/400 mg

Ingredients	Functions	Quantity (mg/Tablet)	Quantity (kg/Batch)
Ibuprofen	Active		
Oxycodone Hydrochloride, USP	Active	5.0	
Sodium Starch Glycolate, NF			
Stearic Acid, NF			
Calcium Stearate, NF			
CORE TABLET WEIGHT	N/A		
COATING SOLUTION			
Opadry® II White, Y-22-7719 [3]	Coating		
Purified Water, USP [4]			
COATED TABLET WEIGHT		618.0	

[3] Opadry II Film Coat Dispersion (White) is added — Opadry II White, Y-22-7719 contains titanium dioxide, polydextrose, hypromellose, triacetin and polyethylene glycol 8000.
[4] The water does not appear in the finished product. It is removed during processing.

Route of administration: Oral

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

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-378 are owned by Forest Laboratories or are data for which Forest Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 21-378 that Forest Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Forest Laboratories does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-378.

Studies reviewed within this submission:

1. Sponsor Study No:OXYTX02000: Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with —

2. Sponsor Study No: OXYTX03000 In Vivo Mouse Micronucleus Assay with —

Studies not reviewed within this submission: **None**

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: No pharmacology studies have been submitted with the NDA. Opioids have diverse actions on the body via interactions both peripheral and central opioid receptors. Oxycodone administration produces typical μ-opioid receptor-mediated effects, including analgesia, sedation, respiratory depression, muscle rigidity, euphoria, miosis and alterations in neuroendocrine parameters. Opioids act within the CNS via binding to opioid receptors and inhibiting the activity of nociceptive afferent neurons. Ibuprofen, a non-competitive reversible cyclooxygenase inhibitor, produces analgesia via decreased production of prostaglandins. The analgesic activity of ibuprofen, therefore, is mediated primarily in the periphery. As such, combinations of opioids and NSAIDs are effective analgesics for post-operative and inflammatory pain syndromes. The combination of drugs from these classes reduces the side effects of each individual drug and increases the efficacy of the pain relief. In conclusion, the pharmacology of oxycodone and ibuprofen individually has been well characterized. The side effect profile of these drugs used individually is also well known. Vicoprofen, a combination product containing hydrocodone bitartrate and ibuprofen, has been approved by the FDA.

The combination of oxycodone and ibuprofen would provide yet another combination drug product for the treatment of post-operative and inflammatory pain conditions.

2.6.2.2 Primary pharmacodynamics:

Oxycodone: Oxycodone is a semi-synthetic opioid-receptor agonist. Administration of oxycodone produces analgesia, anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression.

Ibuprofen: Ibuprofen is an aryl-propionic acid derivative which is an effective non-steroidal anti-inflammatory drug (NSAID) with analgesic and anti-pyretic activities.

Mechanism of action:

Oxycodone: The mechanism of action of oxycodone is thought to be mediated by interaction with μ-opioid receptors primarily in the central nervous system. It shows approximately 53-fold higher affinity for μ than δ receptors and 38-fold higher affinity for μ compared to κ-opioid receptors.

***In vitro* Binding Affinities for Oxycodone** (Monory, et al., 1999)

K_i (nM)		
μ	δ	κ
18.0 ± 4.2	958.0 ± 499	677 ± 326

Ligand binding to rat brain homogenates was examined via [^{3}H]DAMGO (μ), [^{3}H]naltrindole (δ) and [^{3}H]U69593 (κ).

Ibuprofen: Ibuprofen is thought to act by inhibition of the activity of the enzyme cyclooxygenase. Inhibition of this enzyme inhibits the production of prostaglandins and related autocoids and thereby reduces inflammation and sensitization of pain afferent fibers. Ibuprofen does not inhibit the enzyme 5-lipoxygenase and therefore the production of leukotrienes remains intact.

Drug activity related to proposed indication:

Oxycodone: The analgesic effects of opioids such as oxycodone 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.

Ibuprofen: Ibuprofen is a mild analgesic, particularly in setting where inflammatory mediators cause sensitization of the pain receptors. Ibuprofen is thought to produce analgesia primarily via the nonselective, reversible, competitive inhibition of

cyclooxygenase enzymes. Cyclooxygenase converts arachidonic acid to the unstable intermediates prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2). There are two forms of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed in most normal cells and tissues. COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators. Importantly, COX-1, but not COX-2 is expressed in the stomach. Prostaglandins can sensitize pain receptors to mechanical and chemical stimulation and thereby lowering their firing threshold.

Because ibuprofen (like aspirin and other NSAIDs) is an organic acid, it accumulates at sites of inflammation which makes it particularly effective as an anti-inflammatory. Ibuprofen, like all NSAIDS, is most effective for post-operative pain or pain arising from inflammation. However, there is also evidence that NSAIDs may produce analgesia in part by actions within the central nervous system independent of their effects on cyclooxygenase.

2.6.2.3 Secondary pharmacodynamics:

Oxycodone: 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 decrease 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.

Ibuprofen: There is some evidence that NSAIDS also work to reduce **pain** by altering the activity of peripheral and central neurons. Ibuprofen is thought to act as an **antipyretic** via inhibition of prostaglandin E_2 production at the level of the preoptic nucleus of the hypothalamus. NSAIDs inhibit **platelet function** by blockade of the production of thromboxane A_2 (TXA_2), a pro-aggregating agent, and thereby increasing bleeding time. NSAIDs promote the retention of salt and water by reduction in prostaglandin-mediated inhibition of chloride reabsorption in the kidney. This may produce edema in some individuals.

2.6.2.4 Safety pharmacology

No studies were submitted to this NDA. The following sections summarize the information known concerning the drug components.

Neurological effects:

Oxycodone: Opioids such as oxycodone have well characterized effects on the central nervous system (CNS). In humans, opioids produces analgesia, drowsiness, changes in mood, mental clouding, and, in some individuals, euphoria. When individuals who are not in pain are administered opioids, 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.

Ibuprofen: Ibuprofen acts predominantly in the periphery and has little effects within the CNS. However, headache, tinnitus, dizziness, blurred vision and seizures have been reported following ibuprofen administration and overdose.

Cardiovascular effects:

Oxycodone: In the supine patient, therapeutic doses of μ-opioids do not significantly alter blood pressure or heart rate. Therapeutic doses produce peripheral vasodilation, reduced peripheral resistance and inhibition of baroreceptor reflexes and therefore orthostatic hypotension may occur. These effects may be partially mediated by peripheral histamine release. 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.

Ibuprofen: NSAIDs do not directly alter the activity of the cardiovascular system. Cardiovascular toxicity including hypotension, bradycardia, tachycardia and atrial fibrillation has been reported in cases of ibuprofen overdose. Administration of NSAIDs during the third trimester is contra-indicated as they can lead to premature closure of the ductus arteriosus. Closure of the ductus arteriosus increases prenatal mortality.

Pulmonary effects:

Oxycodone: In the clinical setting, respiratory depression is a common side effect of μ-receptor agonists such as oxycodone. 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.

Ibuprofen: Hypersensitivity reactions to NSAIDs are well known. This hypersensitivity reaction can manifest itself as vasomotor rhinitis with profuse watery secretions, angioneurotic edema, generalized urticaria and bronchial asthma to laryngeal edema and bronchoconstriction, flushing, hypotension and shock. The mechanism of this hypersensitivity is not known, although it does not appear to be immune mediated. One hypothesis is that NSAIDs divert the metabolism of arachidonic acid from the cyclooxygenase pathway to the 5-lipoxygenase pathway and over production of leukotrienes.

Renal effects:

Oxycodone: 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 beds (Lessard and Bachelard, 2002). These effects are mediated by alterations in the autonomic nervous system.

Ibuprofen: Acute renal failure has been reported following NSAID drug administration in adults. This effect appears to occur mainly in individuals who have pre-existing renal disease or other condition which is associated with low intravascular volume or low cardiac output. Under this condition, renal blood flow is regulated by prostaglandin production and inhibition of such production by NSAIDs further reduces renal blood flow and glomerular filtration. The result may be acute renal failure and interstitial nephritis (Clive and Stoff, 1984).

Gastrointestinal effects:

Oxycodone: 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.

Ibuprofen: Gastrointestinal side effects (epigastric pain, nausea, heartburn, and sensation of fullness) are experienced by approximately 5-15% of the patients who take ibuprofen.

Ibuprofen demonstrates significantly less adverse GI events than aspirin. NSAIDs are known to increase the risk of upper GI bleeding and ulceration. This occurs predominately with aspirin, however has also been reported with ibuprofen. Concurrent use of corticosteroids, anticoagulants and aspirin can increase the risk for upper gastrointestinal bleeding (Mellemkjaer, et al., 2002).

Abuse liability:

Oxycodone: 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. Oxycodone is a Schedule II controlled substance with an abuse liability similar to morphine.

Ibuprofen: There is no evidence that ibuprofen has any abuse liability.

Other: Not applicable.

Safety pharmacology summary: The nervous system effects of oxycodone include analgesia, drowsiness, changes in mood, mental clouding and euphoria. Cardiovascular effects can include hypotension, bradycardia in susceptible individuals, peripheral vasodilation, reduced peripheral vascular resistance and inhibition of the baroreceptor reflex contributing to orthostatic hypotension. Opioids are also known to decrease gastric motility and therefore can lead to constipation. The primary concern with any opioid therapy, however, is the potential for respiratory depression.

Ibuprofen produces little effects on the CNS, pulmonary or renal systems in healthy individuals. Of primary concern is the increased incidence and severity of gastrointestinal bleeding and the possibility of hypersensitivity reaction in some individuals.

Safety pharmacology conclusions: The primary concerns related to the safety of the oxycodone:ibuprofen combination are largely related to the safety concerns of each individual drug if used alone. The possible exception appears to be the potential for alterations in the gastrointestinal system. The potential for upper GI bleeding and ulceration induced by NSAIDs may be altered in the presence of opioids. For the most part, concurrent opioid therapy inhibition of gastric emptying may lead to an increase in upper gastrointestinal irritation induced by NSAIDs, particularly in individuals prone to such difficulties. This effect may be more pronounced when other concurrent medications or behaviors known to alter GI bleeding are involved, such as corticosteroids, alcohol and stress.

2.6.2.5 **Pharmacodynamic drug interactions:** There were no drug interaction studies completed for this NDA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

There were no nonclinical pharmacology studies submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 **Brief summary:** The PK summary table below was taken from the Pharmacology and Toxicology review of IND 52,310 (N-027) .

TABLE 3: Clinical pharmacokinetic parameters for oxycodone and ibuprofen.

Pharmacokinetic Parameter	Oxycodone[a]	Ibuprofen[b]
Oral Bioavailability, %	60 ± 20[c]	>80
Plasma protein binding, %	(45)	>99
Oral t_{max}, hours	0.83 ± 0.22	–
Clearance	0.78 ± 0.33 l/min	0.75 ± 0.20 ml/min/kg[d]
Volume of distribution, l/kg	2.60 ± 0.52	0.15 ± 0.02[d]
Half-life in plasma, hours	3.7 ± 2.3	2.0 ± 0.5

[a] from Poyhia *et al.*, 1993 (except for data in parentheses).
[b] from Goodman and Gilman, 8th ed.
[c] relative to i.m. administration.
[d] CL/F and V_{ss}/F.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption:

Oxycodone: Opioids are readily absorbed from the gastrointestinal tract. The oral bioavailability of oxycodone has been reported to be between 60 and 87%. The peak concentrations are between 1.3 - 2.1 hours.

Ibuprofen: Ibuprofen is rapidly absorbed following oral administration. The oral bioavailability is approximately 80%. Peak concentrations are observed between 15 and 30 minutes.

2.6.4.4 Distribution:

Oxycodone: Oxycodone binding to plasma proteins is approximately 45%. According to the labeling of Roxicodone™, following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone has been found in breast milk.

Ibuprofen: Ibuprofen is highly bound to plasma proteins (99%). In experimental animals, ibuprofen and metabolites can cross the placenta.

2.6.4.5 Metabolism:

Oxycodone: Oxycodone is metabolized in the liver via N-demethylation, O-demethylation, 6-ketoreduction and glucuronidation. The metabolism is mediated by cytochrome P450 2D6. The major circulating metabolite is noroxycodone that is a weak agonist. O-demethylation of oxycodone produces oxymorphone that is also an agonist. The levels of oxymorphone found in plasma are low.

Ibuprofen: Ibuprofen is administered as a racemic mixture. In the plasma, the R-isomer is metabolized to the S-isomer. The major metabolites are 2-(4-(2 hydroxy 2 methylpropyl))phenyl propionic acid and 2-(4-(2 carboxypropyl))phenyl propionic acid. Neither of these metabolites is active. The formation of these metabolites is mediated by cytochrome P450 2C9.

2.6.4.6 Excretion:

Oxycodone: Oxycodone and metabolites are excreted primarily via the kidney. The elimination half-life of oxycodone is between 3.1 and 3.7 hours after a single dose. Approximately 4% of the parent compound is excreted by the kidney. Conjugated oxycodone constitutes up to 50% of the metabolites found in urine.

Ibuprofen: The elimination half-life of ibuprofen is between 1.8 and 2.6 hours after a single dose. Urinary excretion of unchanged ibuprofen is minimal (0.2%).

2.6.4.7 Pharmacokinetic drug interactions: There were no pharmacokinetic interaction studies submitted for this NDA.

2.6.4.8 Other Pharmacokinetic Studies: N/A

2.6.4.9 Discussion and Conclusions: The pharmacokinetics of oxycodone and ibuprofen are well characterized. There does not appear to be any PK/TK concerns related to this NDA.

2.6.4.10 Tables and figures to include comparative TK summary

N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary: No toxicology studies were submitted with the present NDA submission. In the initial submission, the sponsor investigated the toxicology findings of Oxycodone HCl, and their results are summarized here. Acute toxicity studies in rats demonstrate a highest non-LD of 150 mg/kg with a corresponding lowest LD of 225 mg/kg. Developmental and reproductive toxicology studies in the rat and rabbit were negative, even at doses of 8 mg/kg and 125 mg/kg, respectively.

The sponsor noted that animal toxicity studies show the major effect of ibuprofen administration to be GI ulcerations, renal papillary lesions, and pulmonary/liver lesions. The highest tolerated ibuprofen doses were 300 mg/kg in mice, 180 mg/kg in rats, and 16 mg/kg in dogs. There was no evidence of carcinogenicity in mice and rats up through highest doses (300 – 100 mg/kg/day after 43 weeks) and 120 mg/kg/day. There was no mutagenicity noted in assay batteries but there was evidence of weak genotoxicity in mice bone marrow.

Acute rat toxicology studies of the combination product showed the highest non-LD to be 5/400 mg/kg and the lowest LD was 6.25/500 mg/kg. Two 1-month dog studies suggest that the combination drug had a toxicity profile no different than that of the individual constituents. A combination of Oxy/Ibup at 1:80 was not teratogenic or maternally toxic in rats or rabbits.

For an in-depth discussion of the Pharmacology/Toxicology aspects of this submission, the reader is encouraged to read Dr. Mellon's review of the Original NDA submission.

As requested in the approvable letter sent in October of 2002, the sponsor conducted two genetic toxicology studies of the impurity [redacted] for the second cycle NDA submission. In the Ames bacterial reverse mutation assay [redacted] was not mutagenic. In the in vivo mouse micronucleus assay [redacted] did not produce a statistically significant increase in micronuclei, however, in the presence of metabolic activation; there was a positive trend that the sponsor interpreted as possibly biologically relevant. Upon review, I agree that the data suggests a possible low genotoxic risk to humans.

2.6.6.1 Single-dose toxicity: No new studies were submitted.

2.6.6.3 Repeat-dose toxicity: No new studies were submitted.

2.6.6.4 Genetic toxicology

Study title: Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with [redacted]

Key findings:

- was found negative in the AMES assay.

Study no.: Study No: 6277-151; Genetic Toxicology Assay No.25192-0409
DECD Sponsor Study No:OXYTX02000

Volume # 11 of 11 dated 6/3/04, and page #: 136-188
Conducting laboratory and location:
Date of study initiation: July 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot # RD 0893/123, and % purity: Not provided

Methods

Strains/species/cell line:
The tester strains used were the *Salmonella typhimurium* histidine auxotrophs TA98, TA100, TA1535 and TA1537 (Ames et al, 1975) and the *Escherichia coli* trytophan auxotroph WP2uvrA (Green and Muriel, 1976). The specific genotypes of the strains are shown in the table below.

Table I. Tester Strain Genotypes

Tester Strain	*his/trp* Mutation	Additional Mutations		Plasmid
		Repair	LPS	
TA98	*his*D3052	*uvr*B	*rfa*	pKM101
TA100	*his*G46	*uvr*B	*rfa*	pKM101
TA1535	*his*G46	*uvr*B	*rfa*	–
TA1537	*his*C3076	*uvr*B	*rfa*	–
WP2*uvr*A	*trp*	*uvr*A	–	–

Doses used in definitive study:

Doses tested with all *Salmonella* tester strains were 10.0, 33.3, 100, 333, 1000 and 2500 µg per plate in the presence of S9 mix and 3.33, 10.0, 33.3, 100, 333 and 1000 µg per plate in the absence of S9 mix. Doses tested with tester strain WP2uvrA were 10.0, 33.3, 100, 333, 1000 and 2500 µg per plate in both the presence and absence of S9 mix.

Doses were selected for the confirmatory assay based on the results of the initial mutagenicity assay. Doses tested in the confirmatory assay with all *Salmonella* tester strains were 3.33, 1 0.0, 33.3, 100, 333 and 1000 µg per plate in both the presence and absence of S9 mix. Doses tested with tester strain WP2uvrA were 10.0, 33.3, 100, 333, 1000 and 2500 µg per plate in both the presence and absence of S9 mix.

Basis of dose selection: Results of the dose range finding study were used to select doses tested in the initial mutagenicity assay.

Negative controls: DMSO was used as vehicle and used as negative control. Vehicle controls were plated for all tester strains in the presence and absence of S9 mix. The dimethylsulfoxide (DMSO) vehicle control was plated, using a 200 µL aliquot in Trial A 1 and a 100 µL aliquot in Trials B1, C1 and D1 (equal to the maximum aliquot of test article solution plated), along with a 100 µL aliquot of the appropriate tester strain and a 500 µL aliquot of S9 mix (when necessary), on selective agar.

Positive Controls: The combinations of positive controls, activation conditions, and tester strains plated concurrently with the assay are indicated in the following table.

Table II. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	–	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

Incubation and sampling times: Mutagenicity assay was designed using tester strains TA98, TA100, TA1535, TA1537, and WP2uvrA in the presence and absence of S9 mix. The doses of test article were selected based on the results of the dose range finding study. The results of the initial mutagenicity assay were confirmed in an independent experiment. The tester strains were exposed to test article via the plate incorporation methodology (Ames, et al., 1975;Maron and Ames, 1983). This methodology has been shown to detect a wide range of classes of chemical mutagens. In the plate incorporation methodology, the test article, the tester strain, and the S9 mix (where appropriate) were combined in molten agar, which was overlaid onto a minimal agar plate. Following incubation, revertant colonies were counted. All doses of the test article, the vehicle controls, and the positive controls were plated in triplicate.

Each plate was labeled with a code which identified the test article, test phase, tester strain, activation condition, and dose level. The S9 mix and dilutions of the test article were prepared immediately prior to their use. When S9 mix was not required, 100 µL of tester strain and 100 µL of vehicle or test article dose (200 µL in the dose range finding study) were added to 2.5 mL of molten selective top agar (maintained at 45 ± 2°C). When S9 mix was required, 500 µL of S9 mix, 100 µL of tester strain and 100 µL of vehicle or test article dose (200 µL in the dose range finding study) were added to 2.0 mL

of molten selective top agar. After the required components had been added, the mixture was vortexed and overlaid onto the surface of 25 mL of minimal bottom agar contained in a 15 x 100-mm Petri dish. After the overlay solidified, the plates were inverted and incubated for 52 ± 4 hours at 37 ± 2°C. Positive control articles were plated using a 50 µL plating aliquot. Plates, which were not evaluated immediately following the incubation period, were held at >0°C to 10°C until such time that colony counting and bacterial background lawn evaluation could take place. Condition of the bacterial background lawn was evaluated for evidence of cytotoxicity and test article precipitate. Evidence of cytotoxicity was scored relative to the vehicle control and recorded along with the revertant counts for that dose. Revertant colonies were counted by automated colony counter or by hand.

Results

Study validity: The initial as well as the confirmatory mutagenicity assay were done using three replicated plating of the test article and positive control, the mean revertants per plate and the standard deviation are shown in the table below. The assay design described above followed the ICH guidelines and is valid. Tester strain integrity was demonstrated by the presence of the rfa wall mutation, in the *Salmonella typhimurium* tester strain cultures which exhibit the sensitivity to crystal violet. The presence of the pKM 101 plasmid was demonstrated by the cultures of the appropriate tester strains that exhibited resistance to ampicillin. The requirement for histidine or tryptophan was demonstrated by the tester strain cultures that exhibited a characteristic number of spontaneous revertants per plate when plated along with the vehicle under selective conditions. The acceptable ranges for the mean vehicle controls were as follows:

TA98	8 - 60
TA100	60 - 240
TA1535	4 - 45
TA1537	2 - 25
WP2uvrA	5 - 40

The appropriate numbers of bacteria strains were plated, the density of tester strain cultures were greater than or equal to 0.5 x 10^9 bacteria per mL and/or had reached a target level of turbidity demonstrated to produce cultures with a density greater than or equal to 0.5 x 10^9 bacteria per mL. The tester strains were demonstrated to be capable of identifying a mutagen (the mean value of a positive control for a respective tester strain exhibited at least a 3-fold increase over the mean value of the vehicle control for that strain). To demonstrate that the S9 mix was capable of metabolizing a promutagen to its mutagenic form(s), the mean value of the positive control for a respective tester strain in the presence of the S9 mix exhibited at least a 3-fold increase over the mean value of the vehicle control for that strain. There fore the positive control results in the presence and the absence of S9 were proven to be valid. Cytotoxicity was detectable as a decrease in the number of revertants colonies per plate and/or by a thinning or disappearance of the bacterial background lawn compared to the appropriate vehicle control. A thinning of the

bacterial background lawn that was not accompanied by a reduction in the number of revertants per plate was not evaluated as an indication of cytotoxicity.

All the criteria for the study validity were made for the present study according to the regulatory guidance.

Study outcome: The data tables representing the results of the dose range finding study, initial mutagenicity study and the confirmatory study are presented below:

Dose Rangefinding Study:

Table 1 : Dose Rangefinding Study

Test Article ID: —

Assay No.: 25182-0-409OECD Trial No.: A1

Date Plated: 03-Sep-03 Vehicle: DMSO

Date Counted: 10-Sep-03 Plating Aliquot: 200 µL

		Revertants per Plate			
	Dose/Plate	TA100	Background Lawn[a]	WP2*uvr*A	Background Lawn[a]
Microsomes: Rat Liver					
Vehicle Control		86	N	19	N
Test Article	6.67 µg	103	N	9	N
	10.0 µg	93	N	18	N
	33.3 µg	101	N	8	N
	66.7 µg	81	N	16	N
	100 µg	66	N	7	N
	333 µg	79	N	6	N
	667 µg	63	N	8	N
	1000 µg	13	N	7	N
	3330 µg	0	A	0	N
	5000 µg	0	A	0	A
Microsomes: None					
Vehicle Control		73	N	10	N
Test Article	6.67 µg	67	N	10	N
	10.0 µg	78	N	11	N
	33.3 µg	51	N	13	N
	66.7 µg	61	N	14	N
	100 µg	60	N	18	N
	333 µg	49	N	12	N
	667 µg	7	N	5	N
	1000 µg	0	R	4	N
	3330 µg	0	A	0	R
	5000 µg	0	A	0	A

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

Initial Test:

Table 3 : Mutagenicity Assay Results – Summary

Test Article ID: [redacted]

Assay No.: 25182-0-409OECD Trial No.: B1

Date Plated: 07-Oct-03 Vehicle: DMSO

Date Counted: 14-Oct-03 Plating Aliquot: 100 µL

		Mean Revertants Per Plate with Standard Deviation								
	Dose/Plate	TA98		TA100		TA1535		TA1537		Background Lawn[a]
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver										
Vehicle Control		18	1	74	8	6	2	7	1	N
Test Article	10.0 µg	17	4	71	1	13	1	4	1	N
	33.3 µg	15	2	74	7	9	2	6	1	N
	100 µg	16	6	62	7	11	4	6	2	N
	333 µg	11	1	46	12	9	1	3	2	N
	1000 µg	2	2	6	5	1	2	0	0	N/R[d]
[redacted]	2500 µg	0	0	0	0	0	0	0	0	A
Positive Control[b]		333	39	588	186	79	18	59	37	N
Microsomes: None										
Vehicle Control		12	4	66	18	8	1	3	2	N
Test Article	3.33 µg	11	2	67	6	10	4	3	2	N
	10.0 µg	8	4	58	3	12	3	4	2	N
	33.3 µg	11	1	60	5	13	6	5	2	N
	100 µg	8	8	60	3	23	2	3	1	N
	333 µg	5	1	38	-	11	2	3	1	N
	1000 µg	0	1	3	2	3	3	0	1	R
Positive Control[c]		262	94	996	40	584	84	948	57	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] TA98 benzo[a]pyrene 2.5 µg/plate
TA100 2-aminoanthracene 2.5 µg/plate
TA1535 2-aminoanthracene 2.5 µg/plate
TA1537 2-aminoanthracene 2.5 µg/plate

[c] TA98 2-nitrofluorene 1.0 µg/plate
TA100 sodium azide 2.0 µg/plate
TA1535 sodium azide 2.0 µg/plate
TA1537 ICR-191 2.0 µg/plate

[d] The first entry is the lawn evaluation for tester strains TA98, TA100, and TA1535. The second entry is the lawn evaluation for tester strain TA1537.

Confirmatory test:

Table 6 : Mutagenicity Assay Results – Summary

Test Article ID:

Assay No.: 25182-0-409OECD Trial No.: C1

Date Plated: 21-Oct-03 Vehicle: DMSO

Date Counted: 23-Oct-03, 24-Oct-03 Plating Aliquot: 100 µL

		Mean Revertants Per Plate with Standard Deviation								
	Dose/Plate	TA98		TA100		TA1535		TA1537		Background Lawn[a]
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver										
Vehicle Control		23	7	98	4	12	5	8	4	N
Test Article	3.33 µg	20	6	92	16	10	4	9	3	N
	10.0 µg	19	0	94	1	10	5	7	5	N
	33.3 µg	18	5	81	11	13	5	7	2	N
	100 µg	16	5	81	7	10	2	6	2	N
	333 µg	9	3	52	4	9	1	2	1	N
	1000 µg	0	1	1	1	3	0	0	0	N
Positive Control[b]		270	10	518	107	90	18	77	20	N
Microsomes: None										
Vehicle Control		11	1	76	18	10	3	5	4	N
Test Article	3.33 µg	11	4	74	5	8	2	5	1	N
	10.0 µg	8	4	82	12	14	3	4	3	N
	33.3 µg	11	3	70	15	9	2	3	2	N
	100 µg	11	7	74	9	6	2	2	2	N
	333 µg	4	3	54	5	9	4	3	4	N
	1000 µg	0	0	1	2	0	0	0	0	R
Positive Control[c]		285	45	865	35	536	87	768	71	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b]
TA98	benzo[a]pyrene	2.5 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate

[c]
TA98	2-nitrofluorene	1.0 µg/plate
TA100	sodium azide	2.0 µg/plate
TA1535	sodium azide	2.0 µg/plate
TA1537	ICR-191	2.0 µg/plate

APPEARS THIS WAY
ON ORIGINAL

Table 8 : Mutagenicity Assay Results – Individual Plate Counts and Summary

Test Article ID: —

Assay No.: 25182-0-409OECD Trial No.: D1

Date Plated: 04-Nov-03 Vehicle: DMSO

Date Counted: 07-Nov-03 Plating Aliquot: 100 µL

	Dose/Plate	Revertants Per Plate WP2*uvr*A			Mean Revertants Per Plate with Standard Deviation WP2*uvr*A		Background Lawn[a]
		1	2	3	Mean	S.D.	
Microsomes: None							
Vehicle Control		15	10	14	13	3	N
Test Article	10.0 µg				10	3	N
	33.3 µg				10	4	N
	100 µg				9	2	N
	333 µg				6	4	N
	1000 µg				5	2	N
	2500 µg				0	0	R
Positive Control[b]					155	40	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] WP2*uvr*A 4-nitroquinoline-N-oxide 1.0 µg/plate

APPEARS THIS WAY
ON ORIGINAL

HISTORICAL CONTROL DATA FOR BACTERIAL MUTAGENICITY STUDIES

Plate Incorporation Method - Report Period: April 2002 to June 2002

Vehicle Controls with S9 Mix					
Strain	TA98	TA100	TA1535	TA1537	WP2*uvr*A
Mean Revertants per Plate	26.4	91.9	12.9	9.5	17.2
Standard Deviation	6.6	15.9	4.5	3.3	5.8
Maximum					
Minimum					
Count					

Vehicle Controls without S9 Mix					
Strain	TA98	TA100	TA1535	TA1537	WP2*uvr*A
Mean Revertants per Plate	15.9	85.4	15.8	7.7	16.4
Standard Deviation	5.2	16.9	6.3	3.9	5.8
Maximum					
Minimum					
Count					

Positive Controls with S9 Mix[a]					
Strain	TA98	TA100	TA1535	TA1537	WP2*uvr*A
Mean Revertants per Plate	400.4	706.4	143.4	118.6	595.0
Standard Deviation	95.3	312.3	75.1	80.2	214.8
Maximum					
Minimum					
Count					

Positive Controls without S9 Mix[b]					
Strain	TA98	TA100	TA1535	TA1537	WP2*uvr*A
Mean Revertants per Plate	238.7	1054.4	749.8	835.6	242.5
Standard Deviation	81.9	191.6	148.5	266.9	113.6
Maximum					
Minimum					
Count					

[a] TA98 benzo[a]pyrene 2.5 µg/plate
TA100 2-aminoanthracene 2.5 µg/plate
TA1535 2-aminoanthracene 2.5 µg/plate
TA1537 2-aminoanthracene 2.5 µg/plate
WP2*uvr*A 2-aminoanthracene 25.0 µg/plate

[b] TA98 2-nitrofluorene 1.0 µg/plate
TA100 sodium azide 2.0 µg/plate
TA1535 sodium azide 2.0 µg/plate
TA1537 ICR-191 2.0 µg/plate
WP2*uvr*A 4-nitroquinoline-N-oxide 1.0 µg/plate

According to the assay evaluation criteria for a test article to be considered positive in the tester strains TA98, TA100, and WP2uvrA the test article had to produce at least a 2-fold increase in the mean revertants per plate of at least one of these tester strains over the mean revertants per plate of the appropriate vehicle control. This increase in the mean number of revertants per plate had to be accompanied by a dose response to increasing concentrations of the test article. Similarly, for a test article to be considered positive, tester strains TA1535 and TA1537 had to produce at least a 3-fold increase in the mean revertants per plate of at least one of these tester strains over the mean revertants per plate of the appropriate vehicle control. This increase in the mean number of revertants per plate had to be accompanied by a dose response to increasing concentrations of the test article.

In the dose range finding assay conducted on the test article using tester strains TA100 and WP2uvrA in both the presence and absence of S9 mix with one plate per dose. Ten doses of article ranging from 6.67 to 5000 µg per plate were tested and results are presented in Table 1. Cytotoxicity was observed in the presence of S9 mix at 1000 µg per plate and above with TA100 and at 3330 µg per plate and above with WP2uvrA as evidenced by a dose-related decrease in the number of revertants per plate and/or reduced bacterial background lawns. Cytotoxicity was observed in the absence of S9 mix at 667 µg per plate and above with both tester strains mix as evidenced by a dose-related decrease in the number of revertants per plate and/or reduced bacterial background lawns.

In the initial mutagenicity assay, Trial B1 all data were acceptable and no positive increases in the mean number of revertants per plate were observed with any of the tester strains in either the presence or absence of S9 mix.

In the confirmatory mutagenicity assay, Trial C1, no valid data were generated with tester strain WP2uvrA in the absence of S9 mix due to the absence of bacterial background lawn growth on the plates. All other data were acceptable, and no positive increases were observed in the mean number of revertants per plate with any of the tester strains in either the presence or absence of S9 mix. The test article was re-tested with tester strain WP2uvrA in the absence of S9 mix in Trial D1.

In the repeat mutagenicity assay, Trial D1 all data were acceptable and no positive increases were observed in the mean number of revertants per plate with WP2uvrA in the absence of S9 mix.

The mean revertants for all strains at the lowest dose fall under within the range of the historical negative controls and do not show any dose response. Therefore, I agree with the sponsor in the conclusion of the results from this assay that is under the condition of the study, the test article the test article , did not cause a positive increase in the mean number of revertants per plate with any of the tester strains either in

the presence or absence of microsomal enzymes prepared from Arocolor™-induced rat liver (S9).

Study tittle: In Vivo Mouse Micronucleus Assay with —

Key findings:

- — . was found negative for using bone marrow toxicity upto 125 mg/kg for 24 hrs.
- — showed a trend (statistically not significant) of bone marrow toxicity at 48 hrs with the high dose.

Study no — Study No: 6277-152; Genetic Toxicology Assay No.25182-0-455OECD Sponsor Study No: OXYTX03000

Volume # 11 of 11 dated 6/3/04, and page #: 189-237
Conducting laboratory and location: —
Date of study initiation: October 2003
GLP compliance: Yes
QA reports: Yes (x) no ( )
Drug, lot # and % purity: — , Lot # RD 0893/123 — . pure

Methods

Strains/species/cell line: — .CD-1 (ICR) BR mouse strain

Doses used in definitive study: Forty-eight animals, approximately 8 weeks old at the time of dosing, with a weight range of 28.4 to 35.3 g, were used in this assay. An outline of the dosing scheme and harvest time points is presented in the following table:

Dosing Scheme for the Micronucleus Assay with —

Target Treatment (mg/kg)	Stock Concentration (mg/mL)	Route of Administration	Dosing Volume (mL/kg)	Animals/Harvest Timepoint[a] 24 Hour Male	48 Hour Male	Replacement Animals[b] Male
31.25	3.125	oral gavage	10	6	-	-
62.5	6.25	oral gavage	10	6	-	-
125	12.5	oral gavage	10	6	6	6
Vehicle Control, 0.5% CMC	0	oral gavage	10	6	6	-
Positive Control, Cyclophosphamide, 80	8	oral gavage	10	6	-	-

[a] Six animals were dosed to ensure the availability of five animals for analysis.
[b] Animals were dosed as potential replacements for the original high-dose groups. Animals not used as replacements were euthanized at the completion of the trial.

Basis of dose selection: Dose selection was based in the dose range finding assay, the target doses of — , for the repeat definitive micronucleus assay were 31.25, 62.5 and 125 mg/kg in male mice only. The high dose, 125 mg/kg was the highest dose that could be administered without excessive mortality. Mortality was 3/6 at 250 mg/kg and 14/18 at 500 mg/kg.

Negative controls: Vehicle control-0.5% CMC was used as negative control.

Positive controls: Cyclophosphamide, 8 mg/kg used as positive control (oral gavage).

Incubation and sampling times: Since no appropriate toxicity data for — , were available (e.g., the same species, strain, same route, etc.), a dose range finding assay was performed using the same treatment regimen used in the micronucleus assay. Both males and females were dosed via oral gavage with 250, 500, 1000 or 2000 mg/kg — . Mortality occurred in 3 of 3 male mice and 3 of 3 female mice at a dose of 2000 mg/kg; 1of 3 male mice and 2 of 3 female mice at 1000 mg/kg; 0 of 3 male mice and 1of 3 female mice at 500 mg/kg; and 0 of 3 male mice and 0 of 3 female mice at 250 mg/kg. Thus, the male and female mice exhibited similar susceptibility to the toxic effects of — In another study the mice were treated with 125, 250 and 500 mg/kg where no death we seen at the low dose 50% death was observed at mid dose and about 77% death was observed at high dose.

Since no relevant differences in toxicity between the sexes were observed in the first dose range finding assay, only males were used in the micronucleus assay. The dosages used for the definitive micronucleus assay were 31.25, 62.5 and 125 mg/kg.

Extraction of Bone Marrow: At the appropriate harvest time points (24 and 48 hrs), the animals were euthanized by $C0_2$ inhalation followed by incision of the diaphragm. The hind limb bones (tibias) were removed for marrow extraction from five surviving animals in each treatment and control group. For each animal, the marrow flushed from the bones was combined in an individual centrifuge tube containing 3 to 5 mL fetal bovine serum (one tube per animal). Animals not needed for bone marrow collection were euthanized at the completion of the assay.

Preparation of Slides: Following centrifugation to pellet the tissue, the supernatant was removed by aspiration and portions of the pellet were spread on Slides and air-dried. The slides were fixed in methanol, stained in May-Grunwald solution followed by Giemsa, and protected by permanently mounted coverslips. For control of bias, all slides were coded prior to analysis.

Slide Analysis: Slides prepared from the bone marrow collected from five animals per group at the designated harvest time points were scored for micronuclei and the PCE to NCE cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined by scoring the number of PCEs and NCEs observed while scoring at least the first 500 erythrocytes per animal.

Results

Study validity: The vehicle control group had less than approximately 0.4% micronucleated PCE and the group mean were within the historical control range. The positive control group had a statistically significantly higher ($p < 0.01$) number of micronucleated PCEs than the vehicle control group and was consistent with historical positive control data.

Data analysis was performed using an analysis of variance (Winer, 1971) on untransformed proportions of cells with micronuclei per animal and on untransformed PCE:NCE ratios when the variances were homogeneous. Ranked proportions were used for heterogeneous variances. If the analysis of variance was statistically significant ($p < 0.05$), a Dunnett's t-test (Dunnett, 1955; 1964) was used to determine which dose groups, if any, were statistically significantly different from the vehicle control. Analyses were performed separately for each sampling time. The criteria for a positive response, was the detection of a statistically significant increase in micronucleated PCEs for at least one dose level, and a statistically significant, dose-related response. A test article that did not induce both of these responses was considered negative.

Reviewer's Comment: Generally the high dose used in the definitive study should reach the limit dose or produce some indication of toxicity, e.g., toxic signs and/or mortality in the test article dosed animals and/or a reduction in the PCE:NCE ratio. The high dose of 125 mg/kg used in the present study did not show any mortality, whereas, a dose of 250 mg/kg produced 50% mortality. The test article did not shown any clinical toxicity in the treated animal when dosed upto 125 mg/kg. At doses of 250 mg/kg and above, the clinical signs prior to death were not mentioned.

Study outcome:

The results from the study as well as the historical control values from the conducting laboratories are tabulated below:

Micronucleus Assay - Summary

Treatment	Dose	Harvest Time	% Micronucleated PCEs Mean of 2000 per Animal ± S.E. Males	Ratio PCE:NCE Mean ± S.E. Males
Controls				
Vehicle	0.5% CMC	24 hr	0.00 ± 0.00	0.68 ± 0.08
		48 hr	0.00 ± 0.00	0.60 ± 0.09
Positive	CP 80 mg/kg	24 hr	3.87 ± 0.50*	0.84 ± 0.05
Test Article	31.25 mg/kg	24 hr	0.02 ± 0.02	0.74 ± 0.12
	62.5 mg/kg	24 hr	0.01 ± 0.01	0.64 ± 0.08
	125 mg/kg	24 hr	0.01 ± 0.01	0.66 ± 0.02
		48 hr	0.01 ± 0.01	0.36 ± 0.09

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
0.5% CMC = 0.5% carboxymethylcellulose
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte

APPEARS THIS WAY
ON ORIGINAL

HISTORICAL CONTROL DATA

Mouse Micronucleus - 1/2002 Through 6/2002

		% Micronucleated PCEs From 2000 PCEs per Animal Mean ± S.E. Males	PCE:NCE Ratio Mean ± S.E. Males
Pooled Vehicle Controls			
24 Hour Harvest	Minimum	0.00	0.13
	Maximum	0.25	1.17
	Average	0.049±0.004	0.564±0.020
	N	125	125
48 Hour Harvest	Minimum	0.00	0.11
	Maximum	0.20	1.16
	Average	0.048±0.005	0.570±0.021
	N	113	113
Positive Controls, Cyclophosphamide			
24 Hour Harvest	Minimum	0.90	0.08
	Maximum	4.90	1.00
	Average	2.669±0.085	0.533±0.015
	N	121	121

PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte
N = Number of animals

The experimental and analytical method used in this study is considered valid. However, the high dose did not show any apparent toxicity.

The PCE-NCE ratios in the treated groups were similar to the control values indicating lack of cytotoxicity to the bone marrow upto 24 hrs. However, the PCE:NCE ratio for the 125 mg/kg 49-hour treatment group was only 0.36 ± 0.09 compared to the corresponding control value of 0.60 ± 0.09 suggesting induced bone marrow toxicity in this group. This observation may be biologically relevant, although the difference was not statistically significant at the $p < 0.05$ level. — did not induce statistically significant increases in micronucleated PCEs at any test article dose examined (31.25, 62.5, and 125 mg/kg).

APPEARS THIS WAY
ON ORIGINAL

The vehicle control group had less than approximately 0.4% micronucleated PCEs and the group mean was within the historical control range. The positive control, cyclophosphamide, induced a statistically significant increase in micronucleated PCEs compared to the vehicle control, with a mean and standard error of 3.87 ± 0.50%.

The test article — , was evaluated as negative in the mouse bone marrow micronucleus assay under the conditions of this assay upto 24 hrs. A trend (not statistically significant) of increased bone marrow toxicity was observed at high dose. The product oxycodone would be used for short-term use for the management of pain. The TDI for — should be maintained according to Q3A guidance. The level of the impurity in the oxycodone product should be kept minimal.

2.6.6.5 Carcinogenicity:

Carcinogenicity studies for oxycodone or ibuprofen were not submitted in support of this NDA. The sponsor indicated that the combination oxycodone:ibuprofen is intended for short-term use only. Following a dispute resolution request to the level of the Office of New Drug level, the sponsor was informed that carcinogenicity studies would not be required for this drug product.

Carcinogenicity testing of ibuprofen has been reported in the literature (Adams, et al., 1970). These investigators describe results of an 80-week oral carcinogenicity assessment in the mouse and a 104-week oral carcinogenicity assessment in the rat. Mice were administered a total 300 mg/kg ibuprofen daily for a total of 43 weeks. Due to high mortality from intestinal ulceration and perforation in the males, the dose was reduced to 100 mg/kg daily for the remainder of the 80-week study. There were no significant differences in tumor incidence for any tumor type. In the rat study, animals were dosed with 180 mg/kg ibuprofen daily for 56 weeks. Due to a high incidence of mortality in both sexes, the dose was reduced to 60 mg/kg daily for the remainder of the two-year study. The results of these two studies indicate that ibuprofen did not induce tumors in either rats or mice under the conditions tested. Of note, however, the duration of the studies is not adequate under current standards.

There is currently no adequate information concerning the carcinogenic potential of oxycodone or ibuprofen. The sponsor could refer to publicly available data if it is available at that time.

2.6.6.6 Reproductive and developmental toxicology:

As reviewed in the original NDA submission, segment II reproductive and developmental toxicology studies were conducted in the rat and the rabbit. Segment I (fertility) and Segment III (peri- and post-natal development) studies were not conducted by the sponsor for this NDA. These studies will be conducted as Phase 4 commitments as discussed with the sponsor during the pre-NDA meeting with the Division on July 26,

2001 and the post action meeting held in October 2002 and the follow-up meeting held April 2, 2004.

The results of the segment II study in rats indicated that DuP 604 produced maternal toxicity at dose levels of 0.5:40 mg/kg/day oxycodone:ibuprofen and above. Maternal toxicity was characterized by alopecia, pallor, facial and peri-anal staining and scabs associated with areas of severe alopecia. DuP 604-related maternal mortality occurred following administration of the high dose combination (2:160 mg/kg/day oxycodone:ibuprofen). One upper mid dose dam (1:80 mg/kg/day oxycodone: ibuprofen) and 3 high dose dams delivered litters early. The NOAEL for maternal toxicity was 0.25:20 mg/kg DuP 604, based upon alopecia and decreased body weight gain in the 0.5:40 mg/kg/day oxycodone:ibuprofen treatment group. This corresponds to 0.12-fold the proposed maximum human daily dose based upon body surface area. Under the conditions employed, DuP 604 did not increase the incidence of fetal malformations or variations. Therefore, the NOAEL for developmental toxicity is 2:160 mg/kg/day, the maximum dose tested. This corresponds to 1-fold the proposed maximum human daily dose of each drug based upon body surface area.

Treatment of rabbits with DuP 604 produced signs of maternal toxicity manifested as mortality at the dose of 3:240 mg/kg and reduced body weights and food consumption at the 1.5:120 mg/kg dose level. Post mortem findings of increased stomach ulcerations in the high dose group were noted; however, these changes did not appear to be restricted to the drug-treatment and were not dose-dependent. The increase in mean nidations and corpora lutea compared to controls was not deemed biologically significant by the sponsor, since the control group responses were low compared to historical controls. The non-significant increase in the number of resorptions (1.1) at the high dose was above the historical control range (0.1-0.8), suggesting that embryolethality may be evident at the high dose treatment. Fetal toxicity was noted in the high dose group and was manifested as growth retardation and weight changes likely due to maternal toxicity. The percentage of fetuses with variations was 4 times the control group mean and 2 times the historical control mean. The NOAEL for maternal toxicity is considered to be 0.75:60 mg/kg, based upon body weight changes. This corresponds to 0.75-fold the proposed maximum daily human dose based upon body surface area. The NOAEL for teratogenic effects is 3:240 mg/kg, while the NOAEL for developmental toxicity is 1.5:120 mg/kg based upon an increase in the number of resorptions over historical controls in the high dose group. This corresponds to 3-fold the proposed maximum daily human dose of each drug based upon body surface area for teratogenicity and 1.5-fold the proposed maximal daily human dose of each drug based upon body surface area for developmental toxicity.

The sponsor completed the requirements for Segment II developmental toxicology studies in support of this NDA. The Segment I and Segment III studies will be conducted as phase 4 commitments. The results of the Segment II studies in rats and rabbits indicate that the combination of oxycodone and ibuprofen produces evidence of maternal toxicity in rats and rabbits and developmental toxicity in rabbits. The developmental toxicity may be secondary to maternal toxicity. The pregnancy category should be "C" based on the developmental effects.

Segment II studies submitted with the original NDA submission were reviewed by Dr Dan Mellon (see detail PT review in DFS). In the approvable letter from October 2002, the Division indicated that depending upon the timing of the resubmission, the Segment I and III studies could be provided as a Phase 4 commitment.

2.6.6.7 Local tolerance: N/A

2.6.6.8 Special toxicology studies N/A

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures: N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The sponsor has provided two genetic toxicology studies on — — an impurity — that contains a structural alert for mutagenicity, specifically, —

Unresolved toxicology issues (if any): Although the in vitro Ames assay and the in vivo micronucleus assay were technically negative, the Division has knowledge of positive findings for — in an in vitro mammalian chromosome aberration assay. The interim specification of NMT — as proposed by Forest Laboratories, is the acceptable interim specification that was negotiated between — and the Division. This interim specification for NDA 21-378, therefore, is acceptable.

Recommendations: From the nonclinical pharmacology and toxicology perspective, NDA 21-387 can be approved, if the sponsor commits to completing the Segment I and Segment III reproductive toxicology studies previously agreed to. In addition, the sponsor should continue to work with the Division and the — to clarify the potential risks associated with the impurity and any other detected impurity with a structural alert for mutagenicity.

Suggested labeling:

NOTE: The following labeling recommendations reflect only the pharmacology toxicology review team recommendations and thus may not represent the final labeling for this drug product. The sponsor's proposed labeling appears in black text, suggested addition appear red and suggested deletions appear blue with strikeout.

3 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

APPENDIX/ATTACHMENTS

Reference List

Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, Mills RF, Nicholson JS and Williams GA (1970) Some aspects of the pharmacology, metabolism, and toxicology of ibuprofen. I. Pharmacology and metabolism. *Rheumatol Phys Med* **10**:Suppl-26.

Ames BN, McCann J and Yamasaki E (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. *Mutat Res* **31**:347-364.

Clive DM and Stoff JS (1984) Renal syndromes associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* **310**:563-572.

Lessard A and Bachelard H (2002) Tonic inhibitory control exerted by opioid peptides in the paraventricular nuclei of the hypothalamus on regional hemodynamic activity in rats. *Br J Pharmacol* **136**:753-763.

Maron DM and Ames BN (1983) Revised methods for the Salmonella mutagenicity test. *Mutat Res* **113**:173-215.

Mellemkjaer L, Blot WJ, Sorensen HT, Thomassen L, McLaughlin JK, Nielsen GL and Olsen JH (2002) Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* **53**:173-181.

Monory K, Greiner E, Sartania N, Sallai L, Pouille Y, Schmidhammer H, Hanoune J and Borsodi A (1999) Opioid binding profiles of new hydrazone, oxime, carbazone and semicarbazone derivatives of 14-alkoxymorphinans. *Life Sci* **64**:2011-2020.

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/s/

Mamata De
11/12/04 01:22:26 PM
PHARMACOLOGIST

R. Daniel Mellon
11/12/04 01:30:44 PM
PHARMACOLOGIST
I concur

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number:	21-378
Review number:	1
Sequence number/date/type submission:	N000 / December 27, 2001 / NDA
Information to sponsor:	Yes (X) No ( )
Sponsor and/or agent:	**Forest Laboratories, Inc.** 909 Third Avenue New York, New York 10022

Manufacturer for drug substance:

Reviewer name:	R. Daniel Mellon, Ph.D.
Division name:	Anesthetics, Critical Care & Addiction Drug Products
HFD #:	170
Review completion date:	October 1, 2002

Drug:

Trade name: Not determined to date.

Generic name (list alphabetically): Oxycodone HCl and Ibuprofen in combination

Code name: DuP 604 (combination product)

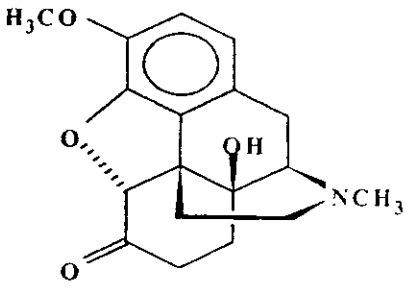
Chemical name: 4,5a-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and (±)-2-(p-isobutylphenyl)propionic acid

CAS registry number: 76-42-6 (Oxycodone hydrochloride)
15687-27-1 (Ibuprofen)

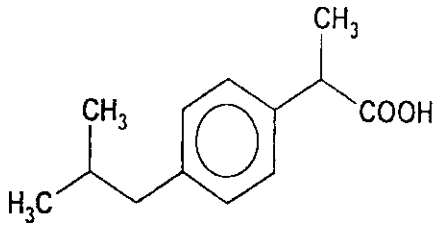
Mole file number: N/A

Molecular formula/molecular weight: $C_{18}H_{21}NO_4 \bullet HCl$ / 351.83 (Oxycodone HCl)
$C_{13}H_{18}O_2$ / 206.29 (Ibuprofen)

Structures:



Oxycodone



Ibuprofen

Relevant INDs/NDAs/DMFs:

IND 52,310 Oxycodone/Ibuprofen Combination (Forest Laboratories, Inc.). Submitted on December 30, 1996, active as of Jan 23, 1997.

As a 505(b)(2) NDA submission, Forest Laboratories relies upon the Agency's evaluation of the Safety and Efficacy on Motrin® and Roxicodone™. The NDAs for these drugs are as follows:

NDA 21-011 Roxicodone™ (oxycodone HCl Tablets, 15 & 30 mg, Elan Pharms, approved on 9/23/1999)
NDA 17-463 Motrin® (ibuprofen, McNeil, approved on 3/21/1973)

DMF
DMF

Drug class: Opioid/NSAID combination.

Indication: Short term management of acute moderate to severe pain.

Clinical formulation: Fixed dose ratio of oxycodone:ibuprofen of 1:80 (5 mg oxycodone to 400 mg ibuprofen) in a tablet form.

Components and Composition of Oxycodone HCl/Ibuprofen Tablets, 5/400 mg

Ingredients	Functions	Quantity (mg/Tablet)	Quantity (kg/Batch)
Ibuprofen,	Active		
Oxycodone Hydrochloride, USP	Active	5.0	
Sodium Starch Glycolate, NF			
Stearic Acid, NF			
Calcium Stearate, NF			
CORE TABLET WEIGHT	N/A		
COATING SOLUTION			
Opadry® II White, Y-22-7719 [3]	Coating		
COATED TABLET WEIGHT		618.0	

[3] Opadry II Film Coat Dispersion (White) is added Opadry II White, Y-22-7719 contains titanium dioxide, polydextrose, hypromellose, triacetin and polyethylene glycol 8000.

Route of administration: Oral.

Proposed use: The drug is intended for the relief of moderate to severe pain, over a limited period of time (3-7 days) at a maximum dose of one tablet given every 6 hours; maximum daily dose of 20 mg oxycodone and 1600 mg ibuprofen.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. **Recommendation on Approvability:** From the non-clinical perspective, this NDA is deemed approvable.

B. **Recommendation for Nonclinical Studies:**

1. As discussed during the pre-NDA meeting on July 26, 2001, Segment I (fertility) and Segment III (peri- and post-natal development) reproductive toxicology studies should be conducted as a Phase 4 commitment. Should this application not be approved in this review cycle, the sponsor could submit these studies prior to approval.

2. Assessment of carcinogenic potential of this drug product will be required, unless the sponsor can demonstrate that the product will not be used chronically. This assessment can be performed post-approval or by reference to adequate public information.

C. **Recommendations on Labeling:** Labeling will be addressed at a later date.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: DuP 604, a — combination of oxycodone to ibuprofen has been tested via single-dose toxicology studies in the rat, repeat-dose toxicology studies in the rat and the dog, and Segment II reproductive toxicology studies in the rat and rabbit. Toxicity is consistent with the known toxic effects of NSAIDs and opioids. The single-dose toxicology studies demonstrate a maximum non-lethal dose of 5 mg/kg oxycodone:400 mg/kg ibuprofen in females and 6.25 mg/kg oxycodone:500 mg/kg ibuprofen in males. Toxicity was characterized as immediate CNS depression followed by delayed general deterioration associated with the ulcerogenic potential of the drug product. Deaths were considered to be due to circulatory collapse secondary to CNS depression.

Administration of the combination of oxycodone:ibuprofen (1.25:100 mg/kg/day) to the rat for 28-days produced decreased red blood cells, hemoglobin and hematocrit and in increase in platelet counts. Histologically, red or black foci on the gastrointestinal mucosa was suggestive of NSAID-induced alterations in the gastric-mucosa. These changes in the gastric mucosa were not altered significantly via the presence of the opioid.

Administration of the combination of oxycodone:ibuprofen (1:80) to the dog for 28-days produced clinical signs of dark tar-like loose stools and fecal occult blood as the highest dose (0.25:20 mg/kg/day oxycodone:ibuprofen). Although these changes were consistent with gastrointestinal irritation, there

was no histological evidence for ulceration in this study. The study was repeated with a 1:40 ratio of oxycodone:ibuprofen. The highest dose tested was 0.5:20 mg/kg oxycodone:ibuprofen. The results of the study demonstrated that the combination product can lead to unformed or liquid stools and positive findings of fecal occult blood. The incidence of fecal occult blood with the combination of the two drugs was far greater than with ibuprofen or oxycodone alone. In addition, the combination of the two drugs produced a significant decrease in red blood cells, hemoglobin and hematocrit which were significantly greater then that produced by ibuprofen alone and consistent with mild blood loss. However, these changes were not correlated with microscopic evidence of GI toxicity. Neither dog study reached a maximum tolerated dose and therefore may not fully predict the potential toxicity to humans.

Segment II reproductive toxicology studies have been completed in both the rat and the rabbit models. The results of the rat study demonstrated no evidence of developmental toxicity at doses that were maternally toxic. The developmental study in the rabbit also indicated that the combination of oxycodone:ibuprofen was maternally toxic at lower doses than those which produced signs of developmental toxicity. The potential for developmental toxicity of the drug combination was manifested as a non-significant increase in the number of resorptions at the highest dose tested and a trend toward in increase in retarded development and fetal variations (delayed skeletal ossification).

B. **Pharmacologic Activity:** Pain is a multi-modal process that involves both central and peripheral mechanisms and a host of chemical mediators and receptors that are involved in the transmission of pain signals to the CNS. As such, treatment of pain with combination products which act via different mechanisms can be more effective while reducing the potential for side effects associated with each compound alone. Combinations of an opioid analgesic with a non-steroidal anti-inflammatory drug (NSAIDs) have proven to be an effective analgesic combination. The FDA has approved combinations of codeine, oxycodone or hydrocodone with acetaminophen, aspirin and/or ibuprofen. This NDA is the first to test the combination of oxycodone with ibuprofen. Oxycodone is an opioid receptor agonist that acts via interaction primarily with the μ-opioid receptor subtype within the central nervous system. Specifically, oxycodone is though to activate of opioid receptors located on the terminals of sensory afferents inhibit substance P release and activation of opioid receptors located on interneurons inhibit 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. In contrast to the opioid, ibuprofen is a well-characterized NSAID. As such, this compound is thought to produce analgesia primarily via the nonselective, reversible, competitive inhibition of cyclooxygenase enzymes. Cyclooxygenase

converts arachidonic acid to the unstable intermediates prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2). Prostaglandins can sensitize pain receptors to mechanical and chemical stimulation and thereby lowering their firing threshold. Therefore, the combination of oxycodone and ibuprofen can act at multiple sites within the pain perception pathways to therefore produce significantly greater analgesia than either compound administered alone at the same dose.

C. **Nonclinical Safety Issues Relevant to Clinical Use:** The potential toxicity of opioids has been well characterized and includes respiratory depression, circulatory depression, constipation, nausea, vomiting and physical dependence. The potential toxicity of ibuprofen is also well characterized and includes renal failure in conditions of low intravascular volume of low cardiac output, gastrointestinal bleeding and/or ulceration and hypersensitivity reactions in sensitive individuals. Repeat dose toxicology studies of the combination of oxycodone and ibuprofen in the dog suggest an increased risk of gastrointestinal toxicity with the combination of oxycodone and ibuprofen compared to ibuprofen alone. A description of this increased gastrointestinal toxicity should be considered for the product label. Additionally, the sponsor should perform Segment I and III reproductive toxicology studies as these components of the reproductive toxicology battery have not been adequately addressed. Assessment of the carcinogenic potential should be performed unless the sponsor demonstrates that the product will not be used chronically.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

Introduction and drug history: The combination of oxycodone:ibuprofen (Dup 604) was originally initiated by DuPont Merck Pharmaceutical Company The combination was licensed to Forest Laboratories, Inc. on October 3, 1996.

Forest Laboratories

Forest Laboratories Inc. filed IND 52,310 with the FDA on December 30, 1996. The current NDA was filed December 20, 2001. Studies submitted to the NDA were conducted by both Dupont Merck and Forest Laboratories. Forest Laboratories has obtained right of reference to the submitted DuPont Merck studies.

In correspondence from the Division dated August 4, 2000, the Division indicated that no further non-clinical studies were required for NDA filing. There are no FDA approved oxycodone:ibuprofen combination drug products currently on the market.

Studies reviewed within this submission:

Study #	Study Title	Ref #	NDA Vol. #
89-9-8	Final Report: The Acute Oral Toxicity of Oxycodone HCl in Rats	16	7
89-8-7	Final Report: The Acute Oral Toxicity of Ibuprofen in Rats	17	7
89-9-5	Final Report: The Acute Oral Toxicity of Oxycodone HCl:Ibuprofen (1:80) Versus Ibuprofen in Rats	18	8
90-9-3	Final Report DuP 604 (Oxycodone-Ibuprofen Combination): One-Month Oral Gavage Toxicity Study in Sprague-Dawley Rats	19	9
90-10-4	Final Report DuP 604 (Oxycodone-Ibuprofen Combination): One-Month Oral Capsule Study in Beagle Dogs	20	10
6277-145	Final Report 28-Day Capsule Toxicity Study in Dogs	21	11
90-9-10	Revised: Pilot Teratogenicity Study of DuP 604 in Rats	23	12
90-9-11	Teratogenicity Study of DuP 604 in Rats	24	12
90-10-16	Revised: Pilot Teratogenicity Study of DuP 604 in Rabbits	25	13
91-2-1	teratogenicity Study of DuP 604 in Rabbits.	26	13

Studies <u>not</u> reviewed within this submission: Not applicable.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

There were no pharmacology studies submitted with this NDA. The following sections summarized the known information concerning the drug components.

Primary pharmacodynamics:

Oxycodone: Oxycodone is a semi-synthetic opioid-receptor agonist. Administration of oxycodone produces analgesia, anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression.

Ibuprofen: Ibuprofen is an aryl-propionic acid derivative which is an effective non-steroidal anti-inflammatory drug (NSAID) with analgesic and anti-pyretic activities.

Mechanism of action:

Oxycodone: The mechanism of action of oxycodone is thought to be mediated by interaction with μ-opioid receptors primarily in the central nervous system. It shows approximately 53-fold higher affinity for μ than δ receptors and 38-fold higher affinity for μ compared to κ-opioid receptors.

***In vitro* Binding Affinities for Oxycodone**[1]

K_i (nM)		
μ	δ	κ
18.0 ± 4.2	958.0 ± 499	677 ± 326

Ligand binding to rat brain homogenates was examined via [^{3}H]DAMGO (μ), [^{3}H]naltrindole (δ) and [^{3}H]U69593 (κ).

Ibuprofen: Ibuprofen is thought to act by inhibition of the activity of the enzyme cyclooxygenase. Inhibition of this enzyme inhibits the production of prostaglandins and related autocoids and thereby reduces inflammation and sensitization of pain afferent fibers. Ibuprofen does not inhibit the enzyme 5-lipoxygenase and therefore the production of leukotrienes remains intact.

Drug activity related to proposed indication:

Oxycodone: The analgesic effects of opioids such as oxycodone 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 inhibit substance P release and activation of opioid receptors located on interneurons inhibit 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

[1] Monory, K., Greiner, E., Sartania, N., Sallai, L., Pouille, Y., Schmidhammer, H., Hanoune, J. and Borsodi, A. 1999. Opioid binding profiles of new hydrazone, oxime, carbazone and semicarbazone derivatives of 14-alkoxymorphinans. Life Sciences 64(22):2011-21020.

inhibit processing of nociceptive afferent signals. Continuous dull pain is relieved more effectively by opioids than acute sharp pain.

Ibuprofen: Ibuprofen is a mild analgesic, particularly in setting where inflammatory mediators cause sensitization of the pain receptors. Ibuprofen is thought to produce analgesia primarily via the nonselective, reversible, competitive inhibition of cyclooxygenase enzymes. Cyclooxygenase converts arachidonic acid to the unstable intermediates prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2). There are two forms of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constituitively expressed in most normal cells and tissues. COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators. Importantly, COX-1, but not COX-2 is expressed in the stomach. Prostaglandins can sensitize pain receptors to mechanical and chemical stimulation and thereby lowering their firing threshold.

Because ibuprofen (like aspirin and other NSAIDs) is an organic acid, it accumulates at sites of inflammation which makes it particularly effective as an anti-inflammatory. Ibuprofen, like all NSAIDS, are most effective for post-operative pain or pain arising from inflammation. However, there is also evidence that NSAIDs may produce analgesia in part by actions within the central nervous system independent of their effects on cyclooxygenase.

Secondary pharmacodynamics:

Oxycodone: 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.

Ibuprofen: There is some evidence that NSAIDS also work to reduce **pain** by altering the activity of peripheral and central neurons. Ibuprofen is thought to act as an **anti-pyretic** via inhibition of prostaglandin E_2 production at the level of the preoptic nucleus of the hypothalmus. NSAIDs inhibit **platelet function** by blockade of the production of thromboxane A_2 (TXA_2), a pro-aggregating agent, and thereby increasing bleeding time. NSAIDs promote the

retention of salt and water by reduction in prostaglandin-mediated inhibition of chloride reabsorption in the kidney. This may produce edema in some individuals.

Pharmacology summary: Opioids have diverse actions on the body via interactions both peripheral and central opioid receptors. Oxycodone administration produces typical μ-opioid receptor-mediated effects, including analgesia, sedation, respiratory depression, muscle rigidity, euphoria, miosis and alterations in neuroendocrine parameters. Opioids act within the CNS via binding to opioid receptors and inhibiting the activity of nociceptive afferent neurons. Ibuprofen, a non-competitive reversible cyclooxygenase inhibitor, produces analgesia via decreased production of prostaglandins. The analgesic activity of ibuprofen, therefore, is mediated primarily in the periphery. As such, combinations of opioids and NSAIDs are effective analgesics for post-operative and inflammatory pain syndromes. The combination of drugs from these classes reduces the side effects of each individual drug and increases the efficacy of the pain relief.

Pharmacology conclusions: The pharmacology of oxycodone and ibuprofen individually have been well characterized. The side effect profile of these drugs used individually is well known. Vicoprofen, a combination product containing hydrocodone and ibuprofen, has been approved by the FDA. The combination of oxycodone and ibuprofen would provide yet another combination drug product for the treatment of post-operative and inflammatory pain conditions.

II. SAFETY PHARMACOLOGY:

No studies were submitted to this NDA. The following sections summarize the information known concerning the drug components.

Neurological effects:

Oxycodone: Opioids such as oxycodone have well characterized effects on the central nervous system (CNS). In humans, opioids produces analgesia, drowsiness, changes in mood, mental clouding, and, in some individuals, euphoria. When individuals who are not in pain are administered opioids, 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.

Ibuprofen: Ibuprofen acts predominantly in the periphery and has little effects within the CNS. However, headache, tinnitis, dizziness, blurred vision and seizures have been reported following ibuprofen administration and overdose.

Cardiovascular effects:

Oxycodone: In the supine patient, therapeutic doses of μ-opioids do not significantly alter blood pressure or heart rate. Therapeutic doses produce peripheral vasodilation, reduced peripheral resistance and inhibition of baroreceptor reflexes and therefore orthostatic hypotension may occur. These effects may be partially mediated by peripheral histamine release. 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.

Ibuprofen: NSAIDs do not directly alter the activity of the cardiovascular system. Cardiovascular toxicity including hypotension, bradycardia, tachycardia and atrial fibrillation have been reported in cases of ibuprofen overdose. Administration of NSAIDs during the third trimester is contra-indicated as they can lead to premature closure of the ductus arteriosus. Closure of the ductus arteriosus increases prenatal mortality.

Pulmonary effects:

Oxycodone: In the clinical setting, respiratory depression is a common side effect of μ-receptor agonists such as oxycodone. 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.

Ibuprofen: Hypersensitivity reactions to NSAIDs are well known. This hypersensitivity reaction can manifest itself as vasomotor rhinitis with profuse watery secretions, angioneurotic edema, generalized urticaria and bronchial asthma to laryngeal edema and bronchoconstriction, flushing, hypotension and shock. The mechanism of this hypersensitivity is not known, although it does not appear to be immune mediated. One hypothesis is that NSAIDs divert the metabolism of arachidonic acid from the cyclooxygenase pathway to the 5-lipoxygenase pathway and over production of leukotrienes.

Renal effects:

Oxycodone: 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 beds[2]. These effects are mediated by alterations in the autonomic nervous system.

Ibuprofen: Acute renal failure has been reported following NSAID drug administration in adults. This effect appears to occur mainly in individuals who have pre-existing renal

[2] Lessard, A. and Bachelard, H. 2002. Tonic inhibitory control exerted by opioid peptides in the paraventricular nuclei of the hypothalamus on regional hemodynamic activity in rats. Br. J. Pharmacol. 136(5):753-763.

disease or other condition which is associated with low intravascular volume or low cardiac output. Under this condition, renal blood flow is regulated by prostaglandin production and inhibition of such production by NSAIDs further reduces renal blood flow and glomerular filtration. The result may be acute renal failure and interstitial nephritis[3].

Gastrointestinal effects:

Oxycodone: 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.

Ibuprofen: Gastrointestinal side effects (epigastric pain, nausea, heartburn, and sensation of fullness) are experienced by approximately 5-15% of the patients who take ibuprofen. Ibuprofen demonstrates significantly less adverse GI events than aspirin. NSAIDs are known to increase the risk of upper GI bleeding and ulceration. This occurs predominately with aspirin, however has also been reported with ibuprofen. Concurrent use of corticosteroids, anticoagulants and aspirin can increase the risk for upper gastrointestinal bleeding[4].

Abuse liability:

Oxycodone: 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. Oxycodone is a Schedule II controlled substance with an abuse liability similar to morphine.

Ibuprofen: There is no evidence that ibuprofen has any abuse liability.

Other: Not applicable.

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[3] Clive, D.M. and Stoff, J.S. 1984. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N. Engl. J. Med. 310(9):563-72.

[4] Mellemkjaer, L., Blot, W.J., Sorensen, H.T., Thomassen, L., McLaughlin, J.K., Nielsen, G.L., Olsen, J.H. 2002. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br.J.Clin.Pharmacol 53(2):173-181.

Safety pharmacology summary: The nervous system effects of oxycodone include analgesia, drowsiness, changes in mood, mental clouding and euphoria. Cardiovascular effects can include hypotension, bradycardia in susceptible individuals, peripheral vasodilation, reduced peripheral vascular resistance and inhibition of the baroreceptor reflex contributing to orthostatic hypotension. Opioids are also known to decrease gastric motility and therefore can lead to constipation. The primary concern with any opioid therapy, however, is the potential for respiratory depression.

Ibuprofen produces little effects on the CNS, pulmonary or renal systems in healthy individuals. Of primary concern is the increased incidence and severity of gastrointestinal bleeding and the possibility of hypersensitivity reaction in some individuals.

Safety pharmacology conclusions: The primary concerns related to the safety of the oxycodone:ibuprofen combination are largely related to the safety concerns of each individual drug if used alone. The possible exception appears to be the potential for alterations in the gastrointestinal system. The potential for upper GI bleeding and ulceration induced by NSAIDs may be altered in the presence of opioids. For the most part, concurrent opioid therapy inhibition of gastric emptying may lead to an increase in upper gastrointestinal irritation induced by NSAIDs, particularly in individuals prone to such difficulties. This effect may be more pronounced when other concurrent medications or behaviors known to alter GI bleeding are involved, such as corticosteroids, alcohol and stress.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK parameters: The PK summary table below was taken from the Pharmacology and Toxicology review of IND 52,310 (N-027) was compiled by Dr. David Brase.

TABLE 3: Clinical pharmacokinetic parameters for oxycodone and ibuprofen.

Pharmacokinetic Parameter	Oxycodone[a]	Ibuprofen[b]
Oral Bioavailability, %	60 ± 20[c]	>80
Plasma protein binding, %	(45)	>99
Oral t_{max}, hours	0.83 ± 0.22	--
Clearance	0.78 ± 0.33 l/min	0.75 ± 0.20 ml/min/kg[d]
Volume of distribution, l/kg	2.60 ± 0.52	0.15 ± 0.02[d]
Half-life in plasma, hours	3.7 ± 2.3	2.0 ± 0.5

[a] from Poyhia *et al.*, 1993 (except for data in parentheses).
[b] from Goodman and Gilman, 8th ed.
[c] relative to i.m. administration.
[d] CL/F and V_{ss}/F.

Absorption:

Oxycodone: Opioids are readily absorbed from the gastrointestinal tract. The oral bioavailability of oxycodone has been reported to be between 60 and 87%. The peak concentrations are between 1.3 - 2.1 hours.

Ibuprofen: Ibuprofen is rapidly absorbed following oral administration. The oral bioavailability is approximately 80%. Peak concentrations are observed between 15 and 30 minutes.

Distribution:

Oxycodone: Oxycodone binding to plasma proteins is approximately 45%. According to the labeling of Roxicodone, following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone has been found in breast milk.

Ibuprofen: Ibuprofen is highly bound to plasma proteins (99%). In experimental animals, ibuprofen and metabolites can cross the placenta.

Metabolism:

Oxycodone: Oxycodone is metabolized in the liver via N-demethylation, O-demethylation, 6-ketoreduction and glucuronidation. The metabolism is mediated by cytochrome P450 2D6. The major circulating metabolite is noroxycodone that is a weak agonist. O-demethylation of oxycodone produces oxymorphine that is also an agonist. The levels of oxymorphone found in plasma are low.

Ibuprofen: Ibuprofen is administered as a racemic mixture. In the plasma, the R-isomer is metabolized to the S-isomer. The major metabolites are 2-(4-(2 hydroxy 2 methylpropyl))phenyl propionic acid and 2-(4-(2 carboxypropyl))phenyl propionic acid. Neither of these metabolites is active. The formation of these metabolites is mediated by cytochrome P450 2C9.

Excretion:

Oxycodone: Oxycodone and metabolites are excreted primarily via the kidney. The elimination half-life of oxycodone is between 3.1 and 3.7 hours after a single dose. Approximately 4% of the parent compound is excreted by the kidney. Conjugated oxycodone constitutes up to 50% of the metabolites found in urine.

Ibuprofen: The elimination half-life of ibuprofen is between 1.8 and 2.6 hours after a single dose. Urinary excretion of unchanged ibuprofen is minimal (0.2%).

Other studies: N/A

PK/TK summary: Oxycodone is rapidly absorbed from the gastrointestinal tract with a T_{max} of approximately 1.3 - 2.1 hours and a t½ of 3.1 - 3.7 hours. Ibuprofen is also readily absorbed from the gastrointestinal tract with a T_{max} of 1.6 - 3.1 hours and a t½ of 1.8 - 2.6 hours. The combination of the two products has been tested by Forest Laboratories. For details of these studies, see the Clinical Pharmacology and Biopharmaceutics review.

PK/TK conclusions: The pharmacokinetics of oxycodone and ibuprofen are well characterized. There does not appear to be any PK/TK concerns related to this NDA.

IV. GENERAL TOXICOLOGY:

Study title: Final Report: The Acute Oral Toxicity of Oxycodone HCl in Rats

Key study findings:

1. Oxycodone administration produced clinical signs of a dose-dependent CNS depression, renal/urinary effects and generalized deterioration. The CNS depressant effects were evident within the first 60 minutes and lasted between 24 and 48 hours. The generalized deterioration and renal/urinary effects were more prolonged and were evident for several days after the CNS depressant effects resolved.
2. NOAEL was < 50 mg/kg.
3. Single oral minimum lethal dose: 225 mg/kg in males; 337.5 mg/kg in females.
4. Maximum non-lethal dose: 150 mg/kg in males; 225 mg/kg in females.

Study no:	89-9-8
Volume #, and page #:	Volume 7, Page 1
Conducting laboratory and location:	E.I. du Pont de Nemours and Company Wilmington, DE 19880-0400.
Date of study initiation:	September 6, 1989
GLP compliance:	Yes
QA report:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	Oxycodone hydrochloride (Lot # RM89-131) as a bulk powder, — pure.
Formulation/vehicle:	0.25% methylcellulose (Lot # MM87111801A)

Methods (unique aspects): Animals were treated with an acute dose of oxycodone and observed continuously for 60 minutes and approximately hourly for the next 4 hours then daily for the next 14 days.

Dosing:

Species/strain: Sprague-Dawley rats — CD BR (Viral Antibody free) from —

#/sex/group or time point (main study): 4/sex/group

Satellite groups used for toxicokinetics or recovery: Not completed.

Age: 5-6 weeks

Weight: Day 1, males were approximately 280 g; females were approximately 180 g.

Doses in administered units: See sponsor's table below:

Group	Dosage Level (mg/kg)	Concentration (mg/mL)* Theoretical	Actual	Number of Rats M	F
Control	0	0	0	4	4
2[1]	50.0	5.0	5.80	4	4
3	100.0	10.0	10.65	4	4
4	150.0	15.0	15.82	4	4
5	225.0	22.5	23.73	4	4
6**	337.5	33.75	35.60	4	4

M = Male; F = Female

*Actual Concentration includes correction for purity
Theoretical Concentration X ___ = Actual Concentration.

**Group 6 added to study approximately 48-hours after dosing of groups control through 5.

[1]Dosage level proposed in protocol was 66.7 mg/kg. Concentration analyses revealed that the actual dosage administered was approximately 50.0 mg/kg.

Route, form, volume, and infusion rate: Oxycodone was administered via oral gavage in a solution of 0.25% methylcellulose at a volume/body weight ratio of 10 ml/kg.

Observations and times:

Clinical signs: Animals were observed daily for abnormalities in appearance and behavior. On the day of dosing, animals were observed continuously for 60 minutes and approximately hourly for the next 4 hours then daily for the next 14 days.

Body weights: Body weights were measured twice pretest, predose on Day 1, and on Days 2, 7 and 14.

Food consumption: Not recorded.

Ophthalmoscopy: Not recorded.

EKG: Not recorded

Hematology: Not recorded

Clinical chemistry: Not recorded

Urinalysis: Not recorded

APPEARS THIS WAY
ON ORIGINAL

Gross pathology: The following organs/tissues were collected and examined:

STUDY NO. 89-9-8

ORGAN/TISSUE EXAMINATION AND COLLECTION LIST

BODY SYSTEM	ORGAN/TISSUE
Cardiovascular	Aorta, Heart
Digestive	Salivary gland (parotid, submandibular), Esophagus, Stomach, Duodenum, Jejunum, Ileum, Cecum, Colon, Liver, Pancreas
Endocrine	Adrenal Glands, Pituitary Gland, Thyroid and Parathyroid Glands
Hematopoietic	Spleen, Sternebrae (Bone Marrow)
Integumentary	Skin (Abdominal, Including Mammary Gland or Remnant)
Lymphatic	Lymph Nodes (mesenteric, mandibular), Thymus (or remnant)
Muscular	M. Biceps Femoris
Nervous	Brain, Spinal Cord, Nerve (sciatic)
Reproductive	Male: Testes, Epididymides, Prostate Gland Female: Uterus, Ovaries
Respiratory	Trachea, Lungs
Sensory	Eyes, Lacrimal Gland
Skeletal	Costo-Chondral Junction
Urinary	Kidneys, Urocyst

Organs weighed: Not completed.
Histopathology: Histopathology was not completed for this study.
Toxicokinetics: Not completed.
Other: N/A

Results:

Mortality: Mortality was noted following a dose of ≥ 225 mg/kg in males and following a dose of 337.5 mg/kg in females.

Incidence of Treatment-Related Deaths:

	Males (n=4)						Females (n=4)					
Dose (mg/kg/d)	**0**	**50**	**100**	**150**	**225**	**337.5**	**0**	**50**	**100**	**150**	**225**	**337.5**
Deaths	0	0	0	0	1	2	0	0	0	0	0	3

There were no mortalities associated with doses of oxycodone doses of 50, 100 or 150 mg/kg. One female in the 150 mg/kg group was sacrificed on Day 7 due to excessive body weight loss likely due to broken incisors. In the 225 mg/kg group 1 of 4 males died approximately 1 hour post-dosing. In the 337.5 mg/kg group 2 of 4 males died within 2 hours of dosing and 3 of 4 females died within 3-4 days post dosing.

Clinical signs: Animals in the **50 mg/kg group** demonstrated a loss of blinking, decreased motor activity, exophthalmus, decreased respiration, body rigidity, loss of righting reflex, urogenital staining and discolored urine. These signs were observed within the first 60 minutes and lasted from 4-24 hours post dosing.

Animals in the **100 mg/kg group** demonstrated similar findings as well as ataxia, cyanosis and perianal staining. Other signs of general deterioration consistent with a lack of normal grooming included facial, hindlimb, forelimb, tail and abdominal staining for up to 5-9 days post-dosing.

Animals in the **150 mg/kg group** demonstrated signs of CNS depression similar to those noted in the 50 and 100 mg/kg group with increased severity in incidence. These included decreased motor activity, loss of blinking reflex, body rigidity, decreased respiration, exophthalmus, loss of righting reflex, ataxia and cyanosis.

Animals in the **225 mg/kg group** demonstrated similar signs consistent with generalized CNS depression. The single animal who died approximately 1 hour post mortem demonstrated decreased motor activity, loss of blinking reflex, increased salvation, material around mouth, and clonic convulsions. Clinical signs in the animals that survived were similar to the lower doses with an increase in the incidence of tail stiffness/straub tail, clonic convulsions and tremors. Signs of CNS depression were observed within 60 minutes and lasted to between 24 and 48 hours. Signs of generalize deterioration were observed for several days after resolution of signs of CNS depression.

Animals in the **337.5 mg/kg** treatment groups demonstrated similar signs as those in the 225 mg/kg treatment group.

GROUP INCIDENCE AND (FREQUENCY) OF CLINICAL SIGNS

CLINICAL SIGN	0.00 MG/KG M[4]	F[4]	50.00 MG/KG M[4]	F[4]	100.00 MG/KG M[4]	F[4]	150.00 MG/KG M[4]	F[4]	225.00 MG/KG M[4]	F[4]	337.50 MG/KG M[4]	F[4]
Ataxia	0	0	0	0	0	2(2)	0	4(4)	1(2)	4(4)	1(1)	4(8)
Tremors	0	0	0	0	0	0	0	0	1(1)	0	0	1(1)
Enophthalmus	0	0	0	0	0	0	0	1(2)	1(1)	0	0	1(1)
Exophthalmus	0	0	3(3)	4(4)	4(4)	4(4)	3(3)	4(4)	1(1)	4(4)	4(4)	4(4)
Loss of Blinking Reflex	0	0	4(4)	4(4)	4(4)	4(4)	4(4)	4(4)	4(4)	4(4)	3(3)	4(4)
Pallor Eye	0	0	0	0	0	0	0	0	0	0	0	1(3)
Loss of Righting Reflex	0	0	1(1)	2(2)	3(3)	4(4)	3(3)	4(4)	2(2)	4(4)	2(2)	4(4)
Motor Activity Decreased	0	0	3(3)	4(4)	4(4)	4(5)	4(6)	4(9)	4(5)	4(5)	4(4)	4(15)

CLINICAL SIGN	0.00 MG/KG M[4]	F[4]	50.00 MG/KG M[4]	F[4]	100.00 MG/KG M[4]	F[4]	150.00 MG/KG M[4]	F[4]	225.00 MG/KG M[4]	F[4]	337.50 MG/KG M[4]	F[4]
Body Rigidity	0	0	1(1)	2(2)	2(2)	4(4)	4(4)	4(4)	1(1)	4(4)	3(3)	4(4)
Tail Stiffness	0	0	0	0	0	0	0	0	0	2(2)	2(2)	3(3)
Dehydration	0	0	0	0	0	0	0	1(2)	0	0	0	2(3)
Cyanosis	0	0	0	0	0	1(1)	1(1)	0	0	0	0	0
Respiration Decreased	0	0	3(3)	4(4)	4(4)	4(4)	4(4)	4(5)	4(4)	4(4)	3(3)	4(4)
Respiration Noisy	0	0	0	0	0	1(1)	1(1)	0	0	0	0	1(1)
Clonic Convulsions	0	0	0	0	0	0	0	0	2(2)	1(1)	4(4)	2(2)
Material on Abdomen	0	0	0	0	0	1(3)	1(6)	2(3)	3(13)	1(2)	2(9)	3(11)

CLINICAL SIGN	0.00 MG/KG M[4]	0.00 MG/KG F[4]	50.00 MG/KG M[4]	50.00 MG/KG F[4]	100.00 MG/KG M[4]	100.00 MG/KG F[4]	150.00 MG/KG M[4]	150.00 MG/KG F[4]	225.00 MG/KG M[4]	225.00 MG/KG F[4]	337.50 MG/KG M[4]	337.50 MG/KG F[4]
Material on Face	0	0	0	0	1(1)	3(7)	2(8)	3(9)	4(10)	3(8)	4(12)	4(14)
Material on Forelimb(s) and/or Hindlimb(s)	0	1(1)	0	0	0	2(6)	0	3(10)	2(7)	4(13)	2(12)	4(13)
Material on Tail	0	0	0	0	0	2(14)	1(8)	4(22)	1(12)	3(26)	2(25)	2(14)
Perianal Staining	0	0	0	0	0	1(1)	2(8)	4(9)	3(16)	3(6)	2(9)	1(4)
Urogenital Staining	0	0	2(2)	0	2(2)	3(3)	4(11)	4(16)	3(9)	4(12)	2(12)	4(9)
Rough Coat	0	0	0	0	0	0	0	0	1(4)	0	1(1)	1(1)
Salivation Increased	0	0	0	0	0	1(1)	1(1)	0	4(4)	1(1)	4(4)	3(3)
Mucoidal Stool	0	0	0	0	0	0	1(1)	0	0	0	0	0

CLINICAL SIGN	0.00 MG/KG M[4]	0.00 MG/KG F[4]	50.00 MG/KG M[4]	50.00 MG/KG F[4]	100.00 MG/KG M[4]	100.00 MG/KG F[4]	150.00 MG/KG M[4]	150.00 MG/KG F[4]	225.00 MG/KG M[4]	225.00 MG/KG F[4]	337.50 MG/KG M[4]	337.50 MG/KG F[4]
Discolored Urine	0	0	1(1)	1(1)	1(1)	2(3)	3(6)	3(6)	3(6)	4(7)	2(3)	2(4)
Alopecia	0	2(16)	1(14)	0	0	1(7)	2(20)	2(16)	1(8)	3(19)	2(20)	2(14)
Sore(s)	0	1(13)	1(7)	0	0	0	1(3)	1(6)	0	1(12)	0	0
Mass on Neck	0	0	0	0	0	0	0	0	1(9)	0	0	0
Swollen Facial Area	0	0	0	0	0	0	2(4)	2(4)	2(4)	1(4)	2(4)	1(2)

Body weights: In male rats, body weights and rate of body weight gain in the 50 and 100 mg/kg group were comparable to controls. Animals treated with 337.5 mg/kg had a significantly lower body weight compared to controls on Study Day 2 and 7 (22% and 17%, respectively). Although body weight was lower on Study Day 14 than controls (13.5%), this effect was not significant.

In female rats treated with 50 mg/kg oxycodone, body weights and body weight gain were similar to those of control animals. Animals treated with 100, 150, 225 and 337.5 mg/kg exhibited decreased body weights from Study Days 1 to 2 compared to controls, these changes were not significant.

Gross pathology: One of the high dose (337.5 mg/kg) female rats that died prior to scheduled sacrifice demonstrated a red fluid in their urinary bladder that was considered to be drug-related by the pathologist. Staining of fur and tail (See table above) were consistent with poor grooming and attributed to the toxic effects of the drug. One in 8 rats (female) treated with 150 mg/kg showed depressed black foci in the stomach and a total of one female each in the 150 or 337.5 mg/kg dose of oxycodone presented with a small or remnant thymus (both of which died prior to scheduled sacrifice).

Summary of individual study findings: Acute administration of oxycodone to the rat produced dose-dependent clinical-signs of CNS depression, renal/urinary effects and generalized deterioration. The CNS depressant effects were evident within the first 60 minutes and lasted between 24 and 48 hours. The generalized deterioration and renal/urinary effects were more prolonged and were evident for several days after the CNS depressant effects resolved. The NOAEL for acute oxycodone dosing is < 50 mg/kg based on clinical observations; no histopathology was performed. The single oral minimum lethal dose was 225 mg/kg in males and 337.5 mg/kg in females. The maximum non-lethal dose was 150 mg/kg in males and 225 mg/kg in females.

Study title: Final Report: The Acute Oral Toxicity of Ibuprofen in Rats

Key study findings:

1. The acute oral administration of ibuprofen to the rat produced clear toxicity characterized by acute CNS depression and delayed complications due to the ulcerogenic potential of ibuprofen.
2. Lethality was attributed to septic peritonitis resulting from ulceration of the gastrointestinal tract.
3. Inflammatory cell infiltration of the small intestine and microscopic ulceration were evident.
4. In addition, splenic hypertrophy with cellular infiltration of the white pulp and mononuclear infiltration of the red pulp was evident.
5. The NOAEL was < 533.3 mg/kg, based on clinical and gross macroscopic observations.
6. The minimum lethal dose was 800 mg/kg in males and females. The maximum non-lethal dose was 533.3 mg/kg.

Study no:	89-8-7
Volume #, and page #:	Volume 7, Page 97
Conducting laboratory and location:	E.I. du Pont de Nemours and Company Wilmington, DE 19880-0400.
Date of study initiation:	September 13, 1989
GLP compliance:	Yes
QA report:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	Ibuprofen concentrate — , Lot 89-PH-663 as a bulk powder at → purity.
Formulation/vehicle:	0.25% methylcellulose (Lot # MM87111801A).

Methods (unique aspects): Animals were treated with an acute dose of ibuprofen and observed

Group	Dosage Level (mg/kg)	Concentration (mg/mL)* Target	Concentration (mg/mL)* Corrected	Number of Rats M	Number of Rats F
Control	0	0	0	4	4
2	533.33	53.33	60.60	4	4
3	800.0	80.0	90.91	4	4
4	1200.0	120.0	136.36	4	4
6	1800.0	180.0	204.55	4	4

M = Male; F = Female

*Corrected Concentration includes correction for purity
Target Concentration X ___ / = Actual Concentration

continuously for 60 minutes and approximately hourly for the next 4 hours then daily for the next 14 days.

Dosing:

Species/strain: Sprague-Dawley rats. CD BR (Viral Antibody Free) from ___

#/sex/group or time point (main study): 4/sex/group

Satellite groups used for toxicokinetics or recovery: N/A

Age: 5-6 weeks of age.

Weight: males approximately 200-210 g, females approximately 150-160 g on Study Day 1.

Doses in administered units: Ibuprofen 533.3, 800, 1200 and 1800 mg/kg grouped as follows:

Route, form, volume, and infusion rate: Ibuprofen or control vehicle was administered via oral gavage at a volume of 10 ml/kg.

Observations and times:

Clinical signs: Animals were observed daily for abnormalities in appearance and behavior. On the day of dosing, animals were observed continuously for 60 minutes and approximately hourly for the next 4 hours then daily for the next 14 days.

Body weights: Body weights were measured twice pretest, predose on Day 1, and on Days 2, 7 and 14.

Food consumption: Not completed.

Ophthalmoscopy: Not completed.

EKG: Not completed.

Hematology: Not completed.

Clinical chemistry: Not completed.

Urinalysis: Not completed.

Gross pathology: All rats were submitted to necropsy, gross postmortem examination and tissue collection. The following tissues were collected:

ORGAN/TISSUE EXAMINATION AND COLLECTION LIST

BODY SYSTEM	ORGAN/TISSUE
Cardiovascular	Aorta, Heart
Digestive	Salivary gland (parotid, submandibular), Esophagus, Stomach, Duodenum, Jejunum, Ileum, Cecum, Colon, Liver, Pancreas
Endocrine	Adrenal Glands, Pituitary Gland, Thyroid and Parathyroid Glands
Hematopoietic	Spleen, Sternebrae (Bone Marrow)
Integumentary	Skin (Abdominal, Including Mammary Gland or Remnant)
Lymphatic	Lymph Nodes (mesenteric, mandibular), Thymus (or remnant)
Muscular	M. Biceps Femoris
Nervous	Brain, Spinal Cord, Nerve (sciatic)
Reproductive	Male: Testes, Epididymides, Prostate Gland Female: Uterus, Ovaries
Respiratory	Trachea, Lungs
Sensory	Eyes, Lacrimal Gland
Skeletal	Costo-Chondral Junction
Urinary	Kidneys, Urocyst

Organs weighed: Not completed.

Histopathology: Sections of the spleen and the small intestines were examined microscopically following gross necropsy findings consistent with a secondary lymphoid proliferative response.

Toxicokinetics: Not completed.

Other: N/A

Results:

Mortality:

Incidence of Treatment-Related Deaths:

	Males (n=4)					Females (n=4)				
Dose (mg/kg/d)	**0**	**533.3**	**800**	**1200**	**1800**	**0**	**533.3**	**800**	**1200**	**1800**
Deaths	0	0	2	3	4	0	0	3	4	4

No mortality was associated with administration of the vehicle or ibuprofen at the lowest dose of ibuprofen tested (533.3 mg/kg). Two of 4 males and 3 of 4 females died between study days 2 and 6 following 800 mg/kg dose of ibuprofen. Three of 4 males and 4 of 4 females died between

days 2 and 8 following 1200 mg/kg ibuprofen. Finally 4 of 4 males and 4 of 4 females died between Study Days 1 and 7 following 1800 mg/kg ibuprofen.

Clinical signs: Ibuprofen administration was associated with signs of CNS depression on Day 1 and delayed toxicity (days 2-15) characterized by generalized deterioration, possibly related to the ulcerogenic potential of ibuprofen.

Administration of **533.3 mg/kg ibuprofen** lead to ataxia, loss of righting reflex, enophthalmus, decreased/noisy respiration and decreased motor activity on day 1. Delayed toxicity was marked by pallor, facial staining, perianal staining, staining of hind/forelimbs and urogenital staining.

Administration of **800 mg/kg ibuprofen** was associated with initial signs of CNS depression within 1 hour of dosing on Study Day 1 and delayed onset of toxicity suggestive of generalized deterioration (study days 2-15). Animals which died from the treatment demonstrated signs of CNS depression and delayed general deterioration including: ataxia, decreased motor nerve activity, decreased/noisy respiration, enophthalmus, loss of righting reflex, pallor, prostration, rough coat and urogenital staining. Animals that survived this treatment also demonstrated signs of CNS depression and signs of generalized deterioration.

Administration of **1200 mg/kg ibuprofen** was associated with lethality between 15 minutes and 24 hours post dose. Clinical signs in these animals were consistent with CNS depression and generalized deterioration as described above.

Administration of **1800 mg/kg ibuprofen** was associated with 100% mortality. Clinical signs in these animals prior to death were consistent with CNS depression and generalized deterioration as described above.

GROUP INCIDENCE AND (FREQUENCY) OF CLINICAL SIGNS

CLINICAL SIGN	0.00 MG/KG		533.33 MG/KG		800.00 MG/KG		1200.00 MG/KG		1800.00 MG/KG	
	M[4]	F[4]	M[4]	F[4]	M[4]	F[4]	M[4]	F[4]	M[4]	F[4]
Ataxia	0	0	2(2)	3(3)	4(5)	3(3)	4(4)	4(4)	4(5)	4(5)
Loss of Righting Reflex	0	0	0	1(1)	1(1)	1(2)	2(2)	1(2)	2(2)	2(2)
Loss of Blinking Response	0	0	0	0	0	1(2)	1(1)	1(2)	1(1)	2(2)
Enophthalmus	0	0	0	1(1)	2(4)	1(2)	1(1)	2(3)	2(2)	2(2)
Decreased Motor Activity	0	0	1(1)	2(2)	3(3)	3(3)	3(6)	3(3)	4(5)	4(4)
Sedation	0	0	0	0	1(1)	0	0	0	0	0
Prostration	0	0	0	0	1(1)	1(2)	1(1)	1(2)	2(2)	2(2)
Decreased Respiration	0	0	1(1)	1(1)	2(3)	2(3)	3(3)	2(3)	2(2)	4(4)

[ ] = number of animals

CLINICAL SIGN	0.00 MG/KG M[4]	F[4]	533.33 MG/KG M[4]	F[4]	800.00 MG/KG M[4]	F[4]	1200.00 MG/KG M[4]	F[4]	1800.00 MG/KG M[4]	F[4]
Increased Respiration	0	0	0	0	0	0	1(1)	0	1(1)	0
Noisy Respiration	0	0	0	1(1)	1(1)	0	0	0	0	1(1)
Dehydration	0	0	0	0	2(13)	1(1)	3(9)	1(2)	2(3)	0
Pallor	0	0	0	2(14)	3(12)	2(2)	3(10)	2(5)	2(6)	1(2)
Piloerection	0	0	0	0	2(7)	0	2(3)	0	0	0
Rough Coat	0	0	0	2(2)	3(12)	1(1)	2(11)	1(2)	2(4)	0
Facial Staining	0	0	1(4)	1(2)	1(2)	0	2(4)	0	1(1)	0
Staining on Hindlimb(s) and/or Forelimb(s)	0	0	0	1(10)	0	0	1(2)	1(1)	2(4)	0

[ ] = number of animals

CLINICAL SIGN	0.00 MG/KG M[4]	F[4]	533.33 MG/KG M[4]	F[4]	800.00 MG/KG M[4]	F[4]	1200.00 MG/KG M[4]	F[4]	1800.00 MG/KG M[4]	F[4]
Perianal Staining	0	0	0	1(1)	0	1(1)	1(1)	1(1)	2(3)	2(4)
Urogenital Staining	0	0	0	1(12)	0	1(1)	1(1)	1(3)	2(5)	2(4)
Tail Staining	0	0	0	0	0	0	0	1(2)	0	0
Alopecia	0	0	1(5)	1(6)	0	0	0	0	0	0

[ ] = number of animals

Body weights: All male animals treated with ibuprofen demonstrated significantly decreased rate of body weight gain compared to controls from Study Day 1 to Day 2. All males in the 533.3 mg/kg group and the surviving males in the 800 and 1200 mg/kg group gained weight between study day 7 and 14. Female animals treated with ibuprofen gained weight between Study Day 1 and 2 with the exception of 1 female in the 800 mg/kg group which had a significantly lower rate of body weight gain compared to control females.

Gross pathology: Gross lesions were found throughout the gastrointestinal tract indicative of inflammation and ulceration of the GI mucosa in 7 of 8 animals at 533.3 mg/kg and all animals at the higher doses. An associated lymphoid system response was noted in several of the surviving animals, particularly in the 533.3 (6 of 8) and 800 mg/kg groups (2 of 3). Three of 4 male rats and 4 of 4 female rats that received 533.3 mg/kg ibuprofen demonstrated evidence of

gastrointestinal mucosal erosions and/or ulcerations which were associated with lymphoproliferative responses in the spleen and/or mesenteric lymph nodes in 3 of 3 males and 3 of 4 females. Gross pathology in the 800 mg/kg group was suggestive of gastrointestinal ulceration and acute septic peritonitis. Two of 3 surviving animals demonstrated signs of an activated lymphoid system (i.e., enlarged spleen and/or mesenteric lymph nodes). Gross pathology in the 1200 mg/kg group demonstrated evidence of ulceration of the gastrointestinal mucosa leading to acute or subacute septic peritonitis. The lymphoid system response in the surviving animals was less defined in this group than that at the lower doses. The gross pathology noted in the 1800 mg/kg group was consistent with inflammatory changes in the gastrointestinal tract and included ulceration and septic peritonitis. There was no evidence of a lymphoid response in these animals, possibly due to the short survival time following drug administration. Given the large number of animals that died during the study, some of the observations below may have occurred post-mortem.

Incidence of Treatment-Related Gross Pathology Findings:

	Males (n=4)					Females (n=4)				
Dose (mg/kg/d)	**0**	**533.3**	**800**	**1200**	**1800**	**0**	**533.3**	**800**	**1200**	**1800**
Stomach:										
Focus, red mucosa	0	1	0	0	1	0	0	1	1	0
Focus, black	0	0	0	0	0	0	0	0	0	1
Duodenum:										
Adhesions	0	0	1	1	2	0	0	0	0	
Red wall	0	0	0	0	1	0	0	0	0	0
Red fluid	0	0	0	0	1	0	0	0	0	2
Jejunum:										
Adhesions	0	0	1	1	2	0	0	0	0	0
Red wall	0	0	0	1	1	0	0	0	1	2
Red fluid	0	0	1	1	1	0	0	0	0	0
Thickened wall	0	3	2	1	0	0	4	1	0	0
Ileum:										
Adhesions	0	0	1	1	2	0	0	0	0	0
Red wall	0	0	0	0	1	0	0	0	0	1
Red fluid	0	0	0	1	1	0	0	0	0	0
Cecum:										
Adhesions	0	0	0	1	1	0	0	0	0	0
Red wall	0	0	0	0	1	0	0	0	0	0
Colon:										
Adhesions	0	0	0	1	1	0	0	0	0	0
Mesenteric Lymph nodes: Enlarged	0	0	0	0	0	0	3	1	0	0
Spleen: Enlarged	0	2	1	0	0	0	1	0	0	0
Thymus:										
Red	0	0	0	1	0	0	0	1	1	0
Small	0	0	0	1	1	0	0	0	1	0
Adrenal Gland: Enlarged	0	0	0	1	0	0	0	2	2	0
Deaths	0	0	2	3	4	0	2	3	4	4

Histopathology: Due to the gross pathology observations in the GI tract, sections of spleen and small intestines were examined microscopically. Control animals demonstrated no histopathological changes. In contrast, rats treated with **533.3 mg/kg ibuprofen** demonstrated

ulceration and inflammatory cell infiltrate with some evidence of granulomatous peritonitis. There was also evidence of splenic hypertrophy, specifically in the white pulp with mild to marked mononuclear cell infiltration of the red pulp. Spleens from the surviving **800 mg/kg-treated** animals also demonstrated signs of mononuclear cell infiltration of the red pulp. One male demonstrated inflammatory cell infiltration of the intestinal tract. There was evidence of mononuclear cell proliferation in the spleen and fibrinous/granulomatous peritonitis in the animals that died during the course of the study as well. Evidence of fibrinous and granulomatous peritonitis was obtained in several animals treated with 1200 mg/kg ibuprofen. Likewise, animals treated with 1800 mg/kg ibuprofen also demonstrated mononuclear cell infiltration in the spleen that was directly related to the number of days these animals survived. Clear evidence of ulceration of the small intestine was obtained in this group as well. The suspected cause of death in these animals was likely septic peritonitis.

Incidence of Treatment-Related Histopathological Findings in Spleen and Intestines only:

	Males					Females				
Dose (mg/kg/d)	**0**	**533.3**	**800**	**1200**	**1800**	**0**	**533.3**	**800**	**1200**	**1800**
Jejunum:										
Granulomatous Peritonitis	0	0	2	1	1	0	3	1	1	1
Ulceration	0	0	1	0	1	0	2	1	0	1
Spleen:										
Activated	0	4	4	4	4	0	4	4	4	4

Summary of individual study findings: Acute administration of 533.3, 800, 1200 and 1800 mg/kg ibuprofen was associated with biphasic toxicity. The initial toxicity on study day 1 was related to general CNS depression (ataxia, decreased motor activity, decreased respiration, sedation, loss of righting reflex, loss of blinking reflex, enophthalmus and/or prostration). On study days 2-7 the toxicity was associated with a general deterioration of the condition on the animals likely associated with ulcerogenic potential of ibuprofen. This toxicity was characterized by pallor, dehydration, rough coat/piloerection, facial staining, urogenital staining, perianal staining, staining of the hindlimbs/forelimbs, tail staining and or prostration. Gross pathology and histological analysis demonstrated dose-dependent ulceration associated with inflammatory cell infiltration of the small intestine. Evidence for an activation of the immune system included enlargement of the spleen with hypertrophy in the white pulp and mild to marked mononuclear cell infiltration of the red pulp in all treatment groups. Mortality at doses greater than 800 mg/kg was likely due to septic peritonitis. Based upon these results, the NOAEL was < 533.3 mg/kg. The minimum lethal dose was 800 mg/kg in males and females. The maximum non-lethal dose was 533.3 mg/kg.

Study title: Final Report: The Acute Oral Toxicity of Oxycodone HCl:Ibuprofen (1:80) Versus Ibuprofen in Rats

Key study findings:

1. The acute toxicity of the combination of oxycodone:ibuprofen in the rat model was greater than ibuprofen alone based upon clinical signs and mortality.

2. The cause of mortality was considered to be circulatory collapse as a result of CNS depression.
3. The single oral MTD for the combination was > 5 mg/kg oxycodone:400 mg/kg ibuprofen but < 6.25 mg/kg oxycodone:500 mg/kg ibuprofen.
4. The single oral MTD for ibuprofen alone was > 625 mg/kg but < 780 mg/kg.
5. Based upon gross morphology, there did not appear to be an increase in ulcerogenic activity by ibuprofen plus oxycodone compared to ibuprofen alone.
6. The minimum lethal doses in males and females were 6.25 mg/kg oxycodone:500 mg/kg ibuprofen in females and 7.8 mg/kg oxycodone:625 mg/kg ibuprofen in males and at 780 mg/kg ibuprofen alone in females.
7. The maximum non-lethal dose combination was 5 mg/kg oxycodone:400 mg/kg ibuprofen for females and 6.25 mg/kg oxycodone:500 mg/kg ibuprofen in males.

Study no:	89-9-5
Volume #, and page #:	Volume 8, Page 1
Conducting laboratory and location:	E.I. du Pont de Nemours and Company Wilmington, DE 19880-0400.
Date of study initiation:	September 28 & 29, 1989
GLP compliance:	Yes
QA report:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	Oxycodone HCl (Lot RM89-131), — Ibuprofen (Lot 89-PH-663), —
Formulation/vehicle:	0.25% methylcellulose vehicle

Methods (unique aspects): Drug concentrations were adjusted for purity levels.

Dosing:

Species/strain:	Sprague-Dawley rat
#/sex/group or time point (main study):	4/sex/group
Satellite groups used for toxicokinetics or recovery:	N/A
Age:	5-6 weeks of age
Weight:	Not indicated.
Doses in administered units:	5 mg/kg oxycodone; 400 mg/kg Ibuprofen 6.25 mg/kg oxycodone; 500 mg/kg Ibuprofen 7.8 mg/kg oxycodone; 625 mg/kg Ibuprofen 9.75 mg/kg oxycodone; 780 mg/kg Ibuprofen 400, 500, 625, 780 mg/kg Ibuprofen alone controls

Route, form, volume, and infusion rate: Oral gavage. Both drugs were administered in a volume of 5 ml/kg. The control animals received a volume of 10 ml/kg in two separate doses of 5 ml/kg.

Observations and times:

Clinical signs: Rats were observed pre-dose, continuously during the first 60 minutes post-dose and approximately once an hour for the next 4 hours. The animals were then observed daily for the next 14 days. Mortality was recorded once daily.

Body weights: Body weight was measured at least twice pretest, predose on day 1 and on days 2, 7 and 14.

Food consumption: Not completed.
Ophthalmoscopy: Not completed.
EKG: Not completed.
Hematology: Not completed.
Clinical chemistry: Not completed.
Urinalysis: Not completed.
Gross pathology: Completed post-mortem. The following organs were examined:

ORGAN/TISSUE EXAMINATION AND COLLECTION LIST

BODY SYSTEM	ORGAN/TISSUE
Cardiovascular	Aorta, Heart
Digestive	Salivary gland (parotid, submandibular), Esophagus, Stomach, Duodenum, Jejunum, Ileum, Cecum, Colon, Liver, Pancreas
Endocrine	Adrenal Glands, Pituitary Gland, Thyroid and Parathyroid Glands
Hematopoietic	Spleen, Sternebrae (Bone Marrow)
Integumentary	Skin (Abdominal, Including Mammary Gland or Remnant)
Lymphatic	Lymph Nodes (mesenteric, mandibular), Thymus (or remnant)
Muscular	M. Biceps Femoris
Nervous	Brain, Spinal Cord, Nerve (sciatic)
Reproductive	Male: Testes, Epididymides, Prostate Gland Female: Uterus, Ovaries
Respiratory	Trachea, Lungs
Sensory	Eyes, Lacrimal Gland
Skeletal	Costo-Chondral Junction
Urinary	Kidneys, Urocyst

Organs weighed: Not completed.
Histopathology: Not completed.
Toxicokinetics: Not completed.

Results:

Mortality:

Incidence of Treatment-Related Deaths (doses are oxycodone:ibuprofen):

	Males (n=4)					Females (n=4)				
Dose (mg/kg/d)	**0**	**5:400**	**6.25:500**	**7.8:625**	**9.75:780**	**0**	**5:400**	**6.25:500**	**7.8:625**	**9.75:780**
Deaths	0	0	0	1	1	0	0	1	1	3
[redacted]										
Dose (mg/kg/d)	**0**	**0:400**	**0:500**	**0:625**	**0:780**	**0**	**0:400**	**0:500**	**0:625**	**0:780**
Deaths	0	0	0	0	0	0	0	0	0	1

One of 4 females in the 6.25 mg/kg oxycodone:500 mg/kg ibuprofen group were found dead on day 2. One of 4 males and one of 4 females in the 7.80 mg/kg oxycodone:625 mg/kg ibuprofen group were found dead on study days 7 and 2 respectively. One of 4 males and 3 of 4 females in the 9.75 mg/kg oxycodone:780 mg/kg ibuprofen group died within 24 hours of dosing. One of 4 females in the 780 mg/kg ibuprofen alone group died within 24 hours of dosing. Cause of death in all animals except the male that died on study day 7 was thought to be due to circulatory collapse resulting from CNS depression.

Clinical signs: Signs of CNS depression were evident immediately following dosing of the combination treatment as well as ibuprofen alone. For completed breakdown of clinical signs, see the sponsor's tables following this section of text.

Oxycodone 5 mg/kg: ibuprofen 400 mg/kg versus ibuprofen 400 mg/kg: Clinical signs in both treatment groups included ataxia, decreased motor activity and altered respiration. Clinical signs unique to the oxycodone:ibuprofen group included loss of righting reflex and loss of blinking reflex. These CNS depression signs were generally observed between 0-60 minutes post treatment and continued for approximately 24 hours. Clinical signs associated with ulcerogenic potential of the drug product included dehydration and pallor. Signs of delayed toxicity included piloerection, rough coat, facial staining, material on paw(s), urogenital staining and sensitivity to touch. These signs of delayed toxicity were evident from 24 hours to 4 days post-dose.

Oxycodone 6.25 mg/kg: ibuprofen 500 mg/kg versus ibuprofen 500 mg/kg: Clinical signs in both treatment groups were similar with the inclusion of a loss of blinking reflex. Clinical signs unique to the oxycodone:ibuprofen group included loss of righting reflex, prostration, cyanosis and body rigidity. Clinical signs associated with ulcerogenic potential of the drug product included dehydration and pallor. Clinical signs of delayed toxicity were similar as above but also included perianal staining, exophthalmus, exophthalmus, erythema on ear(s) and alopecia.

Oxycodone 7.8 mg/kg: ibuprofen 625 mg/kg versus ibuprofen 625 mg/kg: Clinical signs in both treatment groups included ataxia, decreased motor activity, decreased/labored respiration, loss of righting reflex, loss of blinking reflex, body rigidity and prostration. Clinical signs unique to the oxycodone:ibuprofen group included loss of righting reflex, prostration, cyanosis and body rigidity. Additional clinical signs associated with delayed toxicity associated with the ulcerogenic potential of the drug product were noted included staining around the mouth/eyes/nose/perianal area/paws/piloerection, loose stools and rough coat. Overall clinical signs of CNS depression in the oxycodone:ibuprofen group were slightly greater than the ibuprofen alone group at this dose. These signs were more delayed in onset and continued for several days post-dosing.

Oxycodone 9.75 mg/kg: ibuprofen 780 mg/kg versus ibuprofen 780 mg/kg: Additional clinical signs in both treatment groups included prostration and/or tremors. Females demonstrated body rigidity in the combination group.

GROUP INCIDENCE AND (NUMBER OF DAYS OBSERVED) OF CLINICAL SIGNS

CLINICAL SIGN	0.00-OXY/ 0-IBU MG/KG M[4]	F[4]	5.00-OXY/ 400-IBU MG/KG M[4]	F[4]	6.25-OXY/ 500-IBU MG/KG M[4]	F[4]	7.80-OXY/ 625-IBU MG/KG M[4]	F[4]	9.75-OXY/ 780-IBU MG/KG M[4]	F[4]	0.00-OXY/ 400-IBU MG/KG M[4]	F[4]	0.00-OXY/ 500-IBU MG/KG M[4]	F[4]	0.00-OXY/ 625-IBU MG/KG M[4]	F[4]	0.00-OXY/ 780-IBU MG/KG M[4]	F[4]
Ataxia	0	0	3(3)	4(4)	4(5)	2(3)	3(3)	2(2)	4(4)	1(2)	3(3)	1(1)	4(5)	2(2)	4(4)	2(2)	3(3)	4(4)
Loss of Righting Reflex	0	0	2(2)	0	4(4)	3(3)	3(3)	4(4)	2(2)	4(4)	0	0	0	0	0	0	2(2)	1(1)
Decreased Motor Activity	0	0	4(4)	4(4)	4(4)	4(5)	4(4)	4(4)	4(4)	4(4)	3(3)	0	3(3)	1(1)	2(2)	0	4(4)	2(2)
Sedation	0	0	0	0	4(4)	3(3)	3(3)	3(3)	2(2)	1(1)	0	0	1(1)	0	1(1)	0	2(2)	2(2)
Prostration	0	0	0	0	2(2)	2(2)	0	2(2)	2(2)	4(4)	0	0	0	0	0	0	2(2)	1(1)
Altered Respiration	0	0	3(3)	4(4)	4(4)	4(4)	4(5)	4(4)	4(4)	4(4)	2(2)	0	1(1)	1(1)	1(1)	0	2(2)	3(3)
Rigidity in Body	0	0	0	0	0	1(1)	1(1)	3(3)	0	4(4)	0	0	0	0	0	0	0	0
Loss of Blinking Reflex	0	0	4(4)	0	4(4)	4(4)	3(3)	4(4)	3(3)	4(4)	0	0	1(1)	0	0	0	2(2)	1(1)

GROUP INCIDENCE AND (NUMBER OF DAYS OBSERVED) OF CLINICAL SIGNS

CLINICAL SIGN	0.00-OXY/ 0-IBU MG/KG M[4]	F[4]	5.00-OXY/ 400-IBU MG/KG M[4]	F[4]	6.25-OXY/ 500-IBU MG/KG M[4]	F[4]	7.80-OXY/ 625-IBU MG/KG M[4]	F[4]	9.75-OXY/ 780-IBU MG/KG M[4]	F[4]	0.00-OXY/ 400-IBU MG/KG M[4]	F[4]	0.00-OXY/ 500-IBU MG/KG M[4]	F[4]	0.00-OXY/ 625-IBU MG/KG M[4]	F[4]	0.00-OXY/ 780-IBU MG/KG M[4]	F[4]
Enophthalmus	0	0	0	0	1(1)	2(2)	1(1)	2(2)	2(2)	4(16)	0	1(1)	0	0	0	0	2(2)	1(1)
Exophthalmus	0	1(2)	3(3)	3(5)	1(1)	4(6)	0	4(5)	1(1)	4(4)	0	4(9)	0	4(12)	0	3(6)	1(2)	3(7)
Lacrimation	0	0	0	0	0	1(1)	0	3(3)	0	2(2)	0	0	0	0	0	0	0	1(1)
Tremors	0	0	0	0	0	0	0	0	0	1(1)	0	0	0	0	0	0	0	0
Cyanosis	0	0	0	0	1(1)	0	0	1(1)	0	0	0	0	0	0	0	0	0	0
Peiler	0	0	0	2(14)	1(2)	3(26)	2(5)	4(26)	3(22)	1(9)	0	3(18)	2(14)	3(19)	3(17)	3(24)	3(17)	3(31)
Piloerection	0	0	0	1(1)	2(2)	0	3(11)	1(2)	2(14)	0	4(14)	0	4(19)	1(1)	4(21)	3(4)	4(20)	2(16)
gh Cost	0	0	0	1(8)	2(10)	3(10)	4(14)	3(8)	3(22)	1(9)	0	0	2(21)	2(3)	2(16)	1(1)	3(27)	1(9)

GROUP INCIDENCE AND (NUMBER OF DAYS OBSERVED) OF CLINICAL SIGNS

CLINICAL SIGN	0.00-OXY/ 0-IBU MG/KG M[4]	F[4]	5.00-OXY/ 400-IBU MG/KG M[4]	F[4]	6.25-OXY/ 500-IBU MG/KG M[4]	F[4]	7.80-OXY/ 625-IBU MG/KG M[4]	F[4]	9.75-OXY/ 780-IBU MG/KG M[4]	F[4]	0.00-OXY/ 400-IBU MG/KG M[4]	F[4]	0.00-OXY/ 500-IBU MG/KG M[4]	F[4]	0.00-OXY/ 625-IBU MG/KG M[4]	F[4]	0.00-OXY/ 780-IBU MG/KG M[4]	F[4]
Dehydration	0	0	1(2)	2(13)	2(14)	3(10)	4(20)	3(19)	3(23)	1(12)	4(20)	4(12)	4(20)	4(16)	4(31)	3(19)	4(41)	3(20)
Facial Staining	0	0	2(2)	1(1)	2(2)	1(2)	2(3)	2(2)	1(1)	1(2)	1(1)	0	3(3)	0	2(3)	1(1)	2(3)	2(3)
Material on Paw(s)	0	0	1(1)	1(2)	1(1)	2(3)	1(2)	1(1)	0	0	0	1(1)	1(1)	0	1(1)	0	2(2)	0
Staining on Hindlimb(s)	0	0	0	0	0	1(7)	0	0	0	0	0	0	0	0	0	0	0	0
Perianal Staining	0	0	0	0	0	0	2(5)	0	1(2)	0	0	0	1(1)	0	2(12)	0	0	0
Urogenital Staining	0	0	0	1(10)	0	1(8)	0	0	0	1(6)	0	0	0	1(1)	0	1(10)	2(3)	1(2)
Loose Stool	0	0	0	0	0	0	1(2)	0	0	0	0	0	0	0	1(1)	0	0	0
itivity to Touch	0	0	0	0	0	0	0	2(3)	0	0	0	2(2)	1(0)	0	0	0	0	2(4)

CLINICAL SIGN	0.00-OXY/ 0-IBU MG/KG M[4]	F[4]	5.00-OXY/ 400-IBU MG/KG M[4]	F[4]	6.25-OXY/ 500-IBU MG/KG M[4]	F[4]	7.80-OXY/ 625-IBU MG/KG M[4]	F[4]	9.75-OXY/ 780-IBU MG/KG M[4]	F[4]	0.00-OXY/ 400-IBU MG/KG M[4]	F[4]	0.00-OXY/ 500-IBU MG/KG M[4]	F[4]	0.00-OXY/ 625-IBU MG/KG M[4]	F[4]	0.00-OXY/ 780-IBU MG/KG M[4]	F[4]
Erythema on Ear(s)	0	0	0	0	1(1)	0	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	1(16)	0	0	1(0)	0	0	0	1(1)	0	0	0	0
Sore(s) on Forelimb(s)	0	0	0	0	0	0	1(13)	0	0	0	0	0	0	0	0	0	0	0

Body weights: Males in the oxycodone:ibuprofen groups and in the ibuprofen 500, 625 and 780 mg/kg groups demonstrated a decreased rate of body weight gain from study day 1 to study day 2. By study day 7, only males treated with greater than 6.25 mg/kg oxycodone and 500 mg/kg ibuprofen and the males treated with 500 mg/kg or more ibuprofen had a significantly lower body weight than controls. By study day 14, mean body weight was comparable for all males. For females, mean body weight was significantly lower in the animals treated with 5 mg/kg oxycodone:400 mg/kg ibuprofen or 6.25 mg/kg oxycodone:500 mg/kg ibuprofen. Body weights of females treated with 500, 625 and 780 mg/kg ibuprofen alone were also significantly lower than controls. By study day 14, the mean body weights for females were comparable between groups.

Percent Change in Body Weights in Male Rats:

Dose→ Day↓	0:0	5:400	6.25:500	7.8:625	9.75:780	0:400	0:500	0:625	0:780
1		↑1%	↓1%	↑5%	↓4%	↑1%	↑1%	↓1%	↑2%
2	↑18%	↓5%	↓7%	↓2%	↓11% *	↓3%	↓6%	↓9%	↓5% *
7	↑32%	↓15%	↓22% *	↓20% *	↓29% *	↓10%	↓19% *	↓24% *	↓23% *
14	↑45%	↓4%	↓13%	↓9%	↓17%	↑1%	↓11%	↓16%	↓13%

Percent Change in Body Weights in Female Rats:

Dose→ Day↓	0:0	5:400	6.25:500	7.8:625	9.75:780	0:400	0:500	0:625	0:780
1		↓3%	↓5%	↑2%	↑5%	↓1%	↓4%	↓2%	↑1%
2	↑8%	↓6%	↓10%	↓3%	↓13%	↓4%	↓9%	↓6%	↓5% *
7	↑20%	↓12%	↓19% *	↓10%	↓32% *	↓9%	↓14% *	↓14% *	↓13% *
14	↑26%	↓4%	↓9%	↓3%	↓19%	↑3%	↓8%	↓6%	↓6%

* $p < 0.05$ compared to controls

Gross pathology: Post mortem analysis for all treatment groups were consistent with dose-related ulcerogenesis which progressed to generalized peritonitis. No effects were noted in the control groups.

Incidence of Treatment-Related Gross Pathological Findings in Animals Surviving until Sacrfice (doses are oxycodone:ibuprofen):

Dose (mg/kg/d)	5:400		6.25:500		7.8:625		9.75:780		0:400		0:500		0:625		0:780	
Observation	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Thickening of jujunal wall	0/4	1/4	3/4	0/4	3/3	3/3	2/3	0/1	1/4	3/4	2/4	2/4	2/4	1/4	4/4	1/4
Jujunal adhesions	0/4	0/4	0/4	0/4	1/3	0/3	0/3	0/1	0/4	0/4	1/4	1/4	2/4	0/4	1/4	1/4
Black content in jujunum	0/4	0/4	1/4	0/4	0/3	0/3	0/3	0/1	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Enlarged peyer's patch of colon	0/4	0/4	0/4	0/4	0/3	0/3	0/3	0/1	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
Enlarged Mesenteric lymph nodes	0/4	0/4	1/4	0/4	2/3	2/3	1/3	0/1	0/4	2/4	2/4	1/4	3/4	2/4	2/4	2/4
Enlarged spleen	0/4	0/4	1/4	0/4	1/3	1/3	0/3	0/1	0/4	0/4	0/4	0/4	0/4	1/4	0/4	0/4
Enlarged adrenal gland	0/4	0/4	0/4	0/4	0/3	0/3	0/3	0/1	0/4	0/4	0/4	0/4	0/4	0/4	1/4	0/4
Enlarged Kidney	0/4	0/4	0/4	0/4	1/3	0/3	0/3	0/1	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Dilated pelvis of kidney	0/4	0/4	0/4	0/4	1/3	0/3	0/3	0/1	0/4	0/4	0/4	1/4	0/4	1/4	0/4	0/4

Summary of individual study findings: Acute toxicity of the combination of oxycodone and ibuprofen in the rat model was characterized by mortality, clinical signs of CNS depression and generalized toxicity, decreased body weight and gross pathological changes. The clinical signs were more pronounced in the combination treatment compared to ibuprofen alone, specifically with the signs of CNS depression. The minimum lethal dose for the combination product was 6.25:500 mg/kg oxycodone:ibuprofen in females, 7.8:625 mg/kg oxycodone:ibuprofen in males

and 780 mg/kg ibuprofen alone in females. The maximum non-lethal dose for the combination was 5:400 mg/kg in females and 6.25:500 mg/kg in males. For ibuprofen alone, the maximum non-lethal dose was 625 mg/kg in males and greater than 780 mg/kg in females. Mortality with the combination treatment was considered to be related to failing circulation. Based on gross post-mortem analysis the degree of ulcerogenic activity induced by ibuprofen alone was not significantly different from that produced by the combination product. The maximum tolerated dose for the combination product was >5 mg/kg with 400 mg/kg ibuprofen but less than 6.25 mg/kg oxycodone with 500 mg/kg ibuprofen. The single oral MTD for ibuprofen was between 625 and 780 mg/kg.

Study title: Final Report DuP 604 (Oxycodone-Ibuprofen Combination): One-Month Oral Gavage Toxicity Study in Sprague-Dawley Rats

Key study findings: The repeat-dose toxicity of the combination of oxycodone and ibuprofen was characterized in the rat model. The findings were as follows:

1. The oxycodone:ibuprofen combination product may produce gastric mucosal irritation evidenced as microscopic submucosal edema and/or fibrosis.
2. The gastrointestinal irritation appeared to be attributed to the ibuprofen content of the drug product, and was not aggravated by the presence of the oxycodone.
3. Target organs of toxicity, were identified as the stomach and spleen.
4. A NOAEL was identified as 0.313/25 mg/kg in males.
5. A LOAEL of 0.313/25 mg/kg/day could be established in females, due to the finding of a 22% decrease in urine osmolarity at this dose.

Study no:	90-9-3
Volume #, and page #:	Volume 9, Page 1
Conducting laboratory and location:	E.I. du Pont de Nemours and Company Wilmington, DE 19880-0400.
Date of study initiation:	October 16, 1990
GLP compliance:	Yes
QA report:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	Oxycodone HCl (Lot No. RM90-033), ' — Ibuprofen (Lot No. 90PH-798), —
Formulation/vehicle:	0.25% methylcellulose solution.

Methods (unique aspects): Animals were treated for 34-36 days with oxycodone:ibuprofen. Rats were housed individually for this study.

Dosing:

Species/strain: Sprague-Dawley rats — .DC BR (Virus Antibody Free)

#/sex/group or time point (main study): 10/sex/group as follows:

Group	Oxycodone (mg/kg/day)	Ibuprofen (mg/kg/day)
1	0	0
2	0.313	25
3	0.625	50
4	1.25	100
5	1.25	0
6	0	100

Satellite groups used for toxicokinetics or recovery: N/A
Age: 6 weeks on arrival, 9 weeks at beginning of dosing period.
Weight: Ranged from 287-375 g for males; 183-248 g from females.
Doses in administered units: See table above.
Route, form, volume, and infusion rate: Oral gavage, 5 ml/kg for each treatment.

Observations and times:

Clinical signs: Following dosing, rats were observed for 1-2 hours. Mortality checks were completed each afternoon.

Body weights: Body weights were measured prior to and once weekly during the dosing period.

Food consumption: Food consumption was measured concurrently with body weight.
Ophthalmoscopy: Completed once pretest and again during the week prior to necropsy.
EKG: Not completed.
Hematology: Obtained once pre-test and again on study day 37.
Clinical chemistry: Obtained once pre-test and again on study day 37.
Urinalysis: Obtained once pre-test and again on study day 37.
Gross pathology: Examined post mortem.
Organs weighed: Examined post mortem. See histopathology inventory table on page 46.

Histopathology: Examined post mortem. See histopathology inventory table on page 46. Tissues from all animals were evaluated.
Toxicokinetics: Not completed.
Other: Not completed.

Results:

Mortality: None.
Clinical signs: There were no drug-related clinical signs at any dose level.
Body weights: There were no significant differences in body weights between any groups (male or female) at any time point examined during this study. Male rats which received either 100 mg/kg ibuprofen alone or with 1.25 mg/kg oxycodone had a decreased body weight gain during the first week of the study. Rats in the combination group were slightly more affected than ibuprofen alone. After day 8, body weight gain and food consumption were the same as control animals (i.e, there were no significant differences by the end of the study). There were no effects on body weight gain in the female animals.

Mean Total Body Weight Gain (% control) in Males (oxycodone:ibuprofen):

Day	0.313:25	0.625:50	1.25:100	1.25:0	0:100
8	-6%	-12%	-41% *	-5%	-28% *
15	-2%	-9%	-22% *	-7%	-19%
22	-2%	-10%	-22%	-8%	-15%
29	-1%	-5%	-16%	-4%	-9%

* $p < 0.05$ compared to control value (Dunnetts)

Food consumption: Compared to controls, male rats in the 1.25:100 mg/kg oxycodone:ibuprofen group and the 0:100 mg/kg oxycodone:ibuprofen group consumed 15 and 12% less food, respectively, on Day 8. There were no other significant differences in food consumption in males. There were no significant changes in food consumption in female animals.

Ophthalmoscopy: There were no drug-related changes noted.

Electrocardiography: N/A

Hematology: Rats in the 100 mg/kg/day ibuprofen group with or without the 1.25 mg/kg/day oxycodone demonstrated decreased red blood cell counts, hemoglobin concentration and hematocrit. These animals also demonstrated a significant increase in platelet counts.

Summary of Changes Hematological Parameters:

	Males					Females				
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0.313:25	0.625:50	1.25:100	1.25:0	0:100	0.313:25	0.625:50	1.25:100	1.25:0	0:100
RBC Counts	↑3	↓2	↓7.3 *	↓0.4	↓9 *	↓3	↓4	↓12 *	↓3	↓11 *
Hemoglobin	↑0.6	↓4	↓10 *	↓2	↓13 *	↓1	↓4	↓10 *	↑0.6	↓10 *
Hematocrit	↑2	↓3	↓7.5 *	↓2	↓10 *	↓1	↓4	↓8 *	↑0.7	↓9 *
Platelets	↓1	↑11	↑15 *	↑6	↑18 *	↑5	↑6	↑23 *	↑0.2	↑16 *

* $p < 0.05$ compared to control value (Dunnetts).

Clinical chemistry: Rats in the 100 mg/kg/day ibuprofen group with or without the 1.25 mg/kg/day oxycodone demonstrated a slight but significant decrease in serum total protein concentrations, albumin and/or globulin concentrations in these groups as well.

Summary of Changes in Clinical Chemistry:

	Males					Females				
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0.313:25	0.625:50	1.25:100	1.25:0	0:100	0.313:25	0.625:50	1.25:100	1.25:0	0:100
Total Protein	--	↓3	↓8 *	↓1.6	↓13 *	--	↓5	↓11 *	↑2	↓5
Albumin	↑2.6	--	↓8 *	↓2.6	↓10 *	↑2	↓2	↓7 *	--	↓5
Globulin	↓4	↓9	↓9	--	↓17 *	↓9	↓9	↓13 *	↑4	↓4

* $p < 0.05$ compared to control value (Dunnetts).

-- no change

Urinalysis: There were no drug-related changes noted in the summary report. However, there was a significant increase in urine volume in males at the 0.625/50 and 1.250/100 mg/kg oxycodone/ibuprofen groups and in females at the 0.625/50, 1.25/100 and 0/100 mg/kg oxycodone/ibuprofen groups that may be drug-related. These changes were frequently associated with decreased urine osmolarity as indicated in the table below. The significant decrease in pH of the urine in females only following administration of 100 mg/kg/day ibuprofen was not evident in males or in the oxycodone:ibuprofen 1.25:100 mg/kg/day group and therefore is not likely related to drug treatment.

Summary of Changes in Urinalysis:

	Males					Females				
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0.313:25	0.625:50	1.25:100	1.25:0	0:100	0.313:25	0.625:50	1.25:100	1.25:0	0:100
Urine Volume	↑15	↑34 *	↑38 *	↓2	↑25	↑56	↑70 *	↑77 *	↑23	↑63 *
pH	↓1	↑1	--	↓1	↓1	↓5	↓8	↓3	↓6	↓15 *
Urine osmolarity	↓5	↓12	↓12	↓0.1	↓7.3	↓22 *	↓23 *	↓21 *	↓8	↓15

* $p < 0.05$ compared to control value (Dunnetts).
-- no change

Organ weights: A slight increase in both absolute (14%) and relative (12%) liver weight was noted in females that received 100 mg/kg ibuprofen alone and in increase in relative liver weight (9%) in animals that received 100 mg/kg ibuprofen with 1.25 mg/kg oxycodone.

Gross pathology: Control animals demonstrated red or black foci on the glandular mucosa of the stomach (1 of 10 control males and 1 of 10 control females). This observation was increased to a total of 1/20, 2/20, 4/20 in the low, intermediate and high dose combination groups, 1/20 in the oxycodone group and 3/20 in the ibuprofen group. There is no dose-related effect in males, whereas, the effect is most pronounced in females.

Incidence of Observations in Gross Pathology:

Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓**	Males (n=10)						Females (n=10)					
	0:0	0.313:25	0.625:50	1.25:100	1.25:0	0:100	0:0	0.313:25	0.625:50	1.25:100	1.25:0	0:100
Red or black focus on glandular mucosa	1	0	0	1	0	1	1	1	2	3	1	1

Histopathology: Microscopic changes in the gastric mucosa were observed in 1/20 rats that received oxycodone alone, 4/20 rats in the intermediate dose combination group, 2/20 rats in the high-dose combination group and 8/20 rats in the ibuprofen alone group. The pathology report suggests that the lesions were in different stages of healing with some apparently more recent than others. The changes were characterized as recent with evidence of submucosal edema with or without gastric mucosal erosion or as healed or healing given evidence of

submucosal fibrosis. Extramedullary hematopoiesis in the spleen was noted in all dose groups although the severity increased with increasing combination dose. These mild changes were thought to be a secondary response to low level gastric mucosal bleeding. A summary of these changes is listed in the table below:

Incidence of Observations in Histopathology:

	Males (n=10)						Females (n=10)					
Dose → (Oxycodone: Ibuprofen) **Parameter ↓**	0:0	0.313:25	0.625:50	1.25:100	1.25:0	0:100	0:0	0.313:25	0.625:50	1.25:100	1.25:0	0:100
Stomach:												
Submucosal edema	0	0	1	1	0	3	0	0	3	1	1	2
Healed ulceration	0	0	0	0	0	1	0	0	0	0	0	0
Submucosal fibrosis	0	0	0	0	0	4	0	0	0	0	0	1
Mucosal erosion	0	0	2	0	0	0	0	0	2	0	0	0
Necrosis, superficial	0	0	0	0	0	0	0	0	0	1	0	0
Mesenteric Lymph Nodes:												
Plasma cell hyperplasia	0	0	0	3	0	1	0	0	1	5	0	3
Spleen:												
Lymphoid follicular hyperplasia	9	10	10	10	10	10	10	10	10	10	10	10
Intermedullary hematopoiesis:												
Minimal	8	10	7	6	9	4	10	10	10	7	10	9
Mild	1	0	3	4	1	6	0	0	0	3	0	1
Hemosiderin pigment	9	10	10	10	10	10	10	10	10	10	10	10

Summary of individual study findings: Administration of oxycodone:ibuprofen combinations to the rat for 1-month led to decreased body weight gain and food consumption in male animals at the beginning of the study. These changes were significant for the high dose combination (1.25:100 mg/kg) and or ibuprofen alone. Animals that received ibuprofen 100 mg/kg/ with or without day 1.25 mg/kg/day oxycodone demonstrated decreased red blood cell counts, hemoglobin and hematocrit and in increase in platelet counts. Liver weights were increased in female rats in the ibuprofen 100 mg/kg/day alone group and ibuprofen 100 mg/kg/day plus oxycodone 1.25 mg/kg/day treatment groups. The gross pathological observations of red or black foci on the glandular mucosa of the stomach coupled with the microscopic changes in the gastric mucosal in the ibuprofen treated animals is consistent with the known effects of ibuprofen on the gastric mucosa. These changes did not appear to be increased by the presence of the oxycodone and were not induced by oxycodone alone. Extramedullary hematopoiesis in the spleen was evident in the high-dose combination and ibuprofen alone groups and is likely a response to low levels of gastric mucosal bleeding induced by the ibuprofen. Target organs of toxicity, therefore, were identified as the stomach and spleen. The sponsor does not identify a NOAEL for this study. The histopathology report concludes that a NOAEL of oxycodone/ibuprofen was identified as 0.313/25 mg/kg/day. Based upon the results of the study, a NOAEL can be identified in males only at 0.313/25 mg/kg/day. However, a LOAEL of 0.313/25 mg/kg/day could be established, as the only finding at this dose was a 22% decrease in

urine osmolarity in female rats only. These doses correspond to 0.15-fold safety margin for the proposed maximal daily dose of oxycodone:ibuprofen in humans.

Study title: Final Report DuP 604 (Oxycodone-Ibuprofen Combination): One-Month Oral Capsule Study in Beagle Dogs

NOTE: A preliminary review of a summary of this study which was included in an annual report was previously reviewed by Dr. David Brase in 1999. The following review includes analysis of the full histopathology report.

Key study findings: This study was designed to evaluate the toxicity of a 1:80 ratio of oxycodone:ibuprofen following the oral administration to beagle dogs for at least 28 days. The following findings were obtained:

1. The combination of the oxycodone and ibuprofen produced signs of gastrointestinal toxicity consistent with the known properties of NSAIDs to produce gastric ulceration.
2. The combination of oxycodone plus ibuprofen produced a greater incidence of fecal occult blood than ibuprofen alone.
3. A NOAEL of 0.0625 mg/kg oxycodone and 5 mg/kg/day ibuprofen was identified.

Study no: 90-10-4
Volume #, and page #: Volume 10, Page 1
Conducting laboratory and location: E.I. du Pont de Nemours and Company Wilmington, DE 19880-0400.
Date of study initiation: October 1, 1990
GLP compliance: Yes
QA report: Yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxycodone HCl (Lot No. RM90-033), Ibuprofen (Lot No. 90PH-798).
Formulation/vehicle: 0.25% aqueous methylcellulose

Methods (unique aspects): Animals were treated daily for a total of 33-35 days.
Dosing:

Species/strain: Beagle dogs
#/sex/group or time point (main study): 3/sex/group as follows:

Group	Oxycodone (mg/kg/day)	Ibuprofen (mg/kg/day)
1	0	0
2	0.0625	5
3	0.125	10
4	0.250	20
5	0.250	0
6	0	20

Satellite groups used for toxicokinetics or recovery: Not applicable.
Age: Not indicated.
Doses in administered units: See above table.

Route, form, volume, and infusion rate: Oral via liquid filled gelatin capsule. Each dog received two capsules in the morning. Total dose volume to body weight ratio was 1 ml/kg. Each dog's daily dose was calculated based upon the most recent body weight.

Observations and times:

Clinical signs: Animals were observed pre-dose, for approximately 1-2 hours after dosing and daily thereafter.

Body weights: Body weights were measured pre-dose and weekly during the dosing period.

Food consumption: Food consumption was visually estimated daily during the week before dosing and during the dosing period.

Ophthalmoscopy: Ophthalmoscopic examination was conducted once pretest and one again during the week prior to necropsy.

EKG: EKG tracing were obtained on all dogs twice pretest and once during the week right before the scheduled sacrifice. All recordings were made approximately 1-2 hours after dosing.

Hematology: Hematological assessment was completed twice pretest and again on study day 16 (males), study day 18 (females) or study day 33 (both).

Clinical chemistry: Blood serum was collected twice pretest and again on study day 16 (males), study day 18 (females) or study day 33 (both).

Urinalysis: Urine was collected at the same time points as the hematology (pretest, study day 16 for males, study day 18 for females and study day 33 for both groups.

Gross pathology: Animals were sacrificed on study day 34-36 a day following their last dose.

Organs weighed: The weight of the liver, kidneys, adrenal glands, spleen and testes were obtained post mortem.

Histopathology: See table for tissues collected for histopathological analysis. All tissues/organs from all animals were microscopically examined by a consulting veterinary pathologist.

Toxicokinetics: Not completed.

Other: Fecal Occult Blood. Blood samples were analyzed for occult blood via the Hemocult Slide diagnostic system daily during the week prior to study day 1 and during the dosing period.

Results:

Mortality: None.

Clinical signs: Clinical signs included stools that contained red material in the stools and/or dark or tar-like stools in drug-treated animals. There was no incidence of dark tar-like stools or red material in stool in the control animals. There were a total of 42 observations in 5 of 6 dogs that received the high dose combination and a total of 5 observations in 1 of 6 dogs that received ibuprofen alone (See sponsor's table below).

GROUP INCIDENCE (AND NUMBER OF DAYS OBSERVED) OF CLINICAL SIGNS

CLINICAL SIGN	0.0000 / 0 MG/KG/DAY OXY / IBU M[3]	F[3]	0.0625 / 5 MG/KG/DAY OXY / IBU M[3]	F[3]	0.1250 / 10 MG/KG/DAY OXY / IBU M[3]	F[3]	0.2500 / 20 MG/KG/DAY OXY / IBU M[3]	F[3]	0.2500 / 0 MG/KG/DAY OXY / IBU M[3]	F[3]	0.0000 / 20 MG/KG/DAY OXY / IBU M[3]	F[3]
Loose, Soft and/or Mucoidal Stool	2(58)	3(15)	3(30)	3(52)	2(33)	3(33)	3(31)	3(59)	3(26)	3(27)	3(47)	3(11)
Dark and/or Tar-like Stool	0	0	0	0	0	0	0	1(12)	0	0	0	0
Red Material in Stool	0	0	0	0	1(1)	0	2(5)	3(21)	1(2)	0	1(6)	0

Additional clinical signs included increases in the incidence of **ocular hyperemia** at the two higher dose combinations as well as oxycodone alone group in both males and females. In addition, animals in the high dose combination group and the oxycodone group demonstrated **a relaxed nictitating membrane**. The number of animals affected and the incidence (number of days observed) of these changes is presented in the sponsor's table below:

CLINICAL SIGN	0.0000 / 0 MG/KG/DAY OXY / IBU M[3]	F[3]	0.0625 / 5 MG/KG/DAY OXY / IBU M[3]	F[3]	0.1250 / 10 MG/KG/DAY OXY / IBU M[3]	F[3]	0.2500 / 20 MG/KG/DAY OXY / IBU M[3]	F[3]	0.2500 / 0 MG/KG/DAY OXY / IBU M[3]	F[3]	0.0000 / 20 MG/KG/DAY OXY / IBU M[3]	F[3]
Ocular Hyperemia	2(5)	1(6)	3(3)	1(4)	3(24)	2(4)	3(34)	2(4)	3(38)	2(29)	2(4)	1(9)
Relaxed Membrane Nictitans	0	0	0	0	0	0	2(31)	0	3(14)	0	0	1(31)

Fecal Occult Blood: Consistent with the clinical signs of dark or tar-like stool and red material in the stool, dogs that received the high dose combination of 20 mg/kg ibuprofen plus 0.25 mg/kg oxycodone demonstrated a high incidence of positive fecal occult blood. Positive fecal occult blood after drug treatment was observed a total of 2 times in 2 of 6 control animals. In contrast, positive results were observed a total of 62 times in 6 of 6 dogs treated with the high dose combination product and a total of 10 times in 3 of 6 animals that were treated with ibuprofen alone. In contrast, positive fecal occult blood was noted a total of 10 times in 3 of 6 animals treated with just the high dose of ibuprofen, as summarized in the table below:

Incidence of Observations Fecal Occult Blood (number of days observed):

Dose → (Oxycodone: Ibuprofen) Parameter ↓	Males (n=3 per group)						Females (n=3 per group)					
	0:0	0.0625:5	0.125:10	0.250:20	0.250:0	0:20	0:0	0.0625:5	0.125:10	0.250:20	0.250:0	0:20
Fecal Occult Blood:	1(1)	0(0)	0(0)	3(21)	1(9)	2(9)	1(1)	1(1)	1(1)	3(41)	0(0)	1(1)

NOTE: The numbers presented in the table above are slightly different from those listed in previous reviews by Dr. David Brase, who combined males and females in his analysis. The values above represent those listed in the final report.

Body weights: There were no drug-related differences in body weight or body weight gain/loss.

Food consumption: There were no drug-related differences in food consumption in the drug-treated dogs.

Ophthalmoscopy: Ophthalmologic examinations were unremarkable.

Electrocardiography: There were no drug-related effects on the electrocardiogram.

Hematology: There were no drug-related effects noted. Dr. Brase, however, combined the data on hematocrit from males and females and reported the results as follows:

Hematology: No drug-related effects were reported. A spot check of the individual data for hematocrits, however, indicated a possible decrease during treatment, so the data for males and females were combined (see table below) and the values for the mid-dosing samples and 33-day samples were compared with the corresponding pretest-2 samples (i.e., the closest baseline to treatment initiation) by ANOVA, Dunnett's test, and t-test for paired data. No significant differences were identified by ANOVA or Dunnett's test. However, the 33-day samples from the dogs receiving the high dose combination were significantly different from the pretest 2 samples in the t-test for paired data.

Oxy:Ibu doses, mg/kg/d	HEMATOCRITS (mean ± S.D.) FROM MALE AND FEMALE DOGS COMBINED (n=6)		
	PRETEST 2	**MID-DOSING**	**33-DAY SAMPLES**
0:0	43.6 ± 3.4	43.7 ± 3.5	43.0 ± 2.6
0.0625:5	46.0 ± 5.9	46.2 ± 4.7	43.4 ± 4.1
0.125:10	46.0 ± 3.5	45.3 ± 3.2	43.9 ± 3.4
0.250:0	45.9 ± 4.1	45.8 ± 4.0	45.7 ± 3.4
0.250:20	46.3 ± 4.0	45.0 ± 4.8	43.5 ± 4.2*
0:20	47.2 ± 1.4	47.0 ± 2.2	46.7 ± 2.9

*Significantly different from baseline pretest value, $p<0.02$ (t-test for paired data).

Clinical chemistry: There were no drug-related effects noted.

Urinalysis: There were no drug-related effects noted.

Organ weights: There were no drug-related effects on either absolute or relative weights of the adrenal glands, kidneys, liver, spleen or testes.

Gross pathology: One dog in the 0.125 mg/kg oxycodone:10 mg/kg ibuprofen group (female) presented with red discoloration of the gastric mucosa. There was no associated histopathology.

Histopathology: There were no histopathological changes noted which were associated with the drug treatment. There was no histopathological correlate to the red discoloration present on the gastric mucosa as observed via gross pathological analysis. Specifically, the pathologist's report indicted that "DuP 604 has the potential of causing gastrointestinal irritation. The stomach and intestinal tract of dogs receiving the combination or individual doses of either oxycodone or ibuprofen had no microscopic evidence of active or residual inflammatory alterations. Peripheral lymph nodes and spleen also had no increased deposition of hemosiderin pigment, an indicator of localized or more general hemorrhage."

Summary of individual study findings: The study demonstrated that under the conditions tested, the oxycodone:ibuprofen combination may be associated with gastrointestinal pathology consistent with the known effects of NSAIDs of the gastric mucosa. Although there was no histological evidence for gastrointestinal ulceration, the presence of fecal occult blood is evidence for potential gastric ulceration. This potential appears to be associated with the presence of the ibuprofen, however, in this study the incidence of the fecal occult blood was clearly greater in the oxycodone:ibuprofen high dose group than the ibuprofen alone group. The high dose of oxycodone tested in these studies (0.25 mg/kg/day = 5 mg/m^2) is 1.66 fold higher than the proposed human single dose of 5 mg oxycodone based on body surface area (mg/m^2). The high dose of ibuprofen tested in these studies (20 mg/kg/day = 400 mg/m^2) is 1.62 fold higher than the proposed single dose 400 mg of ibuprofen based on body surface area (mg/m^2). The exposure multiples are significantly less when compared to the maximum proposed daily human dose of 20 mg oxycodone and 1600 mg ibuprofen (0.4-fold for both). Target organs of toxicity were not identified, although clinical observations indicated gastrointestinal toxicity. The NOAEL for the combination is 0.0625 mg/kg oxycodone plus 5 mg/kg ibuprofen, based upon both the incidence of ocular hyperemia in the 0.125:10 mg/kg oxycodone:ibuprofen group and the initial observation of red material in the stool of one animal in that group.

Study title: Final Report: 28-Day Capsule Toxicity Study in Dogs

Key study findings: This study was designed to evaluate the toxicity of a 1:40 ratio of oxycodone:ibuprofen following the oral administration to dogs for at least 28 days. The results indicate the following:

1. Treatment with the combination of oxycodone:ibuprofen produced clinical signs of increased incidence of unformed and/or liquid feces and the presence of fecal occult blood.
2. Hematological findings included decreased red blood cell counts, hemoglobin and hematocrit in females at the high dose combination (0.5:20 mg/kg oxycodone:ibuprofen), which is consistent with minor blood loss via gastrointestinal irritation. However, there was no gross or histopathological evidence for GI tract toxicity following treatment.

3. Chronic renal inflammation was noted in animals which received greater than or equal to 5 mg/kg/day ibuprofen which is consistent with the known effects of NSAIDs on the kidney.
4. The target organs of toxicity for the combination are the GI tract and the kidney.
5. The NOAEL for the drug combination in females was 0.125/5 mg/kg/day due to renal inflammation at the next highest dose.
6. The NOAEL for the drug combination in males is 0.0625:2.5 mg/kg oxycodone:ibuprofen, based upon evidence of chronic inflammation of the kidney in 1/3 animals treated and fecal occult blood with the next higher dose combination.

Study no: 6277-145
Volume #, and page #: Volume 11, Page 1
Conducting laboratory and location:

Date of study initiation: October 13, 2000
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxycodone HCl, Lot No. 42554.
Ibuprofen, Lot No. LPL-7091 ME,
Formulation/vehicle: 0.25% methylcellulose

Methods (unique aspects):
Dosing:

Species/strain: Beagle dogs
#/sex/group or time point (main study): 3/sex/group as follows:

Group	Oxycodone (mg/kg/day)	Ibuprofen (mg/kg/day)
1	0	0
2	0.0625	2.5
3	0.125	5
4	0.250	10
5	0.50	20
6	0.5	0
7	0	20

Satellite groups used for toxicokinetics or recovery: N/A
Age: 4 to 6 months at time of dosing initiation.
Weight: Ranged from 6.1 to 8.5 kg for males and 5.9 to 8.2 kg for females.
Doses in administered units: See above table.
Route, form, volume, and infusion rate: Oral administration via a capsule.

Observations and times:

Clinical signs: Observations were made twice daily for mortality and morbundity. Prior to initiation of treatment, heart rate, respiration rate and rectal body temperature were

determined. A complete neurological exam was conducted once prior to dose initiation and on days 12 and 26 (1-2 hours after dosing). The presence of **fecal occult blood** was evaluated once daily, beginning one week prior to dose initiation. Stool samples were analyzed for occult blood using the Hemoccult® brand slides and developing solution.

Body weights: Data was obtained once before dosing, on the first day of treatment and weekly thereafter.

Food consumption: Food consumption was measured weekly beginning 1 week prior to dosing.

Ophthalmoscopy: Examination was conducted prior to treatment and prior to termination during week 4.

EKG: EKG was performed on all dogs at least twice prior to study initiation and prior to scheduled necropsy via a 10-lead system.

Hematology: Blood was collected twice prior to treatment (day -7 and day 1), on day 14 and prior to schedule necropsy.

Clinical chemistry: Blood was collected twice prior to treatment (day -7 and day 1), on day 14 and prior to schedule necropsy.

Urinalysis: Overnight urine collection was completed twice before treatment (Days -7 and 1), on Day 14 and prior to necropsy.

Gross pathology: Necropsy was completed post-mortem and consisted of examination of the external features of the carcass, external body orifices, abdominal, thoracic, and cranial cavities and organs/tissues.

Organs weighed: The following organs were weighed: adrenal glands, brain, heart, kidney, liver with drained gallbladder, ovary, testis with epididymis and spleen.

Histopathology: See histopathology table. All preserved tissues from all dogs were examined microscopically.

Toxicokinetics: Not completed.

Results:

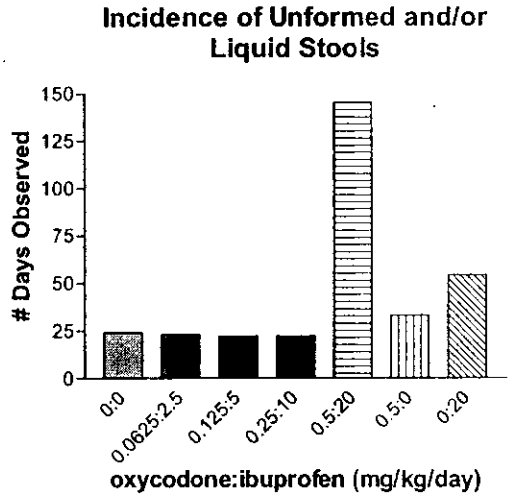
Mortality: There were no early deaths in the study.

Clinical signs: The most common clinical finding was **unformed/liquid stools**. This was present in all groups, but was most prevalent in the oxycodone:ibuprofen 0.5:20 mg/kg/day combination and the ibuprofen 20 mg/kg/day group. Although this was attributed primarily to the presence of the ibuprofen, there was a greater incidence in the combination group than the ibuprofen alone group, as indicated in sponsor's table below:

Text Table 1
Incidence of Unformed and/or Liquid Feces.

Dose: Oxycodone:Ibuprofen (mg/kg/day)	Males		Females	
	No. of Occurrences	No. of Dogs	No. of Occurrences	No. of Dogs
0.0:0.0	7	2	17	2
0.0625:2.5	11	2	12	2
0.125:5.0	12	2	10	3
0.25:10	7	2	15	3
0.5:20	75	3	70	3
0.5:0.0	16	3	17	3
0.0:20	24	3	30	3

The combined occurrences of the incidence of unformed and/or liquid feces is represented graphically in the figure below (generated by the Division from the above data):

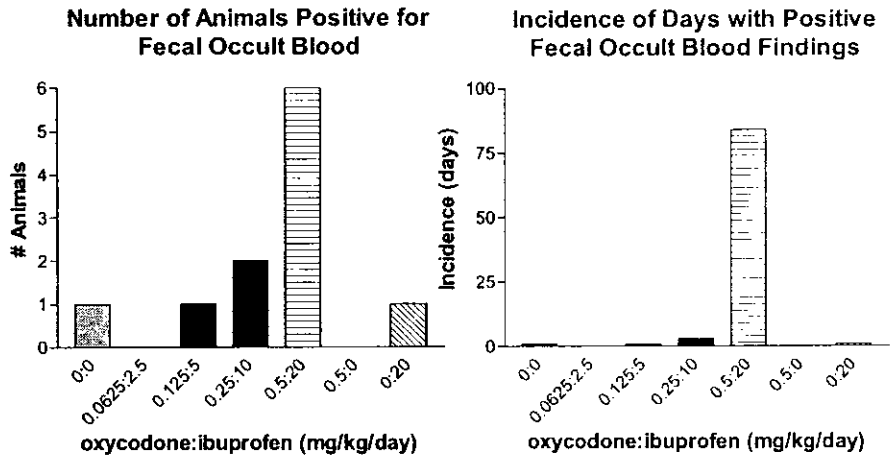


Red discolored feces was noted in one control female, one oxycodone:ibuprofen 0.125:5.0 mg/kg/day female and two male and three females in the oxycodone:ibuprofen 0.5:20 mg/kg/day group. **Fecal occult blood**, detected in dogs given oxycodone:ibuprofen at 0.5:20 mg/kg/day in females and 0.125:5 or greater in males, was considered to be an effect of the treatment with both test materials. A summary of the incidence of fecal occult blood in this study was provided by the sponsor's table below:

Text Table 2
Incidence of Fecal Occult Blood Findings

Dose: Oxycodone:Ibuprofen (mg/kg/day)	Males		Females	
	No. of Occurrences	No. of Dogs	No. of Occurrences	No. of Dogs
0.0:0.0	0	0	1	1
0.0625:2.5	0	0	0	0
0.125:5.0	1	1	0	0
0.25:10	3	2	0	0
0.5:20	34	3	50	3
0.5:0.0	0	0	0	0
0.0:20	0	0	1	1

The data from the above table is represented graphically below:



Body weights: There were no treatment-related findings.

Food consumption: There were no treatment-related findings.

Ophthalmoscopy: There were no treatment-related findings.

Electrocardiography: There were no treatment-related findings.

Hematology: Several hematological findings were made in the high dose combination group (oxycodone:ibuprofen 0.5:20 mg/kg/day) including **decreased mean erythrocyte counts**, **hemoglobin** and **hematocrit** on day 30. These decreases were statistically significant in the female dogs and are consistent with mild intestinal hemorrhage. In addition, there was a significant decrease in circulating **white blood cell counts** and **absolute neutrophil counts** at day 30 which was statistically significant in female animals, although no significant findings were noted at the highest dose combination. Changes in male animals, although frequently of comparable magnitude, were not statistically significant. The changes in leukocyte counts appear to be due primarily to the oxycodone.

Summary of Changes Hematological Parameters:

	Males						Females					
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5:0	0:20	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5: 0	0:20
RBC Counts:												
Day -7	↑2	↑2	--	↑3	↓7	↑3	↓9	↓4	↓7	↓14*	↑1	↓11*
Day 1	↑4	↑3	--	↑5	↓6	↑2	↓3	↑3	↓3	↓7	--	↓9
Day 14	↑11	↑6	↑7	↑3	↑7	↑5	↑3	↑10	↓3	↓13	↑3	↓8
Day 30	--	↓4	↓6	↓12	↓8	↓8	↑6	↑4	↓7	↓19*	↓1	↓10
Hemoglobin:												
Day -7	↑5	↑5	↑2	↑2	↓2	↑4	↓6	↓7	↓7	↓14	↓1	↓13
Day 1	↑8	↑3	--	↑2	↓3	↑3	↑1	↑1	↓2	↓5	↓1	↓6
Day 14	↑14	↑5	↑8	↑2	↑10	↑5	↓7	↑8	↓2	↓12	↓2	↓8
Day 30	↑4	↓3	↓1	↓11	↓4	↓5	↑9	--	↓6	↓19*	↓3	↓11
Hematocrit:												
Day -7	↑4	↑3	--	↑3	↓5	↑3	↓5	↓5	↓5	↓12	↓1	↓10

Day 1	↑5	↑2	↓1	↑3	↓6	↑2	--	↑1	↓3	↓7	↓2	↓7
Day 14	↑13	↑6	↑8	↑2	↑9	↑5	↑7	↑9	↓1	↓10	↑2	↓6
Day 30	↑3	↓2	↓5	↓10	↓6	↓8	↑12	↑1	↓5	↓15*	↓3	↓10
WBC Counts:												
Day -7	↓13	↓20	↓16	↓18	↓37	↑6	↓17	↓10	↓1	↓1	↓20	↓7
Day 1	↑6	↓28	↓23	↓16	↓41	↑3	↓25	↓3	↑8	↑9	↓14	↓6
Day 14	↓18	↓20	↓28	↓17	↓35	↑4	↓16	↑26	↓9	↑22	↓18	↓17
Day 30	↓13	↓16	↓32	↑1	↓12	↑8	↓30*	↓27*	↓29	↑14	↓31*	↓5
Neutrophil Counts:												
Day -7	↓18	↓18	↓16	↓21	↓38	↓9	↓18	↓18	--	↓8	↓38	↓22
Day 1	↓16	↓30	↓26	↓16	↓43	↑8	↓32	↓12	↑9	↓4	↓27	↓9
Day 14	↓20	↓17	↓30	↓24	↓39	↑1	↓23	↑25	↓11	↑27	↓27	↓23
Day 30	↓16	↓19	↓49	↑7	↓7	↑10	↓38*	↓43*	↓40*	↑6	↓49*	↓9

* $p < 0.05$ compared to control group (0:0 mg/kg) values.
-- no change in this parameter compared to control values.

Clinical chemistry: Blood urea nitrogen levels were significantly elevated on Day 30 in female animals only for most treatment groups. There was no apparent dose dependency to this effect. **Total protein** levels were significantly decreased in females only on Day 30 of the study with the largest decrease occurring in the high dose combination group (0.5 mg/kg oxycodone:20 mg/kg ibuprofen). Levels of **albumin** were significantly decreased on days 14 and 30 in the high dose combination females only.

Summary of Changes in Clinical Chemistry Parameters:

	Males						**Females**					
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5:0	0:20	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5: 0	0:20
Blood Urea Nitrogen:												
Day -7	--	↑33	↑8	↑8	↑25	↑17	↑13	↓13	↓13	↓6	--	↓13
Day 1	↑18	↑18	↑36	↑18	↑36	↑36	↓6	↓6	↓24	↓24	--	--
Day 14	↑8	↑25	↑25	↑25	↑33	↑17	↓11	↑32	↑21	↓5	↓21	↓5
Day 30	↑7	--	↑7	↑14	↑43	↑36	↑58*	↑25	↑58*	↑33*	↑33*	↑50*
Total Protein:												
Day -7	↓4	↑4	↓2	--	↓2	↓2	↑4	↑2	↓4	↓6	↑2	↓2
Day 1	↑2	↑4	↓2	--	↓6	↓2	↑2	↑4	↓6	↓4	↓2	↓2
Day 14	↑2	↑7	↑2	↓17	↓2	↓6	↑8	↑6*	↓4	↓15	↑2	↓4
Day 30	↓2	↑4	↑2	↓17	↓2	↓4	↑4	↓5	↓9*	↓18*	↓7*	↓9*
Albumin:												
Day -7	--	↑3	--	--	↑3	--	--	--	↓5	↓8	--	↓14*
Day 1	--	--	↓3	↓3	↓3	↓6	--	↑3	↓3	↓6	↓3	↓9
Day 14	↑3	↓3	↓3	↓21	--	↓6	↑6	↑6	--	↓21*	↑6	↓6
Day 30	--	--	--	↓15	↓3	↓3	↑3	↑3	↓3	↓20*	--	↓9
Globulin:												
Day -7	↓10	--	↓5	--	↓5	↓5	↑12	↑6	--	--	↑6	↑18
Day 1	↑5	↑10	--	↑5	↓10	↑5	↑5	↑5	↓5	--	--	↑10
Day 14	--	↑24	↑10	↓5	↓5	↓5	↑16	↑11	↓5	--	--	↑5
Day 30	↓5	↑10	↑5	↑10	--	↓5	↑5	↓18*	↓14*	↑14*	↓18*	↓9
A/G Ratio:												
Day -7	↑12	↑1	↑8	↓1	↑9	↑2	↓13	↓6	↓2	↓5	↓7	↓25
Day 1	↓3	↓9	↓2	↓7	↑10	↓10	↓9	↓5	↑1	↓10	↓4	↓20
Day 14	↑3	↓20	↓9	↓19	↑8	↓3	↓5	↓4	↑6	↓20*	↑5	↓13
Day 30	↑2	↓9	↓5	↑22	↓2	↓1	↑2	↑25	↑15	↓3	↑21	↑3

Inorganic Phosphorus:												
Day -7												
Day 1	↑1	↑1	↑5	--	↓8	↑9	↑10	↑4	↓1	↑3	↑1	↓4
Day 14	↑1	↑6	↑6	↑3	↓1	↑6	↑13	↑3	↑3	↑4	↑6	↑1
Day 30	↑9	↑7	↑3	↑4	↓1	↑6	↑14*	↑8	↑3	↑20*	↑2	↑2
	↑11	↑9	↑11	--	↑2	↑5	↑17	↑7	↑4	↑15	↑10	↑9

* $p < 0.05$ compared to control group (0:0 mg/kg) values.
-- no change in this parameter compared to control values.

In addition to the above changes, a significant increase (14% and 20%) in **inorganic phosphorus** levels was noted in female rats on Day 14 that were treated with the low dose combination (0.0625 mg/kg oxycodone:2.5 mg/kg ibuprofen) and the high dose combination (0.5 mg/kg oxycodone:20 mg/kg ibuprofen), respectively. This effect was not dose-dependent, was not evident in male animals, and was not significant on Days 1 or 30. As such, this finding unlikely to be treatment-related.

Urinalysis: On male each in the oxycodone:ibuprofen (0.5:20 mg/kg/day group) and oxycodone (0.5 mg/kg/day) group presented with **coarse granular casts**, however, the relationship to drug treatment is not known. No other changes in the urinalysis profile were detected.

Organ weights: There were no treatment-related findings.

Gross pathology: There were no treatment-related findings.

Histopathology: Although the presence of fecal occult blood suggests gastrointestinal hemorrhage, there were no histpathological observations in the gastrointestinal tract. Alterations in the kidney were detected. Specifically, chronic inflammation consisting of interstitial fibrosis and mononuclear infiltration with tubular atrophy, basophilia and dilation were evident in dogs that received ibuprofen (20 mg/kg/day), males that received oxycodone:ibuprofen (0.5:20 mg/kg/day), dogs that received oxycodone:ibuprofen (0.25:10 mg/kg/day) and males that received oxycodone:ibuprofen (0.125:5 mg/kg/day) but not in dogs that received oxycodone 0.5 mg/kg/day only. The lesions were wedge-shaped and extended into the vascular portions of the kidney and therefore suggest that they were vascular in origin. All other histological changes noted did not show dose-dependency, were found in only one sex or were also found in control animals, and therefore did not appear to be attributed to the drug-treatment. The findings are summarized in the table below:

Summary of Histological Changes:

	Males (n=3)							**Females (n=3)**						
Dose (mg/kg) → (Oxycodone: Ibuprofen) **Parameter ↓** (% change vs control)	0:0	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5:0	0:20	0:0	0.0625:2.5	0.125:5	0.25:10	0.5:20	0.5: 0	0:20
Lung:														
Chronic inflammation	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Hemorrhage	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Subplural microcysts	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Alveolar macrophages	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Heart:														
Dilated lymphatics	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Liver:														
Chronic inflammation of the bile duct	0	0	2	1	0	1	0	1	0	0	0	1	0	1

Focal fibrosis	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Kidney:														
Tubule regeneration	2	1	2	0	1	0	0	1	2	0	1	1	2	0
Chronic inflammation	0	0	1	2	1	0	1	0	0	0	3	0	0	2
Dilated tubules	0	0	1	1	1	0	1	0	0	0	0	0	0	2
Stomach:														
Increased calcareous bodies	0	0	0	0	1	0	0	0	0	0	0	0	0	0

Summary of individual study findings: Oral administration of oxycodone:ibuprofen (1:40) to dogs produced clinical signs of gastrointestinal irritation (loose/unformed stool and/or fecal occult blood) and changes in hematology consistent with mild blood loss in females. However, these changes were not correlated with either gross or microscopic histopathology in the gastrointestinal tract. Based upon the presence of unformed and/or loose stools, the NOAEL for the GI effects in females was 0.25 mg/kg/day oxycodone and 10 mg/kg/day ibuprofen and for males was 0.0625 mg/kg oxycodone and 2.5 mg/kg ibuprofen. Chronic renal inflammation was noted in animals that received greater than or equal to 5 mg/kg/day ibuprofen which was consistent with the known effects of NSAIDs. The NOAEL for this effect is 2.5 mg/kg/day ibuprofen in males and 5 mg/kg/day ibuprofen in females. The target organs of toxicity for the combination are the GI tract and the kidney. The NOAEL for the drug combination in females was 0.125 mg/kg/day oxycodone and 5 mg/kg/day ibuprofen. Although the lowest dose of oxycodone:ibuprofen in females (0.0625:2.5 mg/kg/day) produced a 58% increase in blood urea nitrogen on Day 30 and a 14% increase in inorganic phosphorus, a 30% decrease in WBC counts and a 38% decrease in neutrophils, these effects were not dose-related or were not evident at the end of the study. In males, a NOAEL of 0.0625:2.5 mg/kg oxycodone:ibuprofen was established based upon the next higher dose producing evidence of chronic inflammation of the kidney in 1/3 animals and the presence of fecal occult blood.

Toxicology summary: In support of NDA 21-378, Forest Laboratories either conducted or obtained right of reference to acute toxicology studies in the rat for oxycodone alone, ibuprofen alone or the combination of the two drug products. In addition, a 1-month repeat-dose toxicology study in the rat and two 1-month repeat-dose toxicology studies in the dog were completed with the combination drug product. The results of these studies, plus the previous findings of safety and efficacy for Motrin® and Roxicodone™ made by the Agency, provide information regarding the toxicological profile of this combination drug product.

Acute administration of oxycodone to the rat (50, 100, 150, 225, 337.5 mg/kg/day) produced dose-dependent clinical-signs of CNS depression, renal/urinary effects and generalized deterioration. The NOAEL for acute oxycodone dosing is < 50 mg/kg based on clinical observations; no histopathology was performed. The single oral minimum lethal dose was 225 mg/kg in males and 337.5 mg/kg in females. The maximum non-lethal dose was 150 mg/kg in males and 225 mg/kg in females.

Acute administration of ibuprofen in the rat (533.3, 800, 1200 and 1800 mg/kg/day) was associated with biphasic toxicity. The initial toxicity was related to general CNS depression (ataxia, decreased motor activity, decreased respiration, sedation, loss of righting reflex, loss of blinking reflex, enophthalmus and/or prostration). Delayed toxicity was associated with a general deterioration of the condition on the animals, likely associated with ulcerogenic potential

of ibuprofen. This toxicity was characterized by pallor, dehydration, rough coat/piloerection, facial staining, urogenital staining, perianal staining, staining of the hindlimbs/forlimbs, tail staining and or prostration. Gross pathology and histological analysis demonstrated dose-dependent ulceration associated with inflammatory cell infiltration of the small intestine. Evidence for an activation of the immune system included enlargement of the spleen with hypertrophy in the white pulp and mild to marked mononuclear cell infiltration of the red pulp in all treatment groups. Mortality at doses greater than 800 mg/kg was likely due to septic peritonitis. Based upon these results, the NOAEL was < 533.3 mg/kg. The minimum lethal dose was 800 mg/kg in males and females. The maximum non-lethal dose was 533.3 mg/kg.

Acute toxicity of the combination of oxycodone:ibuprofen in the rat (5:400, 6.25:500, 7.8:625 and 9.75:780 mg/kg/day) was characterized by mortality, clinical signs of CNS depression and generalized toxicity, decreased body weight and gross pathological changes. The clinical signs were more pronounced in the combination treatment compared to ibuprofen alone, specifically with the signs of CNS depression. The minimum lethal dose for the combination product was 6.25:500 mg/kg oxycodone:ibuprofen in females, 7.8:625 mg/kg oxycodone:ibuprofen in males and 780 mg/kg ibuprofen alone in females. The maximum non-lethal dose for the combination was 5:400 mg/kg in females and 6.25:500 mg/kg in males. For ibuprofen alone, the maximum non-lethal dose was 625 mg/kg in males and greater than 780 mg/kg in females. Mortality with the combination treatment was considered to be related to failing circulation. Based on gross post-mortem analysis the degree of ulcerogenic activity induced by ibuprofen alone was not significantly different from that produced by the combination product. The maximum tolerated dose for the combination product was >5 mg/kg with 400 mg/kg ibuprofen but less than 6.25 mg/kg oxycodone with 500 mg/kg ibuprofen. The single oral MTD for ibuprofen was between 625 and 780 mg/kg.

A total of 3 1-month repeat dose toxicology studies were completed with the combination product. Results of the 1-month study in rats demonstrated that administration of oxycodone:ibuprofen combination (1:80 ratio; 1.25 mg/kg oxycodone:100 mg/kg ibuprofen) led to decreased body weight gain and food consumption in male animals at the beginning of the study. Animals that received ibuprofen 100 mg/kg/day with or without 1.25 mg/kg/day oxycodone demonstrated decreased red blood cell counts, hemoglobin and hematocrit and in increase in platelet counts. Liver weights were increased in female rats in the ibuprofen 100 mg/kg/day alone group and ibuprofen 100 mg/kg/day plus oxycodone 1.25 mg/kg/day treatment groups. The gross pathological observations of red or black foci on the glandular mucosa of the stomach coupled with the microscopic changes in the gastric mucosal in the ibuprofen treated animals is consistent with the known effects of ibuprofen on the gastric mucosa. These changes did not appear to be increased by the presence of the oxycodone and were not induced by oxycodone alone. Extramedullary hematopoiesis in the spleen was evident in the high-dose combination and ibuprofen alone groups and is likely a response to low levels of gastric mucosal bleeding induced by the ibuprofen. This study suggests a NOAEL of oxycodone/ibuprofen at 0.313/25 mg/kg/day that provides a 0.2 fold safety margin on BSA basis. Significant toxicity in terms of hematological changes and organ weight changes were not evident except at the high dose ibuprofen with or without oxycodone. This dose combination 1.25 mg/kd oxycodone: 100 mg/kd ibuprofen results in an estimated exposure that is 0.6 times the maximum proposed daily human dose of 20:1600 mg/kg/day oxycodone:ibuprofen.

The 1-month repeat-dose toxicology study in the dogs using the (1:80) ratio of oxycodone:ibuprofen (0.0625:5, 0.125:10, 0.250:20 mg/kg/day oxycodone:ibuprofen) demonstrated that, under the conditions tested, the oxycodone:ibuprofen combination may be associated with gastrointestinal pathology consistent with the known effects of NSAIDs of the gastric mucosa. Although there was no histological evidence for gastrointestinal ulceration, the presence of fecal occult blood is evidence for potential gastric ulceration. This potential appears to be associated with the presence of the ibuprofen, however, in this study the incidence of the fecal occult blood was clearly greater in the oxycodone:ibuprofen high dose group than the ibuprofen alone group. The high dose of oxycodone tested in these studies (0.25 mg/kg/day = 5 mg/m^2) is 1.66 fold higher than the proposed human single dose of 5 mg oxycodone based on body surface area (mg/m^2). The high dose of ibuprofen tested in these studies (20 mg/kg/day = 400 mg/m^2) is 1.62 fold higher than the proposed single dose 400 mg of ibuprofen based on body surface area (mg/m^2). Target organs of toxicity were not identified, although clinical observations indicated gastrointestinal toxicity. The NOAEL for the combination is 0.0625 mg/kg oxycodone plus 5 mg/kg ibuprofen, based upon both the incidence of ocular hyperemia in the 0.125:10 mg/kg oxycodone:ibuprofen group and the initial observation of red material in the stool of one animal in that group. These doses correspond to 1.25 mg/m^2/day oxycodone and 100 mg/m^2/day ibuprofen in the dog model based upon body surface area, which provides a 0.1-fold safety margin versus the maximum proposed daily human dose of 20 mg oxycodone:1600 mg ibuprofen on a body surface area basis. The highest doses tested were 0.4 times the maximum proposed daily human dose on a body surface area basis.

The Division expressed concern to the sponsor regarding the increased incidence of fecal occult blood and the limited range of the dosing in the dog study. Following consultations with HFD-180, HFD-550 and Dr. Ken Hastings, Acting ODE II Associate Director of Pharmacology and Toxicology, it was decided that no further toxicology assessment of this combination would be needed.

However, the sponsor subsequently submitted a 28-day dog study that used the same maximum dose of ibuprofen but increased the ratio of oxycodone:ibuprofen from 1:80 to 1:40 by doubling the dose of oxycodone (0.0625:2.5, 0.125:5, 0.25:10, 0.5:20 mg/kg/day oxycodone:ibuprofen). The results of this study indicated that oral administration of oxycodone:ibuprofen (1:40) to dogs produced clinical signs of gastrointestinal irritation (loose/unformed stool and/or fecal occult blood) and changes in hematology consistent with mild blood loss. However, these changes were not correlated with either gross or microscopic histopathology in the gastrointestinal tract. GI effects were observed in females at doses greater than 0.25:10 mg/kg/day oxycodone:ibuprofen and 0.125:5 mg/kg/day oxycodone:ibuprofen in males. These doses are 0.4-fold and 0.2-fold greater than the maximum proposed daily human dose based upon body surface area for oxycodone and ibuprofen, respectively, in females, and 0.2-fold and 0.1-fold greater than the maximum proposed daily human dose based upon body surface area for oxycodone and ibuprofen, respectively. Chronic renal inflammation was noted in animals that received greater than or equal to 5 mg/kg/day ibuprofen which was consistent with the known effects of NSAIDs. This study, therefore, repeated the observations made in the previous dog study and also failed to test multiples of the human dose. The NOAEL identified in this study is 0.0625:2.5 mg/kg/day oxycodone:ibuprofen in males and 0.125:5 mg/kg/day oxycodone:ibuprofen in females based upon findings of fecal occult blood and chronic renal inflammation.

Interestingly, there does appears to be a slight increase in the GI toxicity of ibuprofen when the oxycodone dose was doubled to the (1:40 ratio) compared to (1:80), as measured by the presence of fecal occult blood (See table below). These data support the conclusion that oxycodone is enhancing the GI toxicity of ibuprofen.

Comparison of the Incidence of Observations Fecal Occult Blood (number of days observed) for 1:80 and 1:40 combinations of oxycodone:ibuprofen in dogs:

	Males (n=3)				Females (n=3)			
Dose (mg) → (Ibuprofen) **Parameter ↓**	0	5	10	20	0	5	10	20
Fecal Occult Blood:								
1:80 ratio[1]	1(1)[3]	0(0)	0(0)	3(21)	1(1)	1(1)	1(1)	3(41)
1:40 ratio[2]	0(0)	1(1)	2(3)	3(34)	1(1)	0(0)	0(0)	3(50)

[1]The doses of oxycodone employed were 0.0625:5, 0.125:10 and 0.25:20.

[2]The doses of oxycodone employed were 0.125:5, 0.25:10 and 0.5:20.

[3]The number of dogs affected is followed by the number of days observed in parenthesis.

Toxicology conclusions: Toxicities noted in the acute and repeat dose rat studies are consistent with the known effects of opioids and NSAIDs. The data from the repeat-dose dog studies provide clear evidence that at the highest doses tested, the combination of oxycodone:ibuprofen (1:80 or 1:40) produced greater incidence of unformed and/or liquid feces and incidence of fecal occult blood than ibuprofen alone in this species. However, there was no evidence of gross or histopathological changes in the gastrointestinal tract, suggesting a lack of tissue related toxicity. However, neither dog study reached the maximum tolerated dose and may not adequately predict the potential toxicity to humans. The addition of wording to the product label concerning the increased potential for GI toxicity should be considered.

Histopathology Inventory for NDA # 21-378

Study	90-9-3 (1 month, oral gavage)	90-10-4 (1 month, oral gavage)	6277-145 (1 month, capsule)
Species	Rat	Dog	Dog
Adrenals	X*	X*	X*
Aorta	X	X	X
Bone Marrow smear	X	X	
Bone (femur)	X		X
Brain	X*	X	X*
Cecum	X	X	X
Cervix	X		X
Colon	X	X	X
Duodenum	X	X	X
Epididymis	X	X	X
Esophagus	X	X	X
Eye	X	X	X
Fallopian tube			
Gall bladder			X
Gross lesions	X		X
Harderian gland			
Heart	X	X	X*
Ileum		X	X
Injection site			
Jejunum	X	X	X
Kidneys	X*	X*	X*
Lachrymal gland	X	X	X
Larynx			
Liver	X*	X*	X*
Lungs	X	X	X
Lymph nodes, cervical			
Lymph nodes mandibular	X	X	X
Lymph nodes, mesenteric	X	X	X
Mammary Gland	X	X	X
Nasal cavity			
Optic nerves			X
Ovaries	X	X	X*
Pancreas		X	X
Parathyroid	X	X	X
Peripheral nerve			

Pharynx			
Pituitary	X	X	X
Prostate		X	X
Rectum			X
Salivary gland	X	X	X
Sciatic nerve	X	X	X
Seminal vesicles	X		
Skeletal muscle	X	X	X
Skin	X	X	X
Spinal cord	X	X	X
Spleen	X*	X*	X*
Sternum		X	X
Stomach		X	X
Testes	X*	X*	X*
Thymus	X	X	X
Thyroid	X	X	X
Tongue		X	X
Trachea	X	X	X
Urinary bladder	X		X
Uterus	X	X	X
Vagina	X	X	X
Zymbal gland			
Standard List			

X, histopathology performed
*, organ weight obtained

V. GENETIC TOXICOLOGY:

Oxycodone: There were no genetic toxicology studies submitted by the sponsor in support of this NDA. There is no publicly available mutagenicity data conducted under the referenced NDA (21-011). This is reflected in the current label for Roxicodone™ which does not address mutagenicity. The lack of mutagenicity data in the referenced NDA 21-011 has not been addressed by the sponsor. In contrast, the sponsor has proposed labeling based upon the information presented in the label for Oxycontin (NDA 20-553).

The Division has had numerous discussions with the sponsor regarding the requirements for mutagenicity testing. Under a 505(b)(2) application, the sponsor may refer to a product that has adequate information regarding the genotoxic potential of oxycodone or perform the recommended genotoxicity battery as a phase 4 commitment.

Ibuprofen: The sponsor provided literature references in support of the NDA. Oldham et al. examined the mutagenic potential of ibuprofen in the Ames bacterial reverse mutation assay[5]. This group tested ibuprofen at concentrations of 1, 10, 100, 500, 750 and 1000 µg/plate. Bacterial toxicity and microscopic precipitation was noted at concentrations ≥ 750 µg/plate. The results of the study indicated that ibuprofen did not increase the number of revertant colonies in strains TA98, TA100, TA1535, TA 1537 or TA1538. Acceptable positive controls (without metabolic activation) were employed for strains TA1537 (9-aminoacridine) and TA100/TA1535 (sodium azide). However, the positive control for TA98 (dexon CAS 140-56-7) is not listed in the OECD guideline. The positive control in the presence of metabolic activation was 2-anthramine (a.k.a. 2-aminoantracene) is not recommended as the sole indicator of the efficacy of the S9 mix. This reference does not indicate if the S9 batches were characterized with a mutagen that requires metabolic activation. However, the positive controls used in this study did lead to a significant increase in the revertant colonies.

The second published report on the potential mutagenicity of ibuprofen was provided by Philipose et al. (1997)[6]. This group tested the effects of ibuprofen (1, 10, 100, 1000 or 5000 µg/plate) in the Ames mutagenicity assay using strains TA97a, TA100 and TA102. Ibuprofen at 5000 µg/plate was toxic to the bacteria. Ibuprofen produced a significant increase in the number of revertant colonies of TA97a and TA100 (-S9) at the 1 and 10 µg/plate concentration and TA97a (+S9) at 1, 10 and 100 µg/plate, however, higher concentrations did not and the finding did not repeat in the replicate study. The concentration of 5000 µg/plate was toxic to the bacteria. There was no significant effect of ibuprofen in strain TA102 with or without metabolic activation, however, a positive control for the metabolic activation for this strain was not available for testing. The positive control for strain TA102 (-S9) was methylmethane sulfonate (MMS). MMS, although not listed in the OECD guidance, was acceptable for the WP2 uvrA strain according to Dr. Michael Prival of the Genetic Toxicology Subcommittee of the PTCC. As such, this drug should also be acceptable for the TA102 strain. The positive control for TA97a (-S9) was 4-nitro-o-phenylendiamine (NPD CAS 99-56-9) is also not listed as a positive control in the OECD guidance. The positive control in the presence of S9 was 2-aminofluorene (CAS 153-78-6) is also not listed in the OECD guidelines as an acceptable positive control. However, these compounds clearly increased the number of reverse mutations in the study and therefore should be acceptable.

Overall, these two studies tested ibuprofen in the Ames *Salmonella* assay using strains TA97a, TA98, TA100, TA102, TA1535, TA1537 and TA1538 in the presence or absence of metabolic activation with S9. These strains fulfill the recommendations put forth by OECD for a valid assay.

Philipose et al. also tested ibuprofen in an *in vivo* mammalian bone marrow chromosomal aberration test. For this study, male Swiss albino mice were treated with ibuprofen at 25, 50 and 100 mg/kg, i.p. A second study tested a single dose (270 mg/kg) administered by gavage. The results indicated that ibuprofen tested positive in the *in vivo* mammalian bone marrow

[5] Oldham, J.W., Preston, R.F. and Paulson, J.D. 1986. Mutagenicity testing of selected analgesics in Ames *Salmonella* strains. Journal of Applied Toxicology 6(4):237-243.

[6] Philipose, B., Singh, R., Khan, K.A. and Giri, A.K. 1997. Comparative mutagenic and genotoxic effects of three proprionic acid derivatives ibuprofen, ketoprofen and naproxen. Mutation Research 393:123-131.

chromosomal aberration test, suggesting a clastogenic response. In contrast to the study in rat bone marrow, Kullich and Klein failed to detect any evidence for *in vivo* clastogenicity in human lymphocytes[7].

Genetic toxicology summary:

There are no published reports examining the potential genetic toxicology of oxycodone. The labeling for Oxycontin reads as follows:

> Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

The sponsor should be informed that the referenced compound Roxicodone does not provide the standard mutagenicity data. From a regulatory standpoint, the sponsor should consider referencing the Agency's findings of safety and efficacy on a different product or conduct the standard genotox battery for oxycodone.

Ibuprofen was not mutagenic in the Ames bacterial reverse mutation assay, however, positive genotoxic findings were obtained in the *in vivo* mouse bone marrow chromosomal aberrations test. There are no reports describing the potential for *in vitro* mammalian chromosomal aberrations or mutagenicity.

Genetic toxicology conclusions: The published literature indicates that ibuprofen tested negative in the Ames Bacterial Reverse Mutation Assay and an *in vivo* assay with human lymphocytes, but was positive in an *in vivo* mouse assay.

Although the sponsor has reference Roxycodone for this NDA, they are basing their label on genetic toxicology data provided in the Oxycontin label. The sponsor should either conduct the standard genetic toxicology battery or list a reference drug for this NDA application that has adequate information concerning the genotoxic potential of oxycodone.

Labeling recommendations: Sponsor's proposed labeling:

[7] Kullich, W. and Klein, G. 1986. Investigations of the influence of nonsteroidal antirheumatic drugs on the rates of sister-chromatid exchange. Mutation Research 174(2):131-134.

The labeling concerning the genotoxic potential of ibuprofen should include the information described from the literature. Information for oxycodone should come from studies performed by the sponsor or from a referenced drug for which the standard genotoxicity data is available. A formal review of the product label will be conducted at a later time.

VI. CARCINOGENICITY:

Carcinogenicity summary:

Carcinogenicity studies for oxycodone or ibuprofen were not submitted in support of this NDA. The sponsor indicated that the combination oxycodone:ibuprofen is intended for short-term use only. ICH Guideline S1A (Guideline on the Need for Carcinogenicity studies of Pharmaceuticals) indicates that "Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months (See Note 1)." Note 1 indicates that "It is expected that most pharmaceuticals indicated for 3 months treatment would also likely be used for 6 months." The proposed indication reads: "BRANDNAME tablet is indicated for the :

Carcinogenicity testing of ibuprofen has been reported in the literature[8]. These investigators describe results of an 80-week oral carcinogenicity assessment in the mouse and a 104-week oral carcinogenicity assessment in the rat. Mice were administered a total 300 mg/kg ibuprofen daily for a total of 43 weeks. Due to high mortality from intestinal ulceration and perforation in the males, the dose was reduced to 100 mg/kg daily for the remainder of the 80-week study. The incidence of tumors in the surviving animals in the mouse study is shown in the table below.

TABLE V

TUMOUR INCIDENCE IN MICE ON IBUPROFEN FOR LONGER THAN 43 WEEKS

	Males		Females	
	Control	Dosed	Control	Dosed
Mice examined/Mice with tumours	43/35	29/21	40/34	40/26
Types of tumour:				
Hepatomas	12	5	5	5
Liver haemangiomas	1	1	1	1
Lymphomas	13	14	22	19
Breast adenocarcinomas	0	0	9	1
Others (benign)	16	9	12	15

There were no significant differences in tumor incidence for any tumor type.

In the rat study, animals were dosed with 180 mg/kg ibuprofen daily for 56 weeks. Due to a high incidence of mortality in both sexes, the dose was reduced to 60 mg/kg daily for the remainder of the two year study. The results are presented in the table below:

TABLE VII

TUMOUR INCIDENCE IN RATS ON IBUPROFEN FOR LONGER THAN 56 WEEKS

	Males		Females	
	Control	Dosed	Control	Dosed
Rats examined/Rats with tumours	30/13	22/4	30/16	21/12
Types of tumour:				
Hepatomas	1	0	0	2
Liver haemangiomas	0	1	0	0
Lymphomas	5	1	2	3
Others (malignant)	3	1	5	1
Others (benign)	8	2	20	11

The results of these two studies indicate that ibuprofen did not induce tumors in either rats or mice under the conditions tested. Of note, however, the duration of the studies is not adequate under current standards.

Carcinogenicity conclusions:

There is currently no adequate information concerning the carcinogenic potential of oxycodone or ibuprofen. Regardless of the intended indication, this drug product will likely be used on a chronic basis. The Division informed the sponsor that carcinogenicity studies could be completed as a phase 4 commitment if the drug was demonstrated to be used either intermittently or continuously for 6 months or more (See teleconference minutes of 7/26/2001). Alternatively, the sponsor could refer to publicly available data if it is available at that time.

Recommendations for further analysis: As indicated to the sponsor during the July 26, 2001 teleconference, the Division indicated that "While the proposed indication is for treatment of acute pain (treatment not to exceed 7 days), if post-marketing surveillance shows that the product is being used chronically, assessment of carcinogenic potential will be required." These studies, therefore, could be completed as part of a phase 4 commitment.

Labeling Recommendations:

Sponsor's proposed labeling:

[8] Adams, S.S., Bough, R.G., Cliffe, E.E., Dickinson, W., Lessel, B., McCullough, K.F., Mills, R.F.N., Nicholson, J.S., Williams, G.A.H. 1970. Some aspects of the pharmacology, metabolism, and toxicology of ibuprofen. Rheumatol Phys Med. 10(Suppl 10):9-26.

A formal review of the product label will be conducted at a later time.

Addendum/appendix listing: N/A

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Study title: Pilot Teratogenicity Study of DuP 604 in Rats

Key study findings: This is a pilot study to determine the maximum tolerated dose (MTD) of oxycodone:ibuprofen to use in the definitive Segment II reproductive toxicology study in rats. Based upon the findings in this study the maximum tolerated dose was 2:160 mg of DuP 604 (oxycodone:ibuprofen). Findings in dams included mortality at the two highest doses, reduced body weight gain and reduced food consumption at all doses.

Study no.: 90-9-10
Volume #, and page #: Volume 12, Page 1
Conducting laboratory and location: E.I. du Pont de Nemours and Company
Newark, DE
Date of study initiation: October 5, 1990
GLP compliance: No
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxycodone HCl, Lot No. RM90-033, 96.7%
Ibuprofen, Lot No. 90PH-798, — , purity.
Formulation/vehicle: 0.5% methylcellulose solution.

Methods:

Species/strain: — CD BR rats
Doses employed: 0, 1.5:120, 2:160, 2.5:200, 3:240 mg/kg/day oxycodone:ibuprofen
Route of administration: Oral gavage.
Study design: Animals were dosed on days 7-16 of gestation, with day 1G being the day that copulation was confirmed.
Number/sex/group: 7 female rats/group as follows:

Group	Test Formulation	Daily Dose (mg/kg)		Mated Females
		Oxycodone	Ibuprofen	
1	Vehicle	0	0	7
2	DuP 604	1.5	120	7
3	DuP 604	2.0	160	7
4	DuP 604	2.5	200	7
5	DuP 604	3.0	240	7

Parameters and endpoints evaluated: body weight, clinical signs, food consumption, gross pathology, number and relative position of nidations (life or dead fetuses, early or late resorptions). Collected the incidence of pregnancy and the number of females with total resorptions. Live fetuses were weighed and examined for external alterations.

Results:

Mortality: One female in group 4 (2.5:200 oxy:ibu) was found dead on Day 13. A total of 6 females in group 5 (3:240 oxy:ibu) were found dead during the course of the study. Five of those females died between days 11 and 15 and one died post-dosing on day 18.

Clinical signs: Clinical observations included severe alopecia at doses of 2:160. 2.5:200, and 3.0:240 mg/kg oxycodone:ibuprofen. At the two highest doses, clinical signs included weakness, extreme staining and wetting of facial and underbody regions, and hunched posture.

Body weight: A significant decrease in body weight was noted with all doses during the first few days of treatment (days 7-9) and for the dose combination of 2:160 mg/kg/day oxy:ibu and above for the entire dosing period (Days 7-17). As indicated in the sponsor's table below, the dams lost 17-24 grams from days 7-9. The high dose combination lost a mean of 62.3 grams of body weight during the treatment period.

TABLE 1

MEAN MATERNAL BODY WEIGHT CHANGES[a,b]

GROUP	DAILY DOSE (MG/KG)[c]	N[d]	DAYS OF GESTATION 1-7	7-9†	9-11	11-13†	13-15†	15-17†	7-17†	17-22†
I	0	7	29.9	7.0	11.3	8.9	8.3	19.6	55.1	87.9
II	1.50:120	5	38.2	-17.6*	5.0	5.9	11.8	18.1	23.2	110.7
III	2.00:160	6	31.5	-14.3*	-3.2	0.0	-0.5	3.1	-14.9*	100.9
IV	2.50:200	5	35.6	-23.3*	2.7	-0.8	-7.1	-0.1*	-28.6*	81.6
V	3.00:240	1	22.7	-19.9*	-9.8	-14.0	-0.5	-18.1*	-62.3*	56.4

[a] Data from females that were not pregnant or that died before scheduled sacrifice were excluded. Individual body weight changes and body weights with standard deviations and standard errors are presented in Appendices C and D, respectively.
[b] Grams.
[c] Ratio of oxycodone HCl:ibuprofen.
[d] Number of values used to determine the means.
† Significant trend ($p \leq 0.05$) across groups by linear combination of dose ranks from ANOVA.
* Significantly different ($p \leq 0.05$) from control values by Dunnett's test.

Food consumption: A significant reduction in food consumption (8-13 grams/dam/day) was noted for all experimental groups treated with 2:160 mg/kg oxy:ibu and above over

the course of the treatment period. A breakdown of the changes in mean maternal food consumption is presented by the sponsor's table below:

MEAN MATERNAL FEED CONSUMPTION[a,b]

GROUP	DAILY DOSE (MG/KG)[c]	N[d]	DAYS OF GESTATION 1-7	7-9†	9-11†	11-13†	13-15†	15-17†	7-17†	17-22
I	0	7	24.4	24.2	25.0	25.7	26.1	26.0	25.4	28.0
II	1.50:120	5	25.3	15.7	16.7	18.1	23.4	22.6	19.3	30.8
III	2.00:160	6*	24.5	14.7*	11.6	13.2*	13.5*	10.3*	12.7*	24.3
IV	2.50:200	5	26.6	15.5	13.9	14.1	10.7*	9.4*	12.7*	25.4
V	3.00:240	1	21.9	9.0*	8.5*	6.0*	7.7*	8.3*	7.9*	22.3

[a] Data from females that were not pregnant or that died before scheduled sacrifice were excluded. Individual feed consumed with standard deviations and standard errors are presented in Appendix E.
[b] Grams/dam/day.
[c] Ratio of oxycodone HCl:ibuprofen.
[d] Number of values used to determine the means.
* The N value for interval 17-22G is 5 due to the exclusion of an inaccurate feed measurement.
† Significant trend ($p \leq 0.05$) across groups by linear combination of dose ranks from ANOVA.
* Significantly different ($p \leq 0.05$) from control values by Dunnett's test.

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Terminal and necroscopic evaluations:

Dams:

Of the animals found dead prior to the day 22 sacrifice, 3 of the 6 animals in the 3:240 mg/kg oxycodone:ibuprofen group demonstrated stomach ulcerations. Two or more ulcerations were noted per animal and each was approximately 1 mm in diameter. Distention of the stomach and in one case the intestine was noted in the remaining animals that died prior to day 22.

Offspring: There was a significant increase (16%) in the number of live fetuses in the 2:160 mg/kg oxycodone:ibuprofen treatment group compared to controls. Although no fetus was considered to be stunted, there was a significant downward trend in body weight. Body weight of male offspring in the 1.5:120 and 2:160 mg/kg treatment groups were significantly different than controls (decreased by 2 and 11%, respectively). Non-significant decreases in body weight were also evidence in combined fetal weights for 2:160, 2.5:200 and 3:240 mg/kg animals (9, 12 and 7%, respectively). External examination of the fetuses revealed no developmental alterations. These changes are summarized in the sponsor's table below:

PILOT TERATOGENICITY STUDY OF DUP 604 IN RATS

TABLE 4

REPRODUCTIVE OUTCOME[a]

		GROUP:	I	II	III	IV	V
		DAILY DOSE (HG/KG)[b]:	0	1.50:120	2.00:160	2.50:200	3.00:240
No. Mated			7	7	7	7	7
No. Pregnant			7	5	6	6	7
No. Deaths†			0	0	0	1	6*
No. Females With Total Resorptions			0	0	0	0	0
No. Litters			7	5	6	5	1
Means Per Litter							
Live Fetuses:	Total		15.3	17.2	17.7*	14.4	3.0
	Males		7.4	8.6	8.3	7.0	1.0
	Females		7.9	8.6	9.3	7.4	2.0
Dead Fetuses			0.0	0.0	0.0	0.0	0.0
Resorptions[c]:	Total		1.0	0.8	0.5	2.2	1.0
	Early		1.0	0.4	0.5	2.0	1.0
	Late		0.0	0.4	0.0	0.2	0.0
Nidations			16.3	18.0	18.2	16.6	4.0
Mean Fetal Weight[d]:	Total†		5.14	5.15	4.67	4.55	4.79
	Males†		5.34	5.23*	4.76*	4.65	5.83
	Females†		4.97	5.08	4.60	4.54	4.27
No. Stunted Fetuses			0	0	0	0	0

[a] Individual data with standard deviations and standard errors can be found in Appendix H. Individual fetal weights can be found in Appendix J.
[b] Ratio of oxycodone HCl:ibuprofen
[c] Early Resorption - Nidation comprised of placental tissue and no visible sign of fetal structure.
Late Resorption - Nidation containing fetal tissue with clearly identifiable fetal structures.
[d] Grams
† Significant trend ($p \leq 0.05$) across groups by Jonckheere's test.
* Significantly different ($p \leq 0.05$) from control values by the Mann-Whitney U test.

Summary of individual study findings: Maternal toxicity, as demonstrated by significant body weight loss, was evident at the lowest dose tested 1.5:120 mg/kg oxycodone/ibuprofen and above. Reduced food consumption and increased clinical sign incidence were noted at higher doses. Mortality was noted in 5 out of 6 animals in the 3:240 mg/kg groups and 1/6 animal in the 2.5:200 mg groups. The MTD was determined to be 2:160 mg/kg of DuP 604. A NOAEL for maternal toxicity was not established. Only limited fetal evaluations were completed, therefore no statements regarding developmental toxicity can be made based on the pilot study.

Study title: Teratogenicity Study of DuP 604 in Rats

Key study findings: DuP-604 (oxycodone:ibuprofen) was not teratogenic in the rat model under the conditions tested. The study demonstrated maternal toxicity with DuP-604 at dose levels of 0.5:40 and above. Maternal toxicity was characterized by alopecia, pallor, facial and peri-anal staining and scabs associated with areas of severe alopecia. Maternal mortality at the high dose was observed. One upper mid dose and 3 high dose dams delivered litters early. The NOAEL for the dams was 0.25:20 mg/kg DuP 604. Under the conditions employed, DuP 604 did not increase the incidence of fetal malformations or variations. The NOAEL for developmental toxicity was 2:160 mg/kg, the maximum dose tested.

Study no.: 90-9-11
Volume #, and page #: Volume 12, Page 70
Conducting laboratory and location: E.I. du Pont de Nemours and Company
Newark, DE
Date of study initiation: January 7, 1991
GLP compliance: Yes
QA reports: Yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Oxycodone HCl, Lot R90-033, [redacted] purity.
Ibuprofen, Lot 90PH-798, [redacted] purity.
Formulation/vehicle: 0.5% w/v methyl cellulose in deionized water

Methods: Both drugs were administered as separate formulations.

Species/strain: Female [redacted].CD BR rats (63 days old)
Doses employed: Dose ratio of 1:80 as indicated in table below.
Route of administration: Oral gavage
Study design: Drug was administered daily by oral gavage on days 7-16 of gestation. Dosing volume was 10 ml/kg.
Number/sex/group: 25 female rats/group as follows:

Group	Test Formulation	Daily Dose (mg/kg)		Mated Females
		Oxycodone	Ibuprofen	
1	Vehicle	0	0	25
2	DuP 604	0.25	20	25

3	DuP 604	0.5	40	25
4	DuP 604	1.0	80	25
5	DuP 604	2.0	160	25

Parameters and endpoints evaluated: Body weights and clinical signs, morbidity and mortality and food consumption. Following sacrifice, females were examined for gross pathological changes. Live fetuses were weighed, sexed and examined for external alterations. Visceral and skeletal alterations were examined post-mortem.

Results:

In-life observations:

Mortality: Two females in the 2:160 group died (1 of day 13, other on day 14). A third female from the same group was sacrificed on day 14 due to poor health. These deaths were attributed to the administration of the drug. A 0.25:20 animal was sacrificed early due to gavage trauma.

Clinical signs: Clinical observations are summarized by the sponsor's table below:

CLINICAL OBSERVATIONS[a]

DAY OF GESTATION	OBSERVATION	GROUP : I	II	III	IV	V
	DAILY DOSAGE (MG/KG)[b]:	0	0.25:20	0.50:40	1.00:80	2.00:160
1-6	NO. EXAMINED	25	25	25	25	25
	NO. AFFECTED	1	2	3	2	2
	ALOPECIA	0	1	3	1	2
	SCAB	0	2	0	0	0
	SORE	1	0	0	0	0
7-16	NO. EXAMINED	25	25[c]	25	25	25[d]
	NO. AFFECTED†	1	5	9*	9*	19*
	ABNORMAL GAIT	0	1	0	0	0
	ALOPECIA	1	5	8*	7*	11*
	DISCHARGE VAGINAL OPENING	0	0	1	1	3
	HUNCHED OVER	0	0	0	0	3
	LETHARGY	0	0	0	0	3
	MASS (GAVAGE TRAUMA)	0	1	0	0	0
	PALLOR	0	0	0	0	7*
	RUFFLED FUR	0	0	0	0	2
	SCAB	0	1	1	0	5*
	STAIN FACE	0	0	0	0	1
	STAIN PAW(S)	0	0	0	0	1
	STAIN PERINASAL AREA	0	1	2	0	10*
	STAIN PERINEUM	0	0	0	0	4
	STAIN PERIOCULAR AREA	0	0	0	0	1
	WEAK	0	0	0	0	3
	WET PERINEUM	0	0	0	0	4
17-22	NO. EXAMINED	25	24	25	25	22
	NO. AFFECTED†	2	3	8*	8*	12*
	ALOPECIA	1	3	9*	7*	10*
	DISCHARGE VAGINAL OPENING	0	1	0	1	1
	PALLOR	0	0	0	0	2
	RUFFLED FUR	0	0	0	0	1
	SCAB	0	0	1	0	2
	STAIN PERINASAL AREA	1	0	0	0	1
	STAIN PERINEUM	0	0	0	0	2
	STAIN PERIOCULAR	1	0	0	0	0
	SWOLLEN PAW(S)	1	0	0	0	0

FOOTNOTES:

[a] Individual observations are shown in Appendix F.
[b] Ratio of oxycodone HCl:ibuprofen.
[c] One animal was sacrificed in extremis during observation period. For statistical purposes the number examined was 25.
[d] Two animals were found dead and one animal was sacrificed in extremis during observation period. For statistical purposes the number examined was 25.
† Significant trend ($p \leq 0.05$) across groups by Cochran-Armitage test.
* Significantly different ($p \leq 0.05$) from control values by Fisher's Exact test.

As indicated in the table, a significant number of dams presenting with alopecia was observed following the administration of 0.5:40 mg/kg oxycodone:ibuprofen and above. A significant number of dams treated with the high dose (2 mg:160 mg/kg) oxycodone:ibuprofen presented with pallor, scabs and peri-nasal staining during the treatment period.

Body weight: Dams in treatment groups III-V demonstrated significantly reduced in body weight gain compared to control animals. Decreases in body weight were noted in animals treated with 0.5:40, 1:80 and 2:160 mg/kg oxycodone:ibuprofen on the initial days (7-9) of drug treatment. During the dosing period, maternal body weight gain was reduced by 13%, 21% and 77% in the low mid-dose, high mid-dose and high-dose groups, respectively, compared to control values. A summary of the body weight changes are presented in the sponsor's table below:

MEAN MATERNAL BODY WEIGHT CHANGES[a,b]

GROUP	DAILY DOSAGE (MG/KG)[c]	N[d]	DAYS OF GESTATION 1-7	7-9†	9-11†	11-13†	13-15	15-17	7-17†	17-22†
I	0	23	41.0	7.8	10.7	13.1	8.1	17.7	57.3	88.5
II	0.25:20	22	40.3	5.3	10.6	12.0	11.0	18.6	57.4	87.8
III	0.50:40	22	36.5	1.9*	11.1	7.9	8.6	20.7	50.3	93.7
IV	1.00:80	21	39.0	-1.1*	9.9	7.1*	9.1	20.0	45.1*	91.9
V	2.00:160	19	39.6	-17.6*	-3.5*	8.6	7.4	18.7	13.7*	105.3*

[a] Data from females that were not pregnant, delivered early, were sacrificed in extremis or died prior to scheduled sacrifice were excluded. Individual body weight changes and body weights with standard deviations and standard errors are presented in Appendices C and D, respectively.
[b] Grams.
[c] Ratio of oxycodone HCl:ibuprofen.
[d] Number of values used to determine the means.
† Significant trend ($p \leq 0.05$) across groups by linear combination of dose ranks from ANOVA.
* Significantly different ($p \leq 0.05$) from control values by Dunnett's test.

Food consumption: Reductions in food consumption were noted at the beginning of the dosing schedule (Day 7 to 9) in animals treated with 0.5:40 and above. Overall, during the course of the treatment period, dams in the two highest dose groups consumed significantly less food than control animals (9 and 34%, respectively). The table below summarizes the maternal food consumption.

MEAN MATERNAL FEED CONSUMPTION[a,b]

GROUP	DAILY DOSAGE (HG/KG)[c]	N[d]	DAYS OF GESTATION 1-7	7-9†	9-11†	11-13†	13-15†	15-17†	7-17†	17-22
I	0	23	25.4	24.8	25.0	26.3	26.0	27.0	25.8	29.5
II	0.25:20	22	25.5	24.9	26.4	26.5	26.8	28.2	26.5	29.4
III	0.50:40	22	24.9	22.7	24.0	24.5	23.7	26.7	24.3	29.4
IV	1.00:80	21	25.3	21.6*	23.0	23.7	23.8*	25.9	23.6*	30.2
V	2.00:160	19	25.0	14.5*	13.4*	17.0*	18.8*	21.8	17.1*	30.1*

[a] Data from females that were not pregnant, delivered early, were sacrificed *in extremis* or died prior to scheduled sacrifice were excluded. Individual feed consumed with standard deviations and standard errors are presented in Appendix E.
[b] Grams/dam/day.
[c] Ratio of oxycodone HCl:ibuprofen.
[d] Number of values used to determine the means.
[e] The N value was 18 due to a missed feed measurement.
† Significant trend ($p \leq 0.05$) across groups by linear combination of dose ranks from ANOVA.
* Significantly different ($p \leq 0.05$) from control values by Dunnett's test.

Terminal and necroscopic evaluations:

Dams: There was a significant decrease (17%) in the number of litters in the high dose treatment group (2:160 mg/kg oxycodone:ibuprofen). In addition, one dam treated with 1:80 mg/kg oxycodone:ibuprofen delivered her litter early and 3 of 25 dams in the high dose group (2:160 mg/kg oxycodone:ibuprofen) delivered their litters early. There were 3 early deaths in the high dose group, all of which were attributed to the drug treatment. The dams that died early showed signs of deteriorating condition (allopecia and staining of the fur).

Group (N=25/ group)	Treatment (mg/kg/day)		Post-Mortem Findings
	oxycodone	ibuprofen	
I	0	0	None
II	0.25	20	None
III	0.5	40	None
IV	1	80	1 Dam delivered litter early.
V	2	160	3 early deaths (1 in sacrificed *in extremis*) All animals that died demonstrated signs of deteriorating conditions (allopecia and staining). One animal demonstrated two ulceration sites in the stomach. 3 surviving dams delivered litter early.

Offspring: As indicated in the sponsor's table below, there were no significant differences in mean fetal body weights or the number of stunted fetuses. In addition,

there was no significant increases in the incidence of malformed fetuses (external, visceral or skeletal) or incidences of fetal variations. A summary of the reproductive effects is presented in the sponsor's table below:

REPRODUCTIVE OUTCOME[a]

GROUP:		I	II	III	IV	V
DAILY DOSAGE (MG/KG)[b]:		0	0.25:20	0.50:40	1.00:80	2.00:160
No. Mated		25	25	25	25	25
No. Pregnant		23	22	22	22	24
No. Early Deliveries†		0	0	0	1	3
No. Deaths†		0	1[c]	0	0	3
No. With Total Resorptions		0	0	0	0	0
No. Litters†		23	22	22	21	19*
Means Per Litter						
Live Fetuses:	Total	15.7	15.3	15.4	14.8	16.5
	Males	8.4	8.0	8.4	7.4	7.8
	Females	7.3	7.3	7.0	7.4	8.7
Dead Fetuses		0.0	0.0	0.0	0.0	0.0
Resorptions:[d]	Total	1.1	0.9	0.9	1.0	0.9
	Early	1.0	0.8	0.9	1.0	0.8
	Late	0.1	0.0	0.0	0.0	0.1
Nidations		16.8	16.2	16.3	15.8	17.4
Mean Corpora Lutea		18.5	18.0	17.2	18.1	18.6
Mean Fetal Weight:[e]	Total	5.25	5.27	5.37	5.33	5.21
	Males	5.38	5.40	5.51	5.47	5.41
	Females	5.12	5.12	5.23	5.17	5.04
No. Stunted Fetuses		2	1	2	0	0

[a] Individual data with standard deviations and standard errors are presented in Appendix H; individual fetal weights are present in Appendix J.
[b] Ratio of oxycodone HCl:ibuprofen.
[c] Death due to gavage trauma.
[d] Early Resorption - Nidation comprised of placental tissue and no visible signs of fetal structures.
Late Resorption - Nidation containing fetal tissue with clearly identifiable fetal structures.
[e] Grams. Weights of stunted fetuses were excluded from calculation of means.
† Significant trend ($p \leq 0.05$) across groups by Cochran-Armitage test.
* Significantly different ($p \leq 0.05$) from control values by Fisher's exact test.

Summary of individual study findings: The study demonstrated maternal toxicity at dose levels of 0.5:40 and above. Maternal toxicity was characterized by alopecia, pallor, facial and peri-anal staining and scabs associated with areas of severe alopecia. The DuP 604-related material mortality at the high dose was not surprising based upon the preliminary dose-range finding study in this species. One upper mid dose dam and 3 high dose dams delivered litters early. The NOAEL for maternal toxicity was 0.25:20 mg/kg DuP 604, based upon alopecia and decreased weight gain in the 0.5:40 mg/kg oxycodone:ibuprofen treatment group. Under the conditions employed, DuP 604 did not increase the incidence of fetal malformations or

variations. Therefore, the NOAEL for developmental toxicity is 2:160 mg/kg, the maximum dose tested.

Study title: Pilot Teratogenicity Study of DuP 604 in Rabbits

Key study findings: Maternal administration of DuP 604 up to doses of 1.5:120 mg/kg oxycodone:ibuprofen to female rabbits during gestation days 7-19 produced no clear evidence of a maximum tolerated dose. Although no evidence of reproductive toxicity was noted in the limited fetal observations conducted in this study, no conclusions can be made regarding the potential developmental toxicity of DuP 604.

Study no.: 90-10-16
Volume #, and page #: Volume 13, Page 1
Conducting laboratory and location: E.I. du Pont de Nemours and Company Newark, DE
Date of study initiation: October 22, 1990
GLP compliance: Not indicated
QA reports: yes ( ) no (X)
Drug, lot #, radiolabel, and % purity: Both drugs were administered as separate formulations. Oxycodone HCl, Lot R90-033. ~ purity. Ibuprofen, Lot 90PH-798. ~ purity.
Formulation/vehicle: 0.5% w/v methylcellulose in deionized water

Methods:

Species/strain: Female ~ (New Zealand White) SPF rabbits
Doses employed: Dose ratio of 1:80 as indicated in table below.
Route of administration: Oral gavage
Study design: Drug was administered daily by oral gavage on days 7-19 of gestation. Dosing volume was 2 ml/kg.
Number/sex/group: 7-8 female rats/group as follows:

Group	Test Formulation	Daily Dose (mg/kg)		Mated Females
		Oxycodone	Ibuprofen	
1	Vehicle	0	0	7
2	DuP 604	0.38	30	8
3	DuP 604	0.75	60	8
4	DuP 604	1.13	90	8
5	DuP 604	1.50	120	8

Parameters and endpoints evaluated: Body weights and clinical signs, morbidity and mortality and food consumption. Following sacrifice, females were examined for gross pathological changes. The number location and condition of fetuses were recorded. Fetuses were examined for external alterations.

Results:

In-life observations:

Mortality: None
Clinical signs: There were no significant differences detected among treatment groups.
Body weight: No significant differences in body weight gain for dosing (days 7-19) or post-dosing (days 20-22) were noted.
Food consumption: There were no significant differences in food consumption during the pre- or post-dosing period. A slight (<1%), but significant increase in food consumption was detected for the overall administration period (Day 7-20) for the 0.38:30 mg/kg group. This change is thought to be due to the inadvertent availability of food greater than the targeted restrictive diet of 150 g. Therefore this change was not deemed to be drug-related. There was a significant downward trend across groups toward decreased food consumption over days 16-20 and across the entire dosing periods (days 7-20). The largest magnitude of change in food consumption occurred in the high dose group on days 16-20 at only 6%.

MEAN MATERNAL FEED CONSUMPTION[a,b]

GROUP	DAILY DOSAGE (MG/KG)[c]	N[d]	DAYS OF GESTATION 0-7	7-10	10-13	13-16	16-20†	7-20†	20-22
I	0	6	148.9	149.1	148.0	150.7	150.7	149.7	147.0
II	0.38:30	4	148.8	150.6	150.4	150.3	151.3	150.7*	151.4
III	0.75:60	5	148.8	150.2	150.2	150.5	150.7	150.4	149.5
IV	1.13:90	6	148.6	150.6	149.7	150.2	149.8	150.1	149.4
V	1.50:120	6	149.8	142.1	140.4	150.3	141.1	143.3	146.9

[a] Data from females that were not pregnant were excluded. Individual feed consumed with standard deviations and standard errors are presented in Appendix E.

[b] Grams/dam/day.

[c] Ratio of oxycodone HCl:ibuprofen.

[d] Number of values used to determine the means.

† Significant trend ($p \leq 0.05$) across groups by linear combination of dose ranks from ANOVA when analysis is conducted on the ranks of the values.

* Significantly different ($p \leq 0.05$) from control values by Dunnett's test when analysis is conducted on the ranks of the values.

Terminal and necroscopic evaluations:

Dams: Ulceration of the stomach of one of the upper mid dose dams (1.13:90 mg/kg) was noted upon necropsy. The size of the ulcer was 3 mm in diameter. This was possibly due to the drug administration, however, no ulcerations were noted at the

higher dose. There was a significant increase in the number of live fetuses and nidations at the 0.75:60 and the 1.5:120 mg/kg levels.

Offspring: A significant reduction (13%) in fetal body weight was noted at the 0.75:60 mg/kg dose group. However, the control mean fetal body weight in this study was described as abnormally high and therefore the sponsor does not feel that this changes is biologically significant. This decrease may also be related to the significant increase in the number of live fetuses. Therefore, given the lack of a dose-dependent response in body weight, this reviewer concurs with this assessment. There were no developmental alterations detected in any of the treatment groups during external observations.

REPRODUCTIVE OUTCOME[a]

GROUP:		I	II	III	IV	V
DAILY DOSAGE (HG/KG)[b]:		0	0.38:30	0.75:60	1.13:90	1.50:120
No. Inseminated		7	8	8	8	8
No. Pregnant		6	4	5	6	6
No. Aborted		0	0	0	0	0
No. Deaths		0	0	0	0	0
No. Females with Total Resorptions		0	0	0	0	0
No. Litters		6	4	5	6	6
Means Per Litter						
Live Fetuses:†		3.2	4.8	7.0*	5.5	6.7*
Dead Fetuses		0.0	0.0	0.0	0.0	0.0
Resorptions:[c]	Total	0.5	0.3	0.4	0.3	0.2
	Early	0.5	0.3	0.4	0.3	0.0
	Late	0.0	0.0	0.0	0.0	0.2
Nidations†		3.7	5.0	7.4*	5.8	6.8*
Mean Fetal Weight:[d]		9.00	8.12	7.83*	8.57	8.48
No. Stunted Fetuses		0	0	0	0	0

[a] Individual data with standard deviations and standard errors can be found in Appendix H. Individual fetal weights can be found in Appendix J.

[b] Ratio of oxycodone HCl:ibuprofen.

[c] Early Resorption - Nidation comprised of placental tissue and no visible sign of fetal structure.

Late Resorption - Nidation containing fetal tissue with clearly identifiable fetal structures.

[d] Grams.

† Significant trend ($p \leq 0.05$) across groups by Jonckheere's test.

* Significant differences ($p \leq 0.05$) from control values by Mann-Whitney U test.

Summary of individual study findings: According to the sponsor, a maximum tolerated dose was not established for this study. This reviewer concurs. However, the NOAEL for maternal toxicity is >1.5:120 mg/kg/day oxycodone:ibuprofen. Based upon the limited fetal evaluations conducted in this pilot study, no conclusions regarding the developmental toxicity of DuP 604 can be made (in concurrence with the sponsor).

Study title: Teratogenicity Study of DuP 604 in Rabbits

Key study findings: Administration of DuP 604 to the female rabbit from days 7G-19G produced maternal toxicity manifesting as mortality at a dose of 3:240 mg/kg oxycodone:ibuprofen and reduced body weight and food consumption at doses of 1.5:120 mg/kg oxycodone:ibuprofen or greater. A NOAEL for maternal toxicity was determined to be 0.75:60 mg/kg. A NOAEL for teratogenic effects was 3:240 mg/kg/day oxycodone:ibuprofen. A NOAEL for developmental effects is 1.5:120 due to delayed ossification and reduced fetal body weight at the high dose combination.

Study no.:	91-2-1
Volume #, and page #:	Volume 13, Page 53
Conducting laboratory and location:	E.I. du Pont de Nemours and Company Newark, DE
Date of study initiation:	January 7, 1991
GLP compliance:	Yes
QA reports:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	Oxycodone, Lot RM90-033, — purity Ibuprofen, Lot 90PH-02, — purity
Formulation/vehicle:	0.5% w/v methyl cellulose in distilled water

Methods:

Species/strain:	Female — (New Zealand White) SPF rabbits
Doses employed:	Dose ratio of 1:80 as indicated in table below.
Route of administration:	Oral gavage
Study design:	Drug was administered daily by oral gavage on days 7-19 of gestation. Dosing volume was 2 ml/kg.
Number/sex/group:	7-8 female rats/group as follows:

Group	Test Formulation	Daily Dose (mg/kg)		Mated Females
		Oxycodone	Ibuprofen	
1	Vehicle	0	0	20
2	DuP 604	0.38	30	20
3	DuP 604	0.75	60	20
4	DuP 604	1.50	120	20
5	DuP 604	3.00	240	20

Parameters and endpoints evaluated: Body weights and clinical signs, morbidity and mortality and food consumption. Following sacrifice, females were examined for gross anatomical abnormalities. The gravid uterus was removed, weighed and opened. The types of nidations (live or dead, early or late resorptions) and relative positions were recorded. Corpora lutea were counted and the number recorded for each ovary. Live fetuses were weighed, sexed and examined for external alterations. Fetuses were sacrificed and examined for visceral alterations, the brain and eyes were examined and the fetuses were fixed and evaluated for skeletal alterations.

Results:

In-life observations:

Mortality: A total of three females in the high dose group died prior to sacrifice. One of those animals died as a result of gavage trauma. The other deaths occurred on Day 19G and Day 22G and were thought to be related to drug treatment. Two other deaths were noted which were unrelated to drug treatment. Specifically, one animal in the 1.5:120 mg/kg group suffered a broken leg and was sacrificed *in extremis*, and one control animal died as a result of gavage trauma.

Clinical signs: No clear pattern of clinical observations was evident. Animals treated with Dup 604 appeared to show a greater incidence of a visually stained tail compared to controls, however, this effect was also present prior to dosing and was not dose-dependent.

Body weight: There was a significant weight loss (58.8 and 73.4 grams) during the initial days of dosing (days 7-10) in animals treated with 1.5:120 and 3:240 mg/kg treatment groups. Overall, this contributed to a significant weight loss trend in the high dose group for the overall treatment period (7-20). A significant rebound in weight gain was noted in animals treated with 3:240 mg/kg oxycodone:ibuprofen following cessation of treatment.

MEAN MATERNAL BODY WEIGHT CHANGES[a,b,c]

GROUP	DAILY DOSAGE (MG/KG)[d]	N*	DAYS OF GESTATION 0-7	7-10†	10-13	13-16	16-20	7-20†	20-29†
I	0	14	120.9	8.3	65.0	112.2	-32.0	153.5	134.5
II	0.38:30	16	180.8	-12.4	101.2	66.3	-16.2	138.9	120.7
III	0.75:60	15	138.3	-2.9	93.0	95.3	-46.5	138.9	116.7
IV	1.50:120	17	156.9	-58.8*	74.5	111.4	-63.5	63.5	156.5
V	3.00:240	8	108.9	-73.4*	26.4	78.5	-28.9	2.6*	240.3*

* Data from females that were not pregnant, had total resorptions, aborted and/or died prior to scheduled sacrifice were excluded. Individual body weight changes and body weights with standard deviations and standard errors are presented in Appendices C and D, respectively.
[b] Grams.
[c] Bartlett's test for homogeneity was significant ($p \leq 0.005$); statistical analysis was conducted on the ranks of the original values.
[d] Ratio of oxycodone HCl:ibuprofen.
* Number of values used to determine the means.
† Significant trend (linear combination of dose ranks from ANOVA); $p \leq 0.05$.
* Significantly different from controls (Dunnett's test); $p \leq 0.05$.

Food consumption: A significant reduction in food consumption (20-30%) was noted in the high dose animals (3.0:240 mg/kg oxycodone:ibuprofen) in all time intervals examined during the treatment period. Although not significant, food consumption in animals treated with 1.5:120 mg/kg was also reduced. This is consistent with a significant linear trend across treatment groups, suggesting a dose-dependent trend.

MEAN MATERNAL FEED CONSUMPTION[a,b]

GROUP	DAILY DOSAGE (MG/KG)[c]	N[d]	DAYS OF GESTATION 0-7	7-10†	10-13†	13-16†	16-20†	7-20†	20-29
I	0	14	146.7	150.3	150.3	150.5	150.4	150.4	150.3
II	0.38:30	16	150.3	150.5	151.2	150.1	150.0	150.4	146.6
III	0.75:60	15	149.8	150.7	150.5	148.6	150.5	150.1	147.6
IV	1.50:120	17•	150.2	147.1	140.8	140.0	139.4	142.7	148.2
V	3.00:240	8	150.5	120.8*	106.6*	109.2*	104.2*	109.7*	146.6

[a] Data from females that were not pregnant, had total resorptions, aborted and/or died prior to scheduled sacrifice were excluded. Individual feed consumed with standard deviations and standard errors are presented in Appendix E.
[b] Grams/dam/day.
[c] Ratio of oxycodone HCl:ibuprofen.
[d] Number of values used to determine the means.
• The N value for interval 13-16G is 16 due to missed feed measurements.
† Significant trend (linear combination of dose ranks from ANOVA); $p \leq 0.05$.
* Significantly different from controls (Dunnett's test); $p \leq 0.05$.

Terminal and necroscopic evaluations:

Dams: In the two animals that died prior to scheduled sacrifice, numerous ulceration sites were observed. Stomach ulcerations were also noted in animals which survived to the scheduled sacrifice: two animals in the 3:240 mg/kg dose group, 1 animal in the 0.38:30 mg/kg dose group and two animals in the control group.

Incidence of Stomach Ulcerations in the Dams.

Group I	Group II	Group III	Group IV	Group V
2/20	1/20	0/20	0/20	4/20

There were also isolated cases of liver lesions in the 3:240 mg/kg treatment group. One animal in the control group presented with a missing gallbladder.

Two dams aborted prior to scheduled sacrifice, one in the 1.5:120 mg/kg dose group on day 18G and the other in the 3:240 mg/kg dose group on day 22G. There was a significant increase in the number of nidations (5.0 in this study) and corpora lutea per litter (7.0 in this study) in the high dose group, however, no trend was evident. Historical control data from [redacted] indicates that these values were within the historical control range (mean nidation range of 5.8-9.2; mean corpora leutea range of 9.3-12.6). A non-significant increase in the number of resorptions per litter (1.1) was detected following the high dose treatment which was outside the

historical control values for the laboratory (0.1-0.8) and therefore likely related to maternal toxicity.

Offspring: There were no significant differences in mean fetal body weights at any dose tested. There was a non-significant decrease (11%) in mean fetal body weight at the high dose group. The table below summarizes the reproductive parameters measured in this study:

TERATOGENICITY STUDY OF DUP 604 IN RABBITS

TABLE 4

REPRODUCTIVE OUTCOME[a]

GROUP:		I	II	III	IV	V
DAILY DOSAGE (MG/KG):[b]		0	0.38:30	0.75:60	1.50:120	3.00:240
No. Inseminated		20	20	20	20	20
No. Pregnant		16	16	16	19	13
No. Aborted		0	0	0	1	1
No. Deaths†		1[c]	0	0	1[d]	3[c]
No. With Total Resorptions		1[•]	0	1	0	1
No. Litters		14	16	15	17	8
Means Per Litter						
Live Fetuses:	Total	4.9	6.1	5.3	5.6	6.3
	Males	1.9	2.9[f]	2.6	3.3	2.6
	Females	3.0	3.2[f]	2.7	2.3	3.6
Dead Fetuses		0.0	0.0	0.0	0.0	0.0
Resorptions:[g]	Total	0.1	0.3	0.3	0.2	1.1
	Early	0.1	0.2	0.2	0.2	0.5
	Late	0.0	0.1	0.1	0.1	0.6
Nidations		5.0	6.4	5.7	5.8	7.4*
Mean Corpora Lutea		7.0	8.4	8.4	8.1	9.8*
Mean Fetal Weight:[h]	Total	47.99	46.79	47.60	46.36	42.84
	Males	45.98	46.21	46.90	44.33	41.78
	Females	47.80	46.30	48.27	46.75	42.94
No. Stunted Fetuses		1	0	3	0	1

[a] Individual data with standard deviations and standard errors are presented in Appendix H. Individual fetal weights and alterations are presented in Appendix J.
[b] Ratio of oxycodone HCl:ibuprofen.
[c] One female accidently killed (gavage trauma). Data omitted from statistical analyses.
[d] One female sacrificed in extremis (broken leg). Data omitted from statistical analyses.
[•] Determined by stain.
[f] Due to technical error, the sex of one fetus was not determined.
[g] Early resorption - Nidation comprised of placental tissue and no visible sign of fetal structure.
Late resorption - Nidation containing fetal tissue with clearly identifiable fetal structures.
[h] Grams.
† Significant trend (Cochran-Armitage test); $p \leq 0.05$.
* Significantly different from controls (Mann-Whitney U test); p:

There were no significant increases in the incidence of fetal variations detected. However, there was a significant trend toward retarded development and overall variation data associated primarily with delayed skeletal ossification and delayed kidney development. This trend for overall variations appears to be attributed primarily to the high dose and is likely related to maternal toxicity.

TABLE 6

INCIDENCE OF FETAL VARIATIONS[a,b]

GROUP:	I	II	III	IV	V
DAILY DOSAGE (MG/KG):[c]	0	0.38:30	0.75:60	1.50:120	3.00:240
DEVELOPMENTAL VARIATIONS					
EXTERNAL					
No. examined[d]	68[14][e]	98[16]	80[15]	95[17]	50[8]
No. affected[d]	0[0]	0[0]	0[0]	0[0]	0[0]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	0.0	0.0
VISCERAL					
No. examined	68[14]	98[16]	80[15]	95[17]	50[8]
No. affected	0[0]	0[0]	0[0]	0[0]	0[0]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	0.0	0.0
HEAD					
No. examined	61[13][f]	98[16]	80[15]	95[17]	50[8]
No. affected	0[0]	0[0]	0[0]	0[0]	0[0]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	0.0	0.0
SKELETAL					
No. examined	68[14]	98[16]	80[15]	95[17]	50[8]
No. affected	1[1]	0[0]	1[1]	0[0]	0[0]
Mean percent affected per litter (S.E.)	1.2	0.0	1.0	0.0	0.0
(S.D.)	(1.19)		(0.95)		
	(4.45)		(3.69)		
Sternebra - Fused	1(1)	...[g]	1(1)	...	...
TOTAL WITH DEVELOPMENTAL VARIATIONS	1(1)	0(0)	1(1)	0(0)	0(0)
MEAN PERCENT AFFECTED PER LITTER (S.E.)	1.2	0.0	1.0	0.0	
(S.D.)	(1.19)		(0.95)		
	(4.45)		(3.69)		

TERATOGENICITY STUDY OF DUP 604 IN RABBITS

TABLE 6 (CONT.)

INCIDENCE OF FETAL VARIATIONS[a,b]

GROUP:	I	II	III	IV	V
DAILY DOSAGE (MG/KG):[c]	0	0.38:30	0.75:60	1.50:120	3.00:240
VARIATIONS DUE TO RETARDED DEVELOPMENT					
EXTERNAL					
No. examined	68[14]	98[16]	80[15]	95[17]	50[8]
No. affected	0[0]	0[0]	0[0]	0[0]	0[0]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	0.0	0.0
VISCERAL					
No. examined	68[14]	98[16]	80[15]	95[17]	50[8]
No. affected	0[0]	0[0]	0[0]	2[2]	2[2]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	1.5	4.34
(S.D.)				(1.01)	(2.86)
				(4.15)	(8.08)
Kidney					
- Small Papilla - Size 1	...	...	...	1(1)	1(1)
- Small Papilla - Size 2	...	...	...	1(1)	1(1)
HEAD					
No. examined	61[13][f]	98[16]	80[15]	95[17]	50[8]
No. affected	0[0]	0[0]	0[0]	0[0]	0[0]
Mean percent affected per litter (S.E.)	0.0	0.0	0.0	0.0	0.0
SKELETAL					
No. examined	68[14]	98[16]	80[15]	95[17]	50[8]
No. affected	4[3]	9[3]	12[3]	7[5]	8[4]

TABLE 6 (CONT.)

INCIDENCE OF FETAL VARIATIONS[a,b]

GROUP:	I	II	III	IV	V
DAILY DOSAGE (MG/KG):[c]	0	0.38:30	0.75:60	1.50:120	3.00:240
VARIATIONS DUE TO RETARDED DEVELOPMENT CONT.					
SKELETAL (Cont.)					
Mean percent affected	4.6	9.5	9.3	10.9	18.8
per litter (S.E.)	(2.71)	(5.60)	(5.64)	(6.04)	(8.88)
(S.D.)	(10.14)	(21.68)	(21.84)	(24.90)	(25.13)
Rib - Wavy	...	...	...	1(1)	...
Skull - Partially Ossified	...	...	2(2)	...	...
- Bent Hyoid	1(1)	1(1)	...	2(1)	3(2)
Sternebra					
- Partially Ossified	2(2)	7(3)	12(3)	4(3)	4(2)
- Unossified	1(1)	1(1)	...	...	1(1)
Vertebra - Partially Ossified	...	...	...	1(1)	...
TOTAL WITH VARIATIONS DUE TO RETARDED DEVELOPMENT†	4(3)	9(3)	12(3)	8(6)	10(5)
MEAN PERCENT AFFECTED	4.6	9.5	9.3	11.6	23.1
PER LITTER (S.E.)	(2.71)	(5.60)	(5.64)	(6.00)	(8.87)
(S.D.)	(10.14)	(21.68)	(21.84)	(24.74)	(25.08)
TOTAL NUMBER FETUSES WITH VARIATIONS†	5(3)	9(3)	12(3)	8(6)	10(5)
MEAN PERCENT FETUSES	5.8	9.5	9.3	11.6	23.1
WITH VARIATIONS (S.E.)	(3.75)	(5.60)	(5.64)	(6.00)	(8.87)
(S.D.)	(14.02)	(21.68)	(21.84)	(24.74)	(25.08)

[a] Individual fetal alterations are presented in Appendix J.
[b] No significant difference from control values (Fisher's Exact test).
[c] Ratio of oxycodone HCl:ibuprofen
[d] In calculating the percent affected per litter, malformed fetuses were omitted from the number examined and the number affected.
[e] Number examined and affected, including the number affected with the listed variations are expressed as Fetuses [Litters] or Fetuses (Litters).
[f] Due to technical error, one litter was not examined.
[g] For ease of reading, zeros have been replaced with ellipses for the listed variations.
† Significant trend (Cochran-Armitage test); $p \leq 0.05$.

Summary of individual study findings: Treatment of rabbits with DuP 604 produced signs of maternal toxicity manifested as mortality at the dose of 3:240 mg/kg and reduced body weights and food consumption at the 1.5:120 mg/kg dose level or greater. Post mortem findings of increased stomach ulcerations in the high dose group were noted, however, these changes did not appear to be restricted to the drug-treatment and were not dose-dependent. The increase in mean nidations and corpora lutea compared to controls was not deemed biologically significant by the sponsor, since the control group responses were low compared to historical controls. The non-

significant increase in the number of resorptions (1.1) at the high dose was above the historical control range (0.1-0.8), suggesting that embryolethality may be evident at the high dose treatment. Fetal toxicity was noted in the high dose group and was manifested as growth retardation and weight changes likely due to maternal toxicity. The percentage of fetuses with variations was 4 times the control group mean and 2 times the historical control mean. The NOAEL for maternal toxicity is considered to be 0.75:60 mg/kg, based upon body weight changes. The NOAEL for teratogenic effects is 3:240 mg/kg, while the NOAEL for developmental toxicity is 1.5:120 mg/kg based upon an increase in the number of resorptions over historical controls in the high dose group.

Reproductive and developmental toxicology summary: Segment II reproductive and developmental toxicology studies were conducted in the rat and the rabbit. Segment I (Fertility) and Segment III (peri- and post-natal development) studies were not conducted by the sponsor for this NDA. These studies will be conducted as Phase 4 commitments as discussed with the sponsor during the pre-NDA meeting with the Division on July 26, 2001.

The results of the segment II study in rats indicated that DuP 604 produced maternal toxicity at dose levels of 0.5:40 mg/kg/day oxycodone:ibuprofen and above. Maternal toxicity was characterized by alopecia, pallor, facial and peri-anal staining and scabs associated with areas of severe alopecia. DuP 604-related maternal mortality occurred following administration of the high dose combination (2:160 mg/kg/day oxycodone:ibuprofen). One upper mid dose dam (1:80 mg/kg/day oxycodone:ibuprofen) and 3 high dose dams delivered litters early. The NOAEL for maternal toxicity was 0.25:20 mg/kg DuP 604, based upon alopecia and decreased body weight gain in the 0.5:40 mg/kg/day oxycodone:ibuprofen treatment group. This corresponds to 0.12-fold the proposed maximum human daily dose based upon body surface area. Under the conditions employed, DuP 604 did not increase the incidence of fetal malformations or variations. Therefore, the NOAEL for developmental toxicity is 2:160 mg/kg/day, the maximum dose tested. This corresponds to 1-fold the proposed maximum human daily dose of each drug based upon body surface area.

Treatment of rabbits with DuP 604 produced signs of maternal toxicity manifested as mortality at the dose of 3:240 mg/kg and reduced body weights and food consumption at the 1.5:120 mg/kg dose level. Post mortem findings of increased stomach ulcerations in the high dose group were noted, however, these changes did not appear to be restricted to the drug-treatment and were not dose-dependent. The increase in mean nidations and corpora lutea compared to controls was not deemed biologically significant by the sponsor, since the control group responses were low compared to historical controls. The non-significant increase in the number of resorptions (1.1) at the high dose was above the historical control range (0.1-0.8), suggesting that embryolethality may be evident at the high dose treatment. Fetal toxicity was noted in the high dose group and was manifested as growth retardation and weight changes likely due to maternal toxicity. The percentage of fetuses with variations was 4 times the control group mean and 2 times the historical control mean. The NOAEL for maternal toxicity is considered to be 0.75:60 mg/kg, based upon body weight changes. This corresponds to 0.75-fold the proposed maximum daily human dose based upon body surface area. The NOAEL for teratogenic effects is 3:240 mg/kg, while the NOAEL for developmental toxicity is 1.5:120 mg/kg based upon an increase in the number of resorptions over historical controls in the high dose group. This corresponds to 3-fold the proposed maximum daily human dose of each drug based upon body surface area for

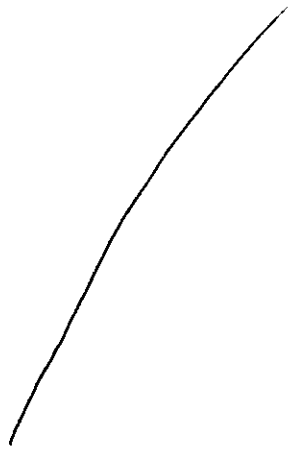
teratogenicity and 1.5-fold the proposed maximal daily human dose of each drug based upon body surface area for developmental toxicity.

Reproductive and developmental toxicology conclusions: The sponsor completed the requirements for Segment II developmental toxicology studies in support of this NDA. The Segment I and Segment III studies will be conducted as phase 4 commitments. The results of the Segment II studies in rats and rabbits indicate that the combination of oxycodone and ibuprofen produces evidence of maternal toxicity in rats and rabbits and developmental toxicity in rabbits. The developmental toxicity may be secondary to maternal toxicity. The pregnancy category should be "C" based on the developmental effects.

Labeling recommendations:

Sponsor's proposed labeling as follows:

Pregnancy Category C:



A formal label review will be conducted at a later time.

VIII. SPECIAL TOXICOLOGY STUDIES:

No special toxicology studies were submitted for this NDA.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: The efficacy of oxycodone and ibuprofen as individual treatments for pain relief has been well documented via extensive human experience with the drug substances. The combination of the two drugs, as proposed in this NDA, follows well-documented effects of combinations of opioids and NSAIDs. The non-clinical pharmacology and toxicology of the combination drug product containing oxycodone (5 mg) and ibuprofen (400 mg) has been tested adequately for drug marketing based largely on extensive human experience with both drugs individually and similar combination opioid:NSAID drug products.

The acute toxicity of oxycodone alone, ibuprofen alone and the combination of oxycodone:ibuprofen (1:80) was characterized in the rat model. Oxycodone administration produced characteristic opioid-receptor mediated effects including signs of CNS depression, renal/urinary effects and generalized deterioration. The NOAEL was < 50 mg/kg based on clinical observations in the rat model. Acute administration of ibuprofen to the rat produced characteristic NSAID-related pathology including acute CNS depression and delayed complications, such as inflammatory cell infiltration of the gastrointestinal tract and splenic hypertrophy with cellular infiltration of the white pulp. These changes are consistent with the known ulcerogenic potential of NSAIDs. The NOAEL was < 533.3 mg/kg based upon clinical and gross macroscopic observations. Acute administration of the combination of oxycodone and ibuprofen (1:80) produced greater toxicity than ibuprofen alone. Increased evidence for acute CNS depression coupled with delayed evidence for generalized deterioration attributed to the ulcerogenic potential of NSAIDs was noted. However, there did not appear to be an increase in the ulcerogenic potential of the combination of oxycodone and ibuprofen compared to ibuprofen alone in acute rat studies.

Repeat-dose toxicology studies (1-month duration) were completed for the combination drug product in both the rat and the dog models. In the rat model, oxycodone and ibuprofen (1:80) administration produced signs of gastric mucosal irritation that was attributed to the ibuprofen content of the drug product. There was no clear evidence that the oxycodone aggravated the gastrointestinal toxicity of the combination product. Target organs of toxicity were the stomach and the spleen. In males, a NOAEL of 0.313:25 mg/kg/day oxycodone:ibuprofen was identified. In females, this dose was considered a LOAEL dose based upon findings of a slight decrease in the urine osmolarity at this dose. These doses correspond to 0.15-fold the proposed maximal daily dose of oxycodone:ibuprofen in humans based on body surface area. In the dog model, oxycodone and ibuprofen (1:80) administration produced signs of gastrointestinal toxicity consistent with the known properties of NSAIDs to produce gastric ulceration. The combination of the two drugs produced a greater incidence of fecal occult blood than ibuprofen alone, suggesting the potential for increased toxicity of the drug combination. A NOAEL of 0.0625 mg/kg/day oxycodone and 5 mg/kg/day ibuprofen was identified. This corresponds to a 0.1-fold the proposed maximum daily dose of oxycodone:ibuprofen in humans based on body surface area. A second study in the dog model tested the combination of oxycodone:ibuprofen at a ratio of 1:40. Similar observations were found, suggesting the potential for increased gastrointestinal toxicity of the drug combination in humans. In males, a NOAEL of 0.0625 mg/kg/day oxycodone and 2.5 mg/kg/day ibuprofen was identified based upon signs of chronic irritation in the kidney and the presence of fecal occult blood. These doses correspond to 0.1 and 0.05-fold the proposed maximum human daily dose of oxycodone and ibuprofen, respectively, based upon

body surface area. In females, a NOAEL of 0.125 mg/kg/day oxycodone and 5 mg/kg/day ibuprofen was identified based upon signs of renal inflammation. These doses correspond to 0.2-fold and 0.1-fold the proposed maximum human daily dose of oxycodone and ibuprofen, respectively, based upon body surface area.

There were no genetic toxicology studies submitted by the sponsor to support the NDA application. The sponsor has proposed labeling based upon the information presented in the label for Oxycontin (NDA-20-553). The sponsor should submit patent certification information for these data. The sponsor provided literature references for the genetic toxicology of ibuprofen. The references indicate that ibuprofen was not mutagenic in the Ames bacterial reverse mutation assay, however, it was positive in the *in vivo* mouse bone marrow chromosome aberrations test. These observations should be reflected in the labeling.

There is currently no adequate information concerning the carcinogenic potential of oxycodone or ibuprofen in the literature. Although carcinogenicity assessment would not be required for the proposed short term indication, the sponsor has agreed to conduct carcinogenicity assessment in two species should post-marketing data indicate that the drug product is being used either intermittently or continuously for 6 months or more.

The sponsor conducted Segment II reproductive toxicology studies on the combination of oxycodone and ibuprofen in both the rat and the rabbit models. Segment I and III studies were not conducted for this NDA, however, the sponsor has agreed to conduct these studies as part of their Phase 4 commitments. The results of the Segment II study in rats indicated that the combination of oxycodone and ibuprofen produced signs of maternal toxicity, however, there were no signs of developmental toxicity at doses up to 2-fold the proposed maximal human daily dose of oxycodone and ibuprofen based upon body surface area. In the rabbit, the combination of oxycodone and ibuprofen also produced signs of maternal toxicity. Fetal toxicity (growth retardation and weight changes) was likely the result of maternal toxicity. Developmental toxicity was manifested as a non-significant increase in the number of resorptions over historical control values in the 3:240 mg/kg/day treatment group. The NOAEL for developmental toxicity corresponds to 1.5-fold the proposed maximal daily dose in humans based upon body surface area. A pregnancy category of C is recommended based upon developmental effects.

Overall, the studies conducted in support of this NDA have demonstrated that in addition to the known toxicities for each compound alone, there appears to be an increased risk for gastrointestinal toxicity consistent with mild blood loss and ulcerogenic potential for the combination product compared to ibuprofen alone. This should be described in the product labeling.

General Toxicology Issues: The primary issue raised by the submitted studies is the presence of fecal occult blood in the high-dose combination repeat-dose dog studies. The increased incidence of fecal occult blood was not associated with histopathological evidence of gastrointestinal irritation and/or ulceration. The Division requested formal external consultation from the Division of Gastrointestinal Drug Products (HFD-180) as well as informal consultation from the Division of Anti-inflammatory Drug Products (HFD-550). The opinion of Dr. Choudary from HFD-180 was that the signals produced were not sufficiently strong to warrant inclusion in the label or the investigator's brochure. Dr. Yang from HFD-550 indicated that the

decreased hematocrit was not of sufficient magnitude to constitute toxicity. Both Drs. Choudary and Yang felt that the studies did not reach the maximum tolerated dose and therefore should be repeated. In addition, the dog model is known to be more sensitive to NSAID-induced gastrointestinal toxicity than the rat which is more sensitive than the monkey and presumably the human. Although the finding of increased incidence of fecal occult blood in the dog model suggests the potential for increased risk with this drug product, it does not preclude the approval of the drug product. This should, however, be addressed in the product labeling.

Segment I and III reproductive toxicology studies have not been completed by the sponsor and should be completed as a Phase 4 commitment. In addition, adequate carcinogenicity assessment for the drug product has not been completed. Unless the sponsor demonstrates that the drug product will not be used chronically, carcinogenicity assessment in two species should be completed. This assessment may be provided post-approval.

Recommendations:

1. This NDA application is considered to be approvable from a non-clinical perspective.
2. A description of the increased potential for gastrointestinal toxicity with the combination product versus ibuprofen alone should be considered for the product label.
3. Fertility and pre- and post-natal developmental toxicity studies may be completed as a post-marketing commitment. However, the sponsor is encouraged to submit these studies prior to approval of the marketing application.
4. The carcinogenic potential of this drug product should be assessed in 2 species unless the sponsor can demonstrate post-marketing data that the drug product will not be used chronically.
5. Appropriate patent certification should be provided to support reference to labeled information regarding other marketed products.

Comments 3, 4 and 5 should be communicated to the sponsor.

Labeling with basis for findings: Labeling will be addressed at a later date.

X. APPENDIX/ATTACHMENTS:

Addendum to review: N/A.

Other relevant materials (Studies not reviewed, appended consults, etc.): N/A.

Any compliance issues: N/A.

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/s/

R. Daniel Mellon
10/2/02 01:27:44 PM
PHARMACOLOGIST

Timothy McGovern
10/3/02 08:49:23 AM
PHARMACOLOGIST
I concur.