CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
MEMO TO FILE

Reviewer: Kathleen Haberny, Ph.D.
Date: March 6, 2002

NDA: # 21-260
Submission: # BZ/July 26, 2001
Drug: (morphine sulfate) Extended-Release Capsules
Sponsor: Elan Pharmaceutical Research Corporation

Re: Impurities in drug product

According to information provided by the reviewing chemist, Dr. Ravi Harapanhalli, the proposed drug product specifications for the following impurities are at levels of

*NMT: not more than

Dr. Harapanhalli requested that the sponsor address these specifications and informed the sponsor that qualification would be needed for substances he threshold for qualification of degradation products in new drug products with a maximum total dose of >100mg-2g according to ICHQ3B.

The sponsor submitted limited preclinical and clinical safety information on the impurities listed above in the chemistry section of the NDA resubmission (July 26, 2001) as a rationale for the position that qualification of the above impurities should not be needed. In the submitted rationale the sponsor concluded that these impurities are metabolites of morphine in humans or animals or a decomposition product of morphine that may be a metabolite of and, therefore, likely to have been indirectly investigated in toxicology and clinical studies on morphine.

The Clinical Pharmacologist, Dr. Suliman Alfayoumi, reviewed the published reports on morphine metabolites in humans submitted by the sponsor. According to Dr. Alfayoumi, approximately 90% of a given morphine dose is conjugated to morphine-3-glucuronide

(M3G) and morphine-6-glucuronide (M6G). Codeine and normorphine are known to be minor metabolites of morphine in humans. However, there is very limited information in literature on the remaining metabolites listed. Dr. Alfayoumi noted that a morphine impurity with identical pharmacological properties and HPLC retention time as a previously identified *in vivo* human metabolite was isolated and identified in 1990 (Farsam *et al.* 1990. Pharmaceutical Res 7(11):1205-7), and that position has been hypothesized to be related to hepatotoxicity by morphine (Correia et al, 1986)[1]. Pseudomorphine is a dimer of morphine that occurs naturally in aqueous solutions. The information presented in two published articles on the pharmacology of morphine-N-oxide, a human metabolite of morphine (Fennessy and Fearn. 1969. J Pharm Pharmac 2:668-673; Heimans *et al.*, 1971. J Pharm Pharmac 23:831-836) suggested that morphine-N-oxide does not pose major safety issues in mice or rats (Fennessy and Fearn, 1969) and dogs (Fennessy. 1969. Eur J Pharmacol 8: 261-268). Thus, the impurities identified as morphine metabolites in humans are codeine, 10-hydroxymorphine, and morphine-N-oxide.

In the submitted rationale the sponsor noted that pseudomorphine has been found in marketed morphine products (Vermeire and Remon. 1999. Int J Pharm 187:17-51), at levels as high as 1% in an intrathecal preparation (Caute *et al.* 1988. Pharm Pharmacol 40:644-645). Pseudomorphine was reported to be a metabolite in animals (Roerig *et al.* 1976. Biochem Pharm 25:1075-1080), but has not been identified as a human metabolite. Pseudomorphine toxicity and pharmacological effects were studied in several animal species (mice, cats, rats, rabbits, route of administration not provided) in an early study by Eddy (1936. Studies of morphine codeine and their derivatives. XII. The isomers of morphine and dihydromorphine. 421-431). Pseudomorphine was found to be less acutely toxic than morphine in mice. This study is inadequate to support the safe use of pseudomorphine. The sponsor described as a decomposition product of morphine (Proska. 1984. Pharmazie 39:687-688) that may be metabolized to (Farsam *et al.*, 1990). No preclinical toxicology information was provided to support the safety of

Dr. Harapanhalli noted that these impurities are observed in other morphine products, with typical specifications of for some of them (not specified). Pseudomorphine is a major degradant in aqueous solutions of morphine.

In summary, codeine, 10-hydroxymorphine, and morphine-N-oxide are human metabolites and, thus, do not require further non-clinical qualification. is not identified as a human metabolite. No preclinical toxicology information is available to support the safety of in clinical use at the specification of . Therefore, for an adequate safety evaluation, requires nonclinical qualification according to ICH standards if the specification is not decreased to below Pseudomorphine has not been identified as a human metabolite, and the available nonclinical safety information is inadequate to support the proposed specification at the level For an adequate safety evaluation, qualification is needed for pseudomorphine at levels of according to ICH guidelines. It should be noted that these impurities are observed in previously approved morphine products at levels of or higher.

[1]The publication referred to is Kroweech G, Caldera-Munoz PS, Straub K, Castagnoli N Jr, Correia MA. 1986. Morphine metabolism revisited. III. Confirmation of a novel metabolic pathway. Chem Biol Interact 58(1):29-40. The authors suggest that oxidation at the benzylic C-10 position may form an electrophilic species that can react with nucleophilic thiols (e.g., N-acetylcysteine, glutathione). N-acetyl-cysteine is a precursor to the widely distributed endogenous enzyme glutathione that is involved in detoxification of reactive metabolites via redox reactions to prevent oxidative damage. Therefore, endogenous protection from toxicity by the electrophilic species hypothetically formed by C-10 oxidation is present.

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/s/

Kathy Haberny
3/6/02 01:56:22 PM
PHARMACOLOGIST

Timothy McGovern
3/6/02 02:29:28 PM
PHARMACOLOGIST
I concur.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
MEMO TO FILE

Reviewer: Kathleen Habeny, Ph.D.
Date: March 11, 2002

NDA: # 21-260
Submission: # BZ/July 26, 2001
Drug: morphine sulfate) Extended-Release Capsules
Sponsor: Elan Pharmaceutical Research Corporation

Re: Impurities in rug product

According to information provided by the reviewing chemist, Dr. Ravi Harapanhalli, the proposed drug substance specification for pseudomorphine is
Dr. Harapanhalli informed the sponsor that qualification would be needed for substances the threshold for qualification of degradation products in new drug substances with a maximum total dose of >100mg-2g according to ICHQ3AR.

In the submitted rationale the sponsor noted that pseudomorphine has been found in marketed morphine products (Vermeire and Remon. 1999. Int J Pharm 187:17-51), at levels as high as 1% in an intrathecal preparation (Caute *et al.* 1988. Pharm Pharmacol 40:644-645). Pseudomorphine was reported to be a metabolite in animals (Roerig *et al.* 1976. Biochem Pharm 25:1075-1080), but has not been identified as a human metabolite. Pseudomorphine toxicity and pharmacological effects were studied in several animal species (mice, cats, rats, rabbits, route of administration not provided) in an early study by Eddy (1936. Studies of morphine codeine and their derivatives. XII. The isomers of morphine and dihydromorphine. 421-431). Pseudomorphine was found to be less acutely toxic than morphine in mice. This study is inadequate to support the safe use of pseudomorphine.

Pseudomorphine has not been identified as a human metabolite, and the available nonclinical safety information is inadequate to support the proposed specification at the level of in the drug substance. For an adequate safety evaluation, qualification is needed for pseudomorphine at levels of according to ICHQ3AR guidelines. It should be noted that these impurities are observed in previously approved morphine products at levels or higher.

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/s/

Kathy Haberny
3/11/02 12:55:57 PM
PHARMACOLOGIST

Timothy McGovern
3/11/02 01:23:55 PM
PHARMACOLOGIST
I concur.

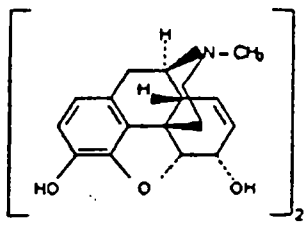
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-260
Review number: 3 (Addendum to the original NDA review)
Sequence number BZ/ July 26, 2001/Response to FDA Approvable Letter of March 30, 2001
Information to sponsor: Yes (x) No ( )
Sponsor: Elan Pharmaceutical Research Corp., 1300 Gould Dr., Gainesville, GA 30504
Manufacturer for drug substance:

Reviewer name: Kathleen Haberny, Ph.D.
Division name: Anesthetics, Critical Care, and Addiction Drug Products
HFD #: 170
Review completion date: February 14, 2002

Drug:

Trade name: (morphine sulfate) Extended-Release Capsules, 30mg, 60mg, 90mg, and 120mg
Generic name: Morphine sulfate USP
Code name: None
Chemical name: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5alpha,6alpha)-, sulfate (2:1) (salt), pentahydrate, or 7,8-Didehydro-4,5alpha-epoxy-17-methylmorphinan-3,6alpha-diol sulfate (2:1) (salt) pentahydrate [*6211-15-0*]
CAS registry number: 6211-15-0 (Pentahydrate form); 64-31-3 (Anhydrous form); 57-27-2
Mole file number: None
Molecular formula/molecular weight: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ / 758.92
Structure:



Relevant INDs/NDAs/DMFs:

[redacted]

Drug Class: Opioid Analgesic

Indication: Relief of chronic moderate to severe pain

Clinical formulation: Sustained hard gelatin capsules containing):

Component	Composition (mg/capsule)			
	Capsule 30mg	Capsule 60 mg	Capsule 90mg	Capsule 120 mg
Morphine sulfate USP	30	60	90	120
Nonpareil seeds USP (sugar sphere NF)				
Fumaric acid NF				
Hydrated magnesium silicate (talc) NF				
Sodium lauryl sulfate, NF				
Povidone USP (polyvinyl pyrrolidone) (Kollidon 30)				
[redacted]				
1 Gelatin Capsule				

Capsule shell contains black ink, gelatin, titanium dioxide, D&C yellow No. 10 (30 mg), FD&C green No. 3 [redacted], FD&C red No. 40 (90 mg), FD&C red No. 3 (120 mg), and FD&C blue No. 1 (120 mg).

Route of administration: Oral

Introduction and drug history: Morphine sulfate, the principle alkaloid substance derived from the opium poppy, was discovered in 1806 and has been used since then for the treatment of moderate to severe pain, and as an antidiarrheal and antitussive agent. The pharmacology and toxicology of morphine have been well characterized and widely reported in the published literature. Morphine sulfate is marketed in injection, oral capsule, solution and tablet, and suppository forms. Sustained release morphine sulfate formulations, such as MS Contin® (Purdue Frederick, up to 400

mg/day) have been approved for clinical use and are widely prescribed. The proposed drug product was developed as a combination of extended release and immediate release components in a once-daily capsule to provide rapid onset of absorption and analgesia and long-acting relief from pain with fewer peak-trough plasma level fluctuations compared to the existing twice-daily dosing forms.

Previous clinical experience: ———™ was evaluated in 140 healthy volunteers in pharmacokinetic/bioavailability studies, and in 740 patients in seven clinical trials on pharmacokinetics, pharmacokinetics/pharmacodynamics, Phase III efficacy and safety at up to 6 months, and in a one year safety study. The pain etiologies included chronic malignant and non-malignant pain, such as osteoarthritis. There were six deaths, all considered to be unrelated to ———™ treatment. The most common treatment-related adverse effects were characteristic of opioid drug effects and included nausea, constipation, somnolence, vomiting, asthenia, peripheral edema, headache, confusion, pruritus and dizziness.

Proposed clinical use: For once-daily, oral administration in the treatment of moderate to severe chronic pain

Note: Portions of this review were excerpted directly from the sponsor's submission.

Studies reviewed within this submission: None. This review summarizes morphine sulfate pharmacology and toxicology reported in the published literature and cited in the original NDA #21-260 submission.

Studies <u>not</u> reviewed within this submission: None

PHARMACOLOGY

The mechanism of action of morphine pharmacological and toxicological effects is due to high-affinity binding to mu and kappa opioid receptors, predominantly in the periacqueductal and periventricular grey matter, ventromedial medulla and spinal cord. Binding to the mu opioid receptor is responsible for analgesia at the supraspinal level, euphoria, respiratory depression and the development of physical dependence. Analgesia at the spinal level, miosis and sedation are mediated in part by action at the kappa-receptor. Direct mu receptor mediated effects in the medulla mediate morphine-induced depression of the cough reflex. Endocrine effects of morphine include increased secretion of anti-diuretic hormone, thyroid stimulating hormone and prolactin, and alterations of glucocorticoid levels, follicle stimulating hormone and luteinizing hormone by effects on corticotropin releasing factor and gonadotropin releasing hormone (see Skoulis *et al.*, 1989, Thomas *et al.*,1985).

The opioid drugs are known to induce tolerance to the pharmacodynamic and side effects, and withdrawal in both animals and humans. Withdrawal signs after chronic exposure in animals include autonomic (increased pulse and blood pressure, diarrhea,

respiratory rate, pupil diameter and body temperature), somatomotor (nociception, neuromuscular reflexes, Straub tail, convulsions) and behavioral (irritability, eating and drinking, sleep, decreased alertness) effects (DHHS/NIDA 1984).

SAFETY PHARMACOLOGY

Neurological effects observed after excessively high doses of morphine are lethargy, coma and seizures. Morphine also induces peripheral arteriolar and venous dilatation by provoking histamine release and blunting reflex vasoconstriction, resulting in hypotension. Morphine-induced reduction in the responsiveness of brain stem respiratory centers to increased CO_2 tension and depression of pontine and medullary centers mediated by a subpopulation of mu receptors (mu2) are responsible for respiratory depression, pulmonary edema and respiratory arrest at high morphine doses. Morphine treatment can result in urinary urgency and urinary retention as a result of increased tone of the detrusor muscle and vesical sphincter, and increased tone and amplitude of contractions of the ureter. Dermatologic effects, such as pruritus, sweating and cutaneous vasodilation are often reported during treatment with morphine.

Opioid drugs including morphine can induce constipation and delayed gastric emptying. Cowan (1977) demonstrated a dose-related decrease in the rate of passage of a charcoal meal in the intestines of rodents. The gastrointestinal slowing is due to effects on cholinergic, tryptaminergic and encephalinergic receptors in the myenteric plexus of the intestine. Other gastrointestinal effects of morphine are nausea and vomiting, believed to be a result of direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla, and spasm of the sphincter of Oddi with increased pressure in the biliary tract .

PHARMACOKINETICS/TOXICOKINETICS

Oral absorption of morphine is variable and decreased by extensive hepatic first-pass metabolism. The bioavailability of orally administered morphine is approximately 20%-33%. Distribution is primarily to the kidneys, liver, lung, and spleen with low concentrations in brain and muscle. The volume of distribution in humans is 2-5 liters/kg. Morphine has been detected in the placenta, milk and sweat. Plasma protein binding is 35%. Protein binding is reduced in acute viral hepatitis, cirrhosis and hypoalbuminemia. Morphine metabolism is primarily by hepatic glucuronidation of the free phenolic hydroxyl group to the inactive metabolite morphine-3-glucuronide. Approximately 5% of orally administered morphine undergoes N-demethylation to normorphine and 10% is metabolized to codeine. Additional metabolites are morphine-6-glucuronide, morphine-3-ethereal sulfate and morphine-3,6-diglucuronide. Morphine-6-glucuronide is active. Up to 90% of an administered dose of morphine is excreted in the urine within 24 hours, 75% as morphine-3-glucuronide and 8.5%-12% as unchanged drug. Clearance is approximately 24 ml/min/kg and is unchanged by increasing age and cirrhosis. However, clearance is reduced in neonates, burn patients,

and uremia. The elimination half-life is between 2.5 and 3 hours, and is unaffected by cirrhosis and uremia but increased in neonates and premature babies.

TOXICOLOGY

Single dose The median lethal dose (LD_{50}) reported in mice is 375 and 506 mg/kg SC (Witkin *et al.*, 1961; Blane *et al.*,1967), 221 and 250 mg/kg IV (Blane *et al.*,1967; Fennessy and Fearn, 1969), and 600 and 1270 mg/kg PO (Witkin *et al.*,1961; Blane *et al.*,1967). In rats, the LD_{50} values were 170 and 572 mg/kg SC (Blane *et al.*, 1967; Finnegan *et al.*,1948), 100 and 237 mg/kg IV (Blane *et al.*,1967; Finnegan *et al.*,1948) and 461 and 905 mg/kg PO (Blane *et al.*,1967; Finnegan *et al.*,1948). The LD_{50} values in rabbits were 266 mg/kg SC and 500 mg/kg IP (Sunshine ed. 1969) and in dogs the LD_{50} was 133 mg/kg IV. The lowest reported lethal dose was 8 mg/kg IV and 190 mg/kg SC in rabbits, 500 mg/kg SC in guinea pigs, 210 mg/kg SC in dogs, 40 mg/kg SC in cats, 900 mg/kg SC in ducks, 250 mg/kg SC and 500 mg/kg PO in pigeons, 600 mg/kg SC in frogs and 3676 mcg/kg by an unreported route in humans. In the preclinical study reports, morphine was 3x-10x more toxic in newborn animals than in adults due to greater permeability of the brain to morphine in newborns (Kupferberg and Way, 1963).

The morphine-induced deaths in animals were associated with convulsions, respiratory failure and circulatory failure (Humphreys, 1988). Adverse effects of high morphine doses in dogs include vomiting, delirium, clonic spasms, and raspy and labored breathing (Humphreys, 1988). Catalepsy, circling, stereotypical behavior, Straub tail, increased motor activity, exophthalmos, and shallow breathing are observed in rodents given high doses of morphine. Histopathological examination after single doses of morphine at 125 mg/kg IP in rats have shown centrilobular and midzonal vacuolation, diffuse fatty degeneration and eosinophilic changes without necrosis in the liver during the period from 2.5 to 18 hours after dosing (Maruta *et al.*,1997).

Acute morphine toxicity in humans includes miosis, constipation, urinary retention, nausea, vomiting, hypothermia, drowsiness, dizziness, apathy, confusion, respiratory depression, hallucinations, distorted perceptions, dyspnea, sleep disturbance, hypotension, cold/clammy skin, coma and pulmonary edema.

Multiple dose A study by Finnegan *et al.* (1948) showed a treatment-related decrease in body weight gain, increased mortality and increased incidence of pneumonia after chronic treatment with oral morphine sulfate at 0.01%-1% (dietary) in male and female rats. Decreased body weights were also observed without other drug-related abnormalities in a study on chronic morphine administration in female rats given 25 mg/kg/d (dietary) for 124 days (Fennessy and Fearn, 1969). Drug-related morphologic changes in the kidneys of rats treated with increasing doses of morphine sulphate from 24 to 96 mg/kg/d SC or 10 mg/kg SC b.i.d. for 6 days were reported in a study by Marchand *et al.* (1969). The changes included large cytoplasmic and intercellular vacuoles, increased thickness of basement membranes, loss of microvilli, larger and clumping mitochondria, increased lysomes and changes in size, shape and density of nuclei in the proximal, distal and collecting tubules. Reduced hepatic glucuronosyl

transferase and N-demethylase have also been reported in rats treated chronically with morphine (Parke, 1968).

In dogs, subcutaneous morphine at 2 or 5 mg/kg/d for 100 days resulted in one death at the high dose on day 70, and weights loss in all of the animals (Finnegan *et al.*,1948). In that study, the biochemical assays showed decreased red blood cell counts and hemoglobin concentrations at the high dose, spleen or lung hemorrhage at the low dose and fatty changes in liver and renal tubular epitheluim in the dog that died.

Tolerance to the analgesic effect and to many of the side effects of morphine, and dependence on the drug resulting in withdrawal signs and symptoms when morphine administration is abruptly stopped, are well known results of chronic treatment. The rapid development of tolerance results in a need for increasing doses over time to produce the same effects.

Adverse effects of chronic injected opioid abuse in humans have included abscesses, anaphylaxis, acute transverse myelitis, arrhythmias, wound botulism, cellulitis, endocarditis, fecal impaction, glomerulonephritis, hyperglycemia, hypoglycemia, osteomyelitis, postanoxic encephalopathy, tetanum, thrombophlebitis, nephropathy, hoarseness, hepatitis, pneumothorax, paraplegia, mycotic aneurysms and leukoencephalopathy (Lewis *et al.*,1980; Wolters *et al.*,1982).

CARCINOGENICITY

No studies to evaluate the carcinogenic potential of morphine sulfate have been conducted by the sponsor or reported in the literature. There was no microscopic evidence of pre-neoplastic or neoplastic changes in repeated dose toxicity studies at up to 25 mg/kg/day (dietary) for 124 days in rats (Finnegan *et al.*,1948; Fennesay and Fearn, 1969) or 5 mg/kg/day (SC) for 100 days in dogs (Finnegan *et al.*, 1948). Morphine was found to inhibit tumor necrosis factor and the growth of several human cancer cell lines and BALB/3T3 cells (Sueoka *et al.*,1996), and the metabolite morphine-6-glucuronide inhibited neuroblastoma and PC-9 cell line growth (Sueoka *et al.*,1998). However, there is evidence of a potential for indirect involvement of morphine in tumorigenesis. Subcutaneous morphine administration at doses of 5 mg/kg and above increased the ethylation of esophageal DNA induced by N-nitrosodiethylamine in rats (Ribeiro-Pinto and Swann, 1997). Morphine administration was associated with immunosuppression in several animal species (LeVier *et al.*, 1994; Liu *et al.*,1992; Fuchs and Pruett, 1993), although immunosuppressive effects have not been observed in clinical studies when morphine was given at therapeutic doses. Also, morphine was clastogenic in several *in vivo* mutagenicity assays (Swain *et al.*,1980; Das and Swain, 1982; Badr and Rabouh, 1983; Couch and Sawant, 1995). Clinical and epidemiological studies have shown that chronic opioid abusers show an increased incidence of chromosomal abnormalities (Li and Lin, 1998) and neoplastic disease including esophageal and urinary cancers (Ribeiro-Pinto and Swann, 1997).

REPRODUCTIVE TOXICOLOGY

The results of reproductive toxicology studies on embryo-fetal development (Segment II) reported in the literature are presented in the following table (reproduced in part from the original NDA submission).

Citation	Species #Treated/Dose Group	Dose (mg/kg/d), Route, Formulation, Dosing Period	Developmental Endpoints	Significant Findings
Lintern-Moore *et al.*, 1979	Rat (immature) 6/timepoint	50 mg/kg/d IP, in saline, 1 or 7 days	Body, pituitary, ovarian, uterine and adrenal weights, histopathology	Altered ovarian follicular development, ↓number of follicles after single dose, ↓initiation of follicular growth and number of follicles after 7 days of administration
James et al., 1980	Rat (male) 15/group	50 mg/kg/d SC in sterile water, for 4 and 9 weeks, or 13 week recovery	Serum LH, FSH, and testosterone, testes, seminal vesicles, prostate and pituitary weights and histopath	↓serum LH and testosterone, secondary sex organ weights, modified secretory activity of pituitary gonadotrophic cells, ↓spermatogenic cell populations (particularly early spermatids), all effects reversed after 13 weeks
Harpel & Gautieri, 1968	Mouse 5-32/group	0, 100-500 SC Morphine sulfate in distilled water, Gestation days 8 or 9	Embryo-Fetal: viability, implantation sites, resorptions, body weights, lengths, gross&skeletal observations	Clinical signs, ↓maternal food consumption: all doses Day 8: ↓fetal body wt. (≥200 mg/kg) Exencephaly (≥300 mg/kg) Axial skeletal fusions & ↓crown-rump length (≥400 mg/kg) Day 9: Axial skeletal fusions & ↓fetal body wt (≥100 mg/kg) ↑partial fetal resorptions & ↓crown-rump length (≥400 mg/kg) ↓maternal body wt (500 mg/kg)
Iuliucci & Gautieri, 1971	Mouse # not provided	0, 200, 300, 400 IP, Gestation days 8 or 9	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	Clinical signs in all morphine dose groups, deaths at 400 mg/kg. Exencephaly, axial skeletal fusions in ≥1dose grp after treatment on days 8 or 9, ↓fetal body wt at 300 mg/kg, no effects on litter size, resorptions, sex ratios.
Ciociola & Gautieri, 1982	Mouse # not provided	0, 0.15, 1.5, 15 SC infusion, morphine sulfate in saline, gestations days 7-10 daily	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	↓ fetal body wt, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae and xiphoid in morphine treated grps, inversely dose-proportional (perhaps due to tolerance at higher doses)
Glick *et al.*, 1977	Rat 4/group	0, 0.4 g/L, morphine sulfate in drinking water, gestation days 0-21 daily	Embryo-Fetal: Sex ratios, body wts Postnatal: self-administration behavior	Faster acquisition of morphine self-administration behavior in offspring of morphine treated dams. No embryo-fetal effects.
Eriksson & Ronnback, 1989	Rat 5/group	0, 12.5, 25, 50, 100 PO (fluid diet), gestation day 5 through postpartum day 2	Embryo-Fetal: Viability, body wts, litter size Postnatal: nociceptive responses	↓fetal viability, body wts, and postnatal viability, and ↑sensitivity to morphine-induced analgesia at ≥12.5 mg/kg/d, no surviving offspring at ≥25 mg/kg/d
Zagon & McLaughlin, 1977a	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in	Embryo-Fetal: Viability, body,whole	Morphine-induced clinical signs and ↓body wts in dams, ↓litter size, viability, neonatal mortality, fetal neonatal body wts, absolute

		saline, b.i.d. 5 d prior to mating through gestation & lactation	brain, cerebellum wts Postnatal: brain length, cerebrum & cerebellar widths	brain and cerebellar wts at birth and during neonatal period, ↑relative brain and cerebellar wts at postnatal day 60, reduced brain lengths and cerebral & cerebellar widths, cyanotic and hypothermic infants
Zagon & McLaughlin, 1977b	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in saline, b.i.d. 5 d prior to mating through gestation & lactation	Embryo-Fetal: Viability, body wts, gross malformations	Morphine-induced maternal clinical signs and ↓body wt, ↓litter size, viability, neonatal mortality, fetal & neonatal body wts
Siddiqui *et al.*, 1995	Rat 10-23/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, litter size, incidence of stillbirths, cannibalism, body wts, gross malformations Postnatal: hormonal/neuro chemical levels, histopathology (testes)	↓maternal body wt gain, ↑gestation length & # stillbirths/litter, ↓litter size, birth wt & postnatal body wt gain, ↓plasma/testicular levels of luteinizing hormone and testosterone, ↓testes wt (adult), seminiferous tubule shrinkage, germinal cell aplasia, ↓spermatogenesis, ↑hypothalamic norepinephrine
Siddiqui *et al.*, 1997	Rat 6-16/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, viability, litter size, incidence of stillbirths, body wts, Postnatal: ovarian function, reproductive behavior & indices, neurochemical analyses	Abnormal estrus cycles in adult ♀s, ↑ gestational length, ↑ #stillbirths, ↓ body wts at birth and body wt gain during development, delayed sexual maturation in ♀ offspring, mating behavior altered at adulthood, ↓ plasma estradiol, ovarian estradiol, progesterone, hypothalamic norepinephrine in offspring of morphine treated rats
Johannesson & Becker, 1972	Rat 6-9/group	0, 10, 20 SC, morphine sulfate dissolved in distilled water, gestation days 2-5, 7-9, 11-13 or 17-20 daily	Embryo-Fetal: viability, implantation sites, body wts, lengths, gross & skeletal observations	Maternal mortality in 6 animals, ↓ growth rate, ↑ response to nociceptive stimulus in offspring of morphine treated rats
Sobrian, 1977	Rat 9-15/group	40 SC, morphine sulfate dissolved in saline, 5 d prior to mating and gestation days 0-15	Embryo-fetal: viability, sex ratios, body wts, gross malformations Postnatal: motor activity	↓ viability, neonatal mortality in morphine grp, ↓ fetal body wts, ↑ postnatal spontaneous motor activity
Kirby, 1982	Rat # not provided	0, 20 SC, morphine sulfate dissolved in saline, every 4 h, gestation days 12-21	Embryo-Fetal: viability, litter size, body wts, length&volume of 1st thoracic spinal cord segment	↓ maternal food consumption and body wt, ↓ body wt of offspring at birth, ↑ mortality in offspring, ↓ growth of spinal cord components in offspring
Vathy *et al.*, 1983	Rat	20 SC, morphine	Embryo-Fetal:	↑ inter-litter variability for vaginal opening, ↑

	5-6/group	sulfate dissolved in saline, b.i.d. gestation days 5-12	body wts Postnatal: vaginal opening, mating behavior, hypothalamic-preoptic area cytosolic estrogen receptor levels	neonatal body wts, ↓ adult feminine sexual behavior in offspring
Fujinaga & Mazze, 1988	Rat 15-30/group	0, 10, 35, 70 SC infusion, morphine sulfate dissolved in saline, continuous on gestation days 5-17	Embryo-Fetal:viability, sex ratios, resorptions, implantations, body wts, gross & skeletal malformations	Maternal morphine plasma levels: 197 (LD) to 676 (HD) ng/ml, fetal plasma levels 60-292 ng/ml (gestation day 20) Normal maternal blood gasses. ↓pregnancy rates, slightly enlarged cerebral ventricles, ↑ postnatal mortality, ↓ postnatal body wt, Suggests teratogenicity in previous studies due to respiratory depression
Vathy & Katay, 1992	Rat 13-14/group	0, 10, 20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Postnatal: sexual behavior, brain catecholamine content	↑ male and ↓ female hypothalamic norepinephrine and altered sexual behavior
Koyuncuoglu & Aricioglu, 1993	Rat 8/group	0, 10 SC, morphine sulfate dissolved in saline, t.i.d., gestation days 16-21	Embryo-Fetal:body wts Postnatal: morphine dependence	Abstinence clinical signs more pronounced upon morphine withdrawal and naloxone treatment in offspring of morphine treated rats
Ramsey *et al.*, 1993	Rat 21-23/group	0, 20 SC and Oral (drinking water), morphine HCl in water, gestation days 7, 8, 9 (SC b.i.d.), gestation days 10-21 (PO, daily)	Embryo-Fetal: viability, litter size, sex ratios Postnatal: body wts, cocaine and heroin self-administration behavior	No maternal toxicity Enhanced self-administration behavior in offspring
Vathy *et al.*, 1994	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal:body wts Postnatal: neurochemical analyses	Altered norepinephrine content and turnover in sexually dimorphic manner
Vathy *et al.*, 1995	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal: viability, litter size, sex ratios Postnatal: neurochemical analyses	No effects on maternal body wt, fetal viability, litter size, sex ratios Altered development of norepinephrine and dopamine neurotransmitter systems in hypothalamus, preoptic area, striatum, cerebellum in sexually dimorphic manner
Gagin & Shavit, 1996	Rat # not provided	Up to 12 SC, morphine in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: body wts, gross malformations Postnatal: nociceptive responses and sweetness preference	↓ maternal food consumption, body wt at birth Enhanced analgesic responses after morphine challenge postnatally, ↑ preference for saccharin solution
Hol *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Postnatal: behavior	↑ Pinning (play behavior) and social grooming in offspring, less social avoidance in adulthood

Niesink *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Embryo-Fetal: viability, litter size Postnatal: body wt, various behavioral endpoints	No maternal toxicity, no postnatal effects on sensorimotor development Elevated social play, no other behavior affected
Gagin *et al.*, 1997a	Rat 10/group	Up to 48 SC, morphine, slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, normal copulatory behavior but partial feminization (female patterns of receptivity) in males exposed prenatally
Gagin *et al.*, 1977b	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, enhanced morphine reinforcing effect in adulthood in offspring
Shavit *et al.*, 1998	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Postnatal: immune function, nociceptive function, behavior	↓ cytotoxic activity of NK cells in offspring, ↓ LPS-induced fever, ↓ hyperalgesia after LPS administration, altered open-field activity, suggests long-term impairment of host-defense mechanisms
Geber & Schramm, 1975	Hamster 20-120/group	0, 35, 88, 157, 222, 244, 300, 322 SC, morphine sulfate dissolved in unknown vehicle, gestation day 8	Embryo-Fetal: viability, implantation sites, resorptions, body wts, lengths, gross & skeletal observations	Congenital malformations (exencephaly and/or cranioschisis) at ≥88 mg/kg/d
Johnston *et al.*, 1996	Hamster # not provided	0, 10 IP, DuraMorph® aqueous suspension, 4d prior to mating through pregnancy and lactation, daily	Postnatal: sexual behavior	Altered sexual behavior in male offspring
Hunter *et al.*, 1997	Guinea pig 6-8/group	0, 1.5, 5, 15 SC, morphine dissolved in saline, gestation day 32 until parturition, daily	Fetal: gestation duration, viability, litter size, sex ratios Postnatal: respiratory parameters, locomotor activity, body temperature	↓ maternal body wt at ≥1.5 mg/kg/d ↓ birth wts, neonatal minute ventilation and central respiratory drive in early postnatal pd at ≥5 mg/kg/d ↑ locomotor activity in early postnatal pd at ≥15 mg/kg/d
Roloff *et al.*, 1975	Rabbit 11-31/group	0, 10, 20, 40 SC, q.i.d. gestation days 6-14	Embryo-Fetal: viability, litter size, body wt, lung volume, amniotic fluid	↓ maternal body wt in all morphine grps ↑ abortion rate dose-related ↓ fetal body wt at all doses No effects on lung volume, amniotic fluid composition, litter size, intrauterine death or

			composition	% pregnancies with dead fetuses
Raye *et al.*, 1977	Rabbit # not provided	0, 50, 100 SC, morphine sulfate in unspecified diluent, 7d prior to mating through mating and gestation, daily	Embryo-Fetal: viability, body wts, crown-rump lengths, organ weights, gross malformations	↓ maternal body wt and food consumption in all morphine grps ↓ fetal body wt , crown-rump lengths, lung weights and ↑ liver & kidney wts at ≥50 mg/kg/d, ↑ heart and interscapular fat pad wts at 100 mg/kg/d

GENETIC TOXICOLOGY

The results of genotoxicity studies on morphine sulfate, reported in the literature, are presented in the following table (reproduced from the original NDA submission).

Citation	Assay/Test System	#Animals/ Dose Group	Dose Regimen/ Formulation/ Route	Significant Findings
Swain *et al.*, 1980	*In vivo* Cytogenic/ Mouse	5♂ and 5♀	Single-dose: 0, 3.2, 8, 16, 32, 64 mg/kg IP 7 consec days: 3.2 mg/kg/d IP Morphine sulfate dissolved in distilled water	↑#chromosomal aberrations after single IP doses ≥3.2 mg/kg No morphine-related effects following repeated doses presumably due to the development of tolerance
Das and Swain, 1982	Micronucleus/ mouse	5 ♂ or ♀	2 doses separated by 24 h: 0, 3.2, 8, 16, 32 mg/kg IP Morphine sulfate dissolved in distilled water	Dose-related ↑ incidence of micronuclei in polychromatic erythrocytes at doses ≥3.2 mg/kg
Badr and Rabouh, 1983	Dominant Lethal and Spermatocyte test/Male Mouse	12 ♂ mated with 2 ♀ per dose group	3 consec daily doses of 0, 10, 20, 40, 60 mg/kg IP Morphine sulfate dissolved in saline	↑#dominant lethals, particularly early spermatids, & types and frequencies of chromosomal aberrations in dividing spermatocytes at all dose levels
Sawant and Couch, 1995 Couch and Sawant, 1995	*In vivo* & *in vitro* Cytogenetic/Mouse	Unknown	Single IP doses: 0-100 mg/kg Single IV dose 20 mg/kg Morphine sulfate dissolved in phosphate-buffered saline	Dose-related ↑ in micronucleated splenocytes & lymphocytes, blocked by adrenalectomy (suggest ⇑ in corticosteroid plasma level mediate genotoxic response) Morphine added to lymphocytes of cyclophosphamide treated animals at ≥ 10^{-7}M increased # of micronuclei in binucleated cells following *in vitro* stimulation with mitogen In vitro, morphine failed to induce micronuclei in mitogen-stimulated murine splenocytes at up to 10^{-4}M (~30mcg/mL)

Fuchs and Pruett, 1993	*In vivo* & *in vitro* DNA Fragmentation Thymocytes/Mouse	2-4 ♀	75mg SC time-release pellet, morphine released for 12-48 h	DNA fragmentation in thymocytes noted following implantation of morphine pellets. *In vitro*, no DNA fragmentation noted following morphine exposure to murine thymocytes. *In vivo*, DNA fragmentation blocked by opiate & glucocorticoid antagonists suggesting effect at least partially mediated through effect on hypothalamic-pituitary-adrenal axis
Falek *et al*, 1972	Chromosomal Aberration/ Human Leukocytes	Not applicable	*In Vitro*	In morphine treated cells, no evidence of chromosomal aberration at concentrations up to 6 mcg/mL
Knaap and Kramers, 1976	Mutagenicity/ Drosophila melanogaster	Not applicable	*In Vitro*	No evidence of induction of sex-linked recessive lethal mutations, translocations, or dominant lethal mutations
Shafer *et al*,, 1994	Mutagenicity/ Human HUT-78 cells & HRPT mutant cells	Not applicable	*In Vitro*	Morphine alone increased DNA fragmentation at concentrations $\geq 5x10^{-9}$ M Morphine also increased the mutation frequency of the mutagen ethylmethanesulfonate over that of the mutagen alone

OVERALL SUMMARY AND EVALUATION

Morphine sulfate, the principle alkaloid substance derived from the opium poppy, was discovered in 1806 and has been used since then for the treatment of moderate to severe pain, and as an antidiarrheal and antitussive agent. The pharmacology and toxicology of morphine have been well characterized and widely reported in the published literature. Morphine sulfate is marketed in injection, oral capsule, solution and tablet, and suppository forms. Sustained release morphine sulfate formulations, such as MS Contin® (Purdue Frederick, up to 400 mg/day) have been approved for clinical use and are widely prescribed. The proposed drug product was developed as a combination of extended release and immediate release components in a once-daily capsule to provide rapid onset of absorption and analgesia and long-acting relief from pain with fewer peak-trough plasma level fluctuations compared to the existing twice-daily dosing forms.

[redacted]™ was evaluated in 140 healthy volunteers in pharmacokinetic/bioavailability studies, and in 740 patients in seven clinical trials on pharmacokinetics, pharmacokinetics/pharmacodynamics, Phase III efficacy and safety at up to 6 months, and in a one year safety study. The pain etiologies included chronic malignant and non-malignant pain, such as osteoarthritis. There were six deaths, all considered to be unrelated to [redacted]™ treatment. The most common treatment-related adverse effects were characteristic of opioid drug effects and included nausea, constipation,

somnolence, vomiting, asthenia, peripheral edema, headache, confusion, pruritus and dizziness. The proposed clinical use is for once-daily, oral administration in the treatment of moderate to severe chronic pain.

The pharmacology and toxicology of morphine sulfate are well know and widely reported in the published literature. No pre-clinical studies were conducted for this NDA submission. Brief summaries of the published study reports are discussed under PHARMACOLOGY above.

The sponsor was advised in a meeting with the Agency (January 18, 2000) that studies to evaluate the mutagenic and carcinogenic potential of morphine sulfate, and reproductive toxicology studies on embryo-fetal development (Segment II) in 2 species will be needed to support the safety of the proposed drug product. Because the application is submitted under Section 505(b)(2), it is reasonable to obtain this information by reference to the available published literature, provided the material referenced is considered adequate by today's standards. This submission summarized the available literature reports on Segment II reproductive toxicology and genotoxicity of morphine. No studies to evaluate the carcinogenic potential of morphine sulfate were conducted by the sponsor or reported in the literature. Evaluation of the carcinogenic potential of morphine sulfate in two species will be needed as a Phase 4 commitment.

Evidence for indirect involvement of morphine in tumorigenisis was reported in the literature. Increased ethylation of esophageal DNA induced by N-nitrosodiethylamine was observed in rats given doses of 5 mg/kg SC and higher (Ribeiro-Pinto and Swann, 1997). Immunosuppression by morphine, observed in several animal species (LeVier *et al.*, 1994; Liu *et al.*, 1992; Fuchs and Pruett, 1993) can theoretically contribute to an increased risk of carcinogenesis. Morphine was positive for clastogenicity in *in vivo* mutagenicity assays (Swain *et al.*,1980; Das and Swain, 1982; Badr and Rabouh, 1983; Couch and Sawant, 1995), and chronic opioid abusers show increased incidence of chromosomal abnormalities (Li and Lin, 1998) and neoplastic disease (Ribeiro-Pinto and Swann, 1997). On the other hand, there were no pre-neoplastic or neoplastic changes in the histopathology examinations in rats given up to 25 mg/kg/d morphine daily in the diet for 124 days (Finnegan *et al.*, 1948; Fennesay and Fearn, 1969) or in dogs given up to 5 mg/kg/day by daily subcutaneous injection for 100 days (Finnegan *et al.*, 1948). Morphine inhibited tumor necrosis factor and human cancer cell growth *in vitro* in one study (Sueoka *et al.*, 1996) and the morphine metabolite morphine-6-glucuronide inhibited neuroblastoma and PC-9 cell growth (Sueoka *et al.*, 1998). The literature reports that suggest indirect involvement of morphine in tumorigenesis support the need for timely and thorough evaluation of morphine carcinogenic potential in two rodent species according to ICH guidelines.

The sponsor summarized the available literature reports on *in vitro* and *in vivo* assays conducted to evaluate the potential for mutagenicity and clastogenicity in mammalian systems. In one *in vitro* study, morphine sulfate was negative for induction of chromosomal aberration in human leukocytes at concentrations up to 6 mcg/ml (Falek *et al.*, 1972). However, in that study, metabolic activation and positive controls were not used, and therefore the validity of the study was not demonstrated. A study on the potential mutagenic effects of morphine in *Drosophila melanogaster* showed no sex-

linked recessive lethal mutations, translocations and dominant lethal mutations at concentrations of 0.02 – 1.0 mg/ml (Knaap and Kramers, 1976). No positive control was used in that study. Morphine increased the frequency of DNA fragmentation in human HUT-78 cells at concentrations of 5×10^{-9} M and higher, and increased the mutation frequency induced by ethylmethanesulfonate (Shafer *et al.*, 1994), but had no effect on DNA fragmentation in murine thymocytes (Fuchs and Pruett, 1993). In a study in lymphocytes of animals treated with cyclophosphamide, morphine increased the number of micronuclei in binucleated cells at concentrations higher than 10^{-7} M, but had no effect alone at concentrations up to 10^{-4} M. The results of the in vitro studies suggest that morphine may potentiate the mutagenic effects of other agents that induce DNA damage.

The results of *in vivo* studies on morphine genotoxic effects in mouse bone marrow, spermatocytes, splenocytes, lymphocytes, and thymocytes were reported in the literature. Morphine was clastogenic in mouse bone marrow cells at single doses of 3.2 – 6.4 mg/kg IP, but resulted in no chromosomal aberrations after repeated dosing with 3.2 mg/kg/d daily for 7 days (Swain *et al.*, 1980). Das and Swain (1982) reported a dose-related increase in the incidence of micronuclei in polychromatic erythrocytes of mice given 2 morphine doses of 3.2 – 32 mg/kg IP within 24 hours. Morphine was positive in the dominant lethal test in mice, increasing the frequency of chromosomal aberrations in spermatids and in dividing spermatocytes at doses at and above 10 mg/kg/day IP for 3 consecutive days (Badr and Rabouh, 1983). Morphine was also mutagenic in splenocytes and peripheral blood lymphocytes, increasing the frequency of micronuclei in both cell types at doses of 20 mg/kg IP and above (Couch and Sawant, 1995). Implantation of morphine pellets (75 mg SC) increased DNA fragmentation in murine thymocytes (Fuchs and Pruett, 1993). The genotoxic effects observed in splenocytes, peripheral blood lymphocytes and thymocytes may have resulted in part from morphine-induced increases in corticosteroid plasma levels because the effects were blocked in mice that were adrenalectomized prior to dosing (Couch and Sawant, 1995) and in mice that received opiate and glucocorticoid antagonists concurrently with the morphine exposure (Fuchs and Pruett, 1993).

The sponsor provided summaries of 30 literature reports on studies to evaluate morphine reproductive toxicology in mice, rats, hamsters, guinea pigs, and rabbits. Exencephaly and axial skeletal fusions were observed in morphine treated mice at doses of 200-400 mg/kg IP on gestation days 8 or 9 (Iuliucci and Gautieri, 1971). Subcutaneous morphine injections produced exencephaly at doses of 300 mg/kg and greater given on gestation day 8, and axial skeletal fusions at doses of 100 mg/kg and greater on gestation day 9 in mice (Harpel and Gautieri, 1968). In another study in mice, continuous subcutaneous infusion of morphine sulfate at 0.15 – 15 mg/kg/d on gestation days 7 through 10 resulted in fetal exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid (Ciociola and Gautieri, 1982). Additional embryotoxic effects of morphine observed in mice in one or more of these studies include decreased crown-rump length, decreased fetal body weights, and partial fetal resorptions. The relative contribution of maternal toxicity including decreased maternal food consumption and body weights, and hypoxia, to the observed toxicity in the fetal mice is unknown.

Reproductive toxicology studies in rats administered morphine in drinking water, and by IP and SC injection were reported in the literature. Oral morphine sulfate decreased fetal viability, body weights and postnatal viability, and increased the sensitivity to morphine-induced analgesia in rats at doses of 12.5 mg/kg/d and greater given on gestation day 5 through postpartum day 2 in rats (Eriksson and Ronnback, 1989). In that study, there were no surviving offspring at doses greater than 25 mg/kg/d PO. Daily prenatal exposure to morphine in the maternal drinking water at 0.4 g/L on gestation days 0 through 21 resulted in faster acquisition of morphine self-administration behavior in the offspring of the morphine treated rats (Glick *et al.*, 1977).

Intraperitoneal administration of morphine sulfate in rats at doses up to 40 mg/kg/d beginning several weeks before mating through mating, gestation and 10 days into the postpartum period altered several reproductive parameters in both the dams and offspring (Siddiqui *et al.*, 1997). Abnormal estrus cycles, increased gestational length and increased number of stillbirths were observed in the maternal rats. In the offspring, decreased body weights at birth and body weight gain during development, delayed sexual maturation, altered mating behavior at adulthood, and decreased plasma estradiol, ovarian estradiol, progesterone, and hypothalamic norepinephrine were observed. Zagon and McLaughlin (1977a and 1977b) observed decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights at birth and during the neonatal period, brain lengths, and cerebral and cerebellar widths, increased neonatal mortality, and cyanotic and hypothermic infants after morphine sulfate administration at 80 mg/kg/d IP from 5 days before mating through gestation and lactation. Similar effects were observed in a study by Siddiqui *et al* (1995) in rats given 40 mg/kg/d IP morphine sulfate beginning several weeks before mating through the 10th day postpartum. Also reported in that study were decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in the male offspring.

The literature reports of sixteen studies on reproductive toxicology of subcutaneous morphine in rats were summarized (see Johannesson and Becker, 1972; Sovrian, 1977; Kirby, 1982; Vathy *et al.*, 1983; Fujinaga and Mazze, 1988; Vathy and Katay, 1992; Koyuncuoglu and Aricioglu, 1993; Ramsey *et al*,. 1993; Vathy *et al.*, 1994; Vathy *et al.*, 1995; Gagin and Shavit, 1996; Hol *et al.*, 1996; Niesink *et al.*, 1996; Gagin *et al.*, 1997 a and 1997b; Shavit *et al.*, 1998). Doses of 10-70 mg/kg by SC injection or perfusion pumps were studied in paradigms ranging from dosing during various gestation periods of organogenesis (e.g., gestation days 5-12, 11-18, etc.), to dosing from pre-mating through gestation day 15. An early study by Sobrian (1977) showed that subcutaneous morphine administered to pregnant rats at 40 mg/kg/d from 5 days before mating through gestation day 15 resulted in decreased fetal viability and body weights, and increased neonatal mortality and postnatal spontaneous motor activity. Morphine treatment during gestational periods of organogenesis resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: increased pre- and post-natal mortality, inter-litter variability for vaginal opening, incidence of enlarged cerebral ventricles, and increased hypothalamic norepinephrine in males, decreased body weights, growth of spinal cord components, female hypothalamic norepinephrine, and immune function. Also observed in the offspring of

dams administered subcutaneous morphine were enhanced analgesic responses and social play behavior, enhanced adult feminine sexual behavior, and partial feminization in copulatory behavior of male offspring, and altered development of norepinephrine and dopamine neurotransmitter systems in the hypothalamus, preoptic area, striatum and cerebellum. Overall, the NOAEL for fetal toxicity in rats was 10 mg/kg/d SC (associated with a maternal plasma level of 200 ng/ml). No teratogenicity was found at up to 70 mg/kg/d SC morphine (plasma level 668-676 ng/ml). Pregnancy rates were reduced at doses at and above 35 mg/kg/d SC. Maternal toxicity including clinical signs, decreased food consumption and body weights, and hypoxia, and the effects of maternal withdrawal from repeated dosing with morphine may have contributed to the observed embryotoxic effects to an unknown extent.

In reproductive toxicology studies in hamsters, morphine sulfate produced exencephaly and/or cranioschisis at subcutaneous doses of 88 mg/kg/d and greater on gestation day 8 (Geber and Schramm, 1975) and altered sexual behavior in male offspring when given intraperitoneally at 10 mg/kg/d from 4 days before mating through lactation (Johnston *et al.*, 1996). In guinea pigs, morphine sulfate given at doses of 1.5-15 mg/kg/d SC from gestation day 32 until parturition decreased maternal body weights, birth weights, neonatal minute ventilation and central respiratory drive, and increased locomotor activity in the early postnatal period (Hunter *et al.*, 1997). Subcutaneous morphine in rabbits at 50-100 mg/kg/d SC for 7 days before mating through gestation resulted in decreased maternal and fetal body weights, maternal food consumption, fetal crown-rump lengths, and lung weights, and increased fetal liver, kidney, heart and interscapular fat pad weights (Raye *et al.*, 1977). When administered to rabbits at 10-40 mg/kg four times each day on gestation days 6-14, morphine decreased both maternal and fetal body weights and increased the abortion rate in a dose related manner (Roloff *et al.*, 1975).

All excipients in the proposed drug product, sodium lauryl sulfate, USP; fumaric acid, USP; hydrated magnesium silicate (talc), USP; polyvinyl pyrrolidone, USP; nonpareil ——— (sugar spheres); polymeric methacrylates, USP ———————————————————, and the gelatin capsule shell components black ink, gelatin, titanium dioxide, D&C yellow No. 10, FD&C green NO. 3, FD&C red No. 40, FD&C red No. 3, and FD&C blue No. 1 are approved and marketed in other drug products.

There is a theoretical risk that fumaric acid will combine with morphine to form the morphine fumarate salt. If formed, morphine fumarate is expected to dissociate rapidly after systemic absorption. The toxicology of morphine fumarate has not been studied in support of its safety in humans. However, there are several approved and marketed drug products that contain the fumarate moiety, including quetiapine fumarate, ferrous fumarate, bisoprolol fumarate, ibutilide fumarate, and others. Fumaric acid is used in the treatment of psoriasis, as a food additive, an antioxident in beverages, baking powders, resins and dyes, as an acidifier, as a flavoring agent in foods and in multiple drug products.

According to the Hazardous Substances Data Bank (National Library of Medicine, Department of Health and Human Services) the human NOAEL for fumaric acid is 500

mg/day PO daily for one year (> 4x the exposure at the MRHD for ———— . The acute toxicity is low; the LD_{50} in rats is 10,700 mg/kg PO and the LDLo in rabbits is 5,000 mg/kg PO. However, a high single oral dose of 100 mg PO (approximately 500 mg/kg) was nephrotoxic in rats, producing proximal tubular lesions observable in the histological examination. There is a case report of a 21-year old woman who developed acute oligouric renal failure after ingesting 1 g fumaric acid orally in addition to topical treatment (dose not provided) for 24 days (see Anonymous, 1990). In another literature report, four patients developed acute renal failure after treatment with fumaric acid esters. The effect on renal function was reversible in two of the patients but incompletely reversible in the other 2 patients at the time of follow-up evaluation. Oral therapy has also been associated with disturbed liver function (Nugteren-Huying, 1990), adverse gastrointestinal effects (Altmeyer, 1994), and flushing (Kolback and Nieboer, 1990).

Pre-clinical studies on fumaric acid toxicology showed no carcinogenic potential in mice and rats. Fumaric acid was negative in the Ames test and had no effect on DNA synthesis in hepatocytes or hepatoma cells from rats treated with mitomycin C and aflatoxin B1. No teratogenic effects were observed in Drosophila embryo cell cultures. Therefore, the studies reported in the literature show no evidence that fumaric acid will increase the reproductive toxicity, genotoxicity or carcinogenic potential of morphine.

LABELING REVIEW

The proposed Carcinogenicity/Mutagenicity/Impairment of Fertility and Pregnancy sections of the package insert are presented below. Recommended changes are presented under External Recommendations to the Sponsor, below.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, *in vitro* studies have reported that morphine is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with human leukocytes or murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma cell line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in mouse micronucleus test and to induce chromosomal aberrations in spermatids and murine lymphocytes. Some of the *in vivo* clastogenic effects reported with morphine in mice, may be directly related to increases in glucocorticoid levels produced by morphine in this species and not clinically relevant.

Chronic opioid abusers (e.g. heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in nonexposed individuals and in heroin users enrolled in long-term opioid maintenance programs.

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae,

and malformed xiphoid were noted and no maternal toxicity reported. In the rat, morphine is not a significant teratogen even at morphine exposure levels significantly beyond that normally encountered in clinical practice. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg. In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

CONCLUSIONS

The proposed drug product, ———™ (morphine sulfate) Extended-Release Capsules, is approvable from a pharmacology and toxicology point of view. In accordance with the Agency recommendations made during the Pre-NDA meeting with the sponsor on January 18, 2000, literature reports of studies on the mutagenic potential and reproductive toxicology of morphine were submitted and found adequate to support the safety of the product. However, carcinogenicity studies are needed, and may be completed as a Phase IV commitment. Also, changes to the proposed label are recommended as described under RECOMMENDATIONS below.

RECOMMENDATIONS

External Recommendations to the Sponsor:

In accordance with the Agency recommendations made during the Pre-NDA meeting on January 18, 2000, literature reports of studies on the mutagenic potential and reproductive toxicology of morphine were submitted and found adequate to support the safety of the product. However, carcinogenicity studies in two rodent species, conducted according to ICH guidelines, are needed. The carcinogenicity studies may be completed as a Phase IV commitment.

Additionally, the following changes to the label are recommended:

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Kathleen A. Haberny, Ph.D.

Team Leader: Thomas Papoian, Ph.D.

cc: NDA 21,260 Arch
HFD 170/Division File
HFD 170/K Haberny
HFD 170/K Compton

APPEARS THIS WAY
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/s/

Kathy Haberny
1/10/01 02:09:18 PM
PHARMACOLOGIST

Thomas Papoian
1/16/01 08:43:19 AM
PHARMACOLOGIST

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ON ORIGINAL

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
LABELING REVIEW
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD 170/Kathleen Haberny, Ph.D.

KEY WORDS: Morphine sulfate; Oral capsules; Extended release

NDA Number 21-260

Serial Number 000 / May 25, 2000 / Original Application

Review Completion Date: March 26, 2001

Information to sponsor: Yes (x) No ( )

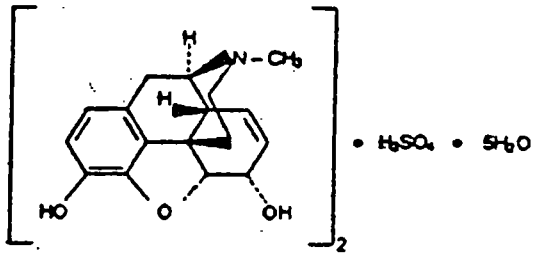
Sponsor: Elan Pharmaceutical Research Corp., 1300 Gould Dr., Gainesville, GA 30504

Manufacturer for drug substance: [redacted]

Drug:

Code Name: None
Generic Name: Morphine sulfate USP
Trade Name: [redacted] (morphine sulfate) Extended-Release Capsules, [redacted] 30mg, 60mg, 90mg, and 120mg
Chemical Name: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5alpha,6alpha)-, sulfate (2:1) (salt), pentahydrate, or 7,8-Didehydro-4,5alpha-epoxy-17-methylmorphinan-3,6alpha-diol sulfate (2:1) (salt) pentahydrate [*6211-15-0*]
CAS Registry Number: 6211-15-0 (Pentahydrate form); 64-31-3 (Anhydrous form); 57-27-2
Molecular Formula/ Molecular Weight: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

Structure:



Drug class: Opioid Analgesic

Indication: Relief of chronic moderate to severe pain

Clinical formulation: Sustained hard gelatin capsules containing):

Component	Composition (mg/capsule)			
	Capsule 30mg	Capsule 60 mg	Capsule 90mg	Capsule 120 mg
Morphine sulfate USP	30	60	90	120
Nonpareil seeds USP (sugar spheres NF)				
Fumaric acid NF				
Hydrated magnesium silicate (talc) NF				
Sodium lauryl sulfate, NF				
Povidone USP (polyvinyl pyrrolidone) (Kollidon 30)				
1 Gelatin Capsule				

Capsule shell contains black ink, gelatin, titanium dioxide, D&C yellow No. 10 (30 mg), FD&C green No. 3 [redacted] mg), FD&C red No. 40 (90 mg), FD&C red No. 3 (120 mg), and FD&C blue No. 1 (120 mg).

Route of administration: Oral

Proposed use: For once-daily, oral administration at doses expected to reach 5 g per day

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

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In this submission the sponsor submitted additional information on formic acid toxicity in animals (see under IIA below), summarized from the published literature, the TNO BIBRA International Toxicity Profile (Charshalton, UK, 1991), and toxicity databases (see under IIA below). Internal discussion with the reviewing medical officer revealed that the high doses to which opioid-tolerant patients could be exposed approach 5 g/day morphine sulfate. This dose would also expose the patients to 5 g fumaric acid daily, during chronic treatment.

The following discussion is excerpted from the original NDA review dated March 26, 2001:

> There is a theoretical risk that fumaric acid will combine with morphine to form the morphine fumarate salt. If formed, morphine fumarate is expected to dissociate rapidly after systemic absorption. The toxicology of morphine fumarate has not been studied in support of its safety in humans. However, there are several approved and marketed drug products that contain the fumarate moiety, including quetiapine fumarate, ferrous fumarate, bisoprolol fumarate, ibutilide fumarate, and others. Fumaric acid is used in the treatment of psoriasis, as a food additive, an antioxidant in beverages, baking powders, resins and dyes, as an acidifier, as a flavoring agent in foods and in multiple drug products.
>
> According to the Hazardous Substances Data Bank (National Library of Medicine, Department of Health and Human Services) the human NOAEL for fumaric acid is 500 mg/day PO daily for one year (> 4x the exposure at a dose of 120 mg/day). The acute toxicity is low; the LD_{50} in rats is 10,700 mg/kg PO and the LDLo in rabbits is 5,000 mg/kg PO. However, a high single oral dose of 100 mg PO (approximately 500 mg/kg) was nephrotoxic in rats, producing proximal tubular lesions observable in the histological examination. There is a case report of a 21-year old woman who developed acute oligouric renal failure after ingesting 1 g fumaric acid orally in addition to topical treatment (dose not provided) for 24 days (see Anonymous, 1990). In another literature report, four patients developed acute renal failure after treatment with fumaric acid esters. The effect on renal function was reversible in two of the patients but incompletely reversible in the other 2 patients at the time of follow-up evaluation. Oral therapy has also been associated with disturbed liver function (Nugteren-Huying, 1990), adverse gastrointestinal effects (Altmeyer, 1994), and flushing (Kolback and Nieboer, 1990).
>
> Pre-clinical studies on fumaric acid toxicology showed no carcinogenic potential in mice and rats. Fumaric acid was negative in the Ames test and had no effect on DNA synthesis in hepatocytes or hepatoma cells from rats treated with mitomycin C and aflatoxin B1. No developmental effects were observed in Drosophila embryo cell cultures. Therefore, the studies reported in the literature show no evidence that fumaric acid will increase the reproductive toxicity, genotoxicity or carcinogenic potential of morphine.

Additional information on formic acid toxicity was provided in this submission. The information on formic acid toxicity in animals was summarized from the published literature, the TNO BIBRA International Toxicity Profile (Charshalton, UK, 1991), and toxicity databases (MEDLINE, IRIS, EMBASE, TOXLINE, Biosis, SciSearch, IPA, Shepard's and TERIS, CHRIS (Chemical Carcinogenesis Research Information System), DART/ETIC (Developmental and Reproductive Toxicology), EMIC (Environmental Mutagen Information Center), Gene-Tox, HAZARDTEXT®, HSDB (Hazardous Substances Data Bank), MEDITEXT®, The ReproTox® System, REPROTEXT®, and RTECS® (Registry of Toxic Effects of Chemical Substances), and TOXNET.

According to the toxicology data summarized in the present submission, the LD_{50} for disodium fumarate and magnesium fumarate were 3.7 and 1.4 g/kg PO, respectively (Locke *et al.*, J Amer Pharm Assoc 31:12-14, 1942), and for fumaric acid was 100-200 mg/kg IP (TNO BIBRA, 1991) in mice. In rats, the NOAEL was 7.05 g/kg/d PO for 3 days (11.4x the human dose of 5 g on a mg/m^2 basis, Levey *et al.*, J Amer Pharm Assoc 35:298-304, 1946). However, in that study, rats showed deaths (60%), loss of body weight, red lungs and gastrointestinal tract fluid with lymphocytic infiltration of gastric mucosa at 8.08 g/kg/d (13x MRHD). The oral LD50 in another study in rats was 9.3-10.7 g/kg fumaric acid (15x MRHD, Vernot *et al.*, Toxic Appl Pharm 42:417, 1977). In rabbits, the oral LD_{50} for fumaric acid was 4.5-5 g/kg (14.6X MRHD on a mg/m^2 basis, TNO BIBRA, 1991).

Subchronic toxicity studies showed no treatment-related effects by dietary sodium fumarate in rabbits at 2800 mg/kg/d for 150 days (Packman *et al.*, Tox Appl Pharm 5;163-167, 1963). However, Locke *et al.* (1942) found 50% mortality in rabbits given dietary sodium fumarate at 2880 mg/kg/d for 17 days.

In a chronic toxicology study in rats, dietary ingestion of fumaric acid at 500 mg/kg/d (0.8x MRHD of 5 g/d on a mg/m^2 basis) for 2 years produced no treatment-related effects (Levey *et al.*, 1946). At the dose of 750 mg/kg/d (1.2X MRHD) for 2 years, rats showed lower survival compared to controls, and testicular atrophy, but no other treatment-related effects (Fitzhugh and Nelson, J Amer Pharm Assoc 36:217-219, 1947). There were no treatment-related effects in guinea pigs given 400 mg/kg/d (0.9X MRHD) fumaric acid (dietary) for 52 weeks (Levey *et al.*, 1946) and in dogs administered 1250 mg/kg/d (6.8X MRHD) fumaric acid (dietary) for 2 years (TNO BIBRA, 1991). A full toxicology assessment was not performed in these studies.

Fumaric acid was not teratogenic in *Drosophila* embryo cell cultures (HSDB), had no effect on testes histology in rabbits at 2800 mg/kg/d (Packman *et al.*, Tox Appl Pharm 5:163-167, 1963), and had no effect on growth, reproduction or lactation in guinea pigs at up to 400 mg/kg/d (dietary, 1.5X MRHD, 2 litters observed only, Levey *et al.*, 1946). Fumaric acid was negative in the Ames test (Ishidate *et al.*, Fd Chem Toxic 22:623-636, 1984; Rapson *et al.*, Bull Environ Contam Toxicol 24:590-6, 1980; Zeiger *et al.*, Environ Mol Mutagen 11 Suppl 12:1-57, 1988) and in a study on chromosome abnormalities in Chinese Hamster Ovary cell cultures in the absence of metabolic activation (information on metabolic activation not provided in summary, Ishidate *et al.*, 1984).

No standard studies to evaluate the carcinogenic potential of fumaric acid were conducted. No tumors were observed in the 2-year studies in rats at 750 mg/kg/d PO (Fitzhugh and Nelson, 1947; Levey *et al.*, 1946).

B. **Pharmacologic Activity:** Fumaric acid has no activity related to the current indication

C. **Nonclinical Safety Issues Relevant to Clinical Use:** Based on the report of proximal tubular lesions in rats given oral fumaric acid at 500 mg/kg (0.8x the potential clinical exposure of 5 g/d), clinical reports of nephrotoxicity after fumaric acid ingestion, and on the inadequacy of the information on chronic fumaric acid toxicity (i.e., studies summarized were approximately 50 years old, non-GLP, and did not provide data for review), patients receiving doses of 5 g [redacted] day should be monitored for potential nephrotoxicity and chronic toxicity studies in rodent and non-rodent species should be conducted as described under IA above.

III. Administrative

A. **Reviewer signature:** _____

B. **Supervisor signature:** **Concurrence -** _____

Non-Concurrence - _____

(see memo attached)

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/s/

Kathy Haberny
2/15/02 09:13:45 AM
PHARMACOLOGIST

Timothy McGovern
2/19/02 01:03:28 PM
PHARMACOLOGIST
I concur.

NDA 21-260 ——— (morphine sulfate) Extended-Release Capsules

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD 170/Kathleen Haberny, Ph.D.

KEY WORDS: Morphine sulfate; Oral capsules; Extended release

NDA Number 21-260

Serial Number 000 / May 25, 2000 / Original Application

Review Completion Date: January 2, 2001

Information to sponsor: Yes (x) No ( )

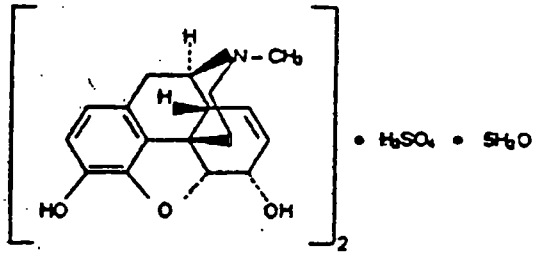
Sponsor: Elan Pharmaceutical Research Corp., 1300 Gould Dr., Gainesville, GA 30504

Manufacturer for drug substance: ———

Drug:

Code Name: None
Generic Name: Morphine sulfate USP
Trade Name: ——— (morphine sulfate) Extended-Release Capsules, ———, 30mg, 60mg, 90mg, and 120mg
Chemical Name: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5alpha,6alpha)-, sulfate (2:1) (salt), pentahydrate, or 7,8-Didehydro-4,5alpha-epoxy-17-methylmorphinan-3,6alpha-diol sulfate (2:1) (salt) pentahydrate [*6211-15-0*]
CAS Registry Number: 6211-15-0 (Pentahydrate form); 64-31-3 (Anhydrous form); 57-27-2
Molecular Formula/ Molecular Weight: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_20$

Structure:



Relevant INDs/NDAs/DMFs:

Relevant INDs/NDAs/DMFs:

[redacted]

Drug Class: Opioid Analgesic

Indication: Relief of chronic moderate to severe pain

Route of administration: Oral

Note: Portions of this review were excerpted directly from the sponsor's submission.

LABELING REVIEW

In agreement with the Agency recommendations made during the Pre-NDA meeting on January 18, 2000, literature reports of studies on the mutagenic potential and reproductive toxicology of morphine were submitted in support of the safety of the proposed drug product. No formal studies on morphine genotoxicity and reproductive toxicity were conducted by the sponsor. No studies to evaluate the carcinogenic potential of morphine sulfate were conducted by the sponsor or reported in the literature. Evaluation of the carcinogenic potential of morphine sulfate in two species will be needed as a Phase 4 commitment.

The sponsor summarized the available literature reports on *in vitro* and *in vivo* assays conducted to evaluate the potential for mutagenicity and clastogenicity. In one *in vitro* study, morphine sulfate was negative for induction of chromosomal aberration in human leukocytes at concentrations up to 6 mcg/ml (Falek *et al.*, 1972). However, in that study, metabolic activation and positive controls were not used, and therefore the validity of the study was not demonstrated. A study on the potential mutagenic effects of morphine in *Drosophila melanogaster* showed no sex-linked recessive lethal mutations, translocations or dominant lethal mutations in the progeny of treated males at concentrations of 0.02 – 1.0 mg/ml (Knaap and Kramers, 1976) when compared to the progeny of saline control-

treated male flies. Morphine increased the frequency of DNA fragmentation in human HUT-78 cells at concentrations of 5×10^{-9} M and higher, and increased the mutation frequency induced by ethylmethanesulfonate (Shafer *et al.*, 1994), but had no effect on DNA fragmentation in murine thymocytes in the *in vitro* assay (Fuchs and Pruett, 1993). In a study in lymphocytes of animals treated with cyclophosphamide, morphine increased the number of micronuclei in binucleated cells at concentrations higher than 10^{-7} M, but had no effect alone at concentrations up to 10^{-4} M (Sawant and Couch, 1995). The results of the *in vitro* studies suggest that morphine may potentiate the mutagenic effects of other agents that induce DNA damage.

The results of *in vivo* studies on the genotoxic effects of morphine in mouse bone marrow, spermatocytes, splenocytes, lymphocytes, and thymocytes were reported in the literature. Morphine was clastogenic in mouse bone marrow cells at single doses of 3.2 – 6.4 mg/kg IP, but resulted in no significant increase in chromosomal aberrations compared to the control values after repeated dosing with 3.2 mg/kg/day daily for 7 days (Swain *et al.*, 1980). Das and Swain (1982) reported a dose-related morphine-induced increase in the incidence of micronuclei in polychromatic erythrocytes of mice at doses of 3.2 – 32 mg/kg IP compared to control incidence, when mice were given morphine twice within 24 hours. Morphine was positive in the dominant lethal test in mice, increasing the frequency of chromosomal aberrations in spermatids and in dividing spermatocytes at doses at and above 10 mg/kg/day IP for 3 consecutive days (Badr and Rabouh, 1983). The effect was dose-related in that study; there was a 2-fold to 4-fold increase in the incidence of abnormal cells compared to controls at 10 and 20 mg/kg/day and a 5-fold increase compared to the control rate at 40 and 60 mg/kg/day.

Morphine was also mutagenic in splenocytes and peripheral blood lymphocytes, increasing the frequency of micronuclei in both cell types at doses of 20 mg/kg IP and above (Couch and Sawant, 1995). Implantation of morphine pellets (75 mg SC) increased DNA fragmentation in murine thymocytes (Fuchs and Pruett, 1993). The genotoxic effects observed in splenocytes, peripheral blood lymphocytes and thymocytes may have resulted in part from morphine-induced increases in corticosteroid plasma levels because the effects were blocked in mice that were adrenalectomized prior to dosing (Couch and Sawant, 1995) and in mice that received opiate and glucocorticoid antagonists concurrently with the morphine exposure (Fuchs and Pruett, 1993).

The sponsor referenced 30 literature reports on studies to evaluate morphine reproductive toxicology in mice, rats, hamsters, guinea pigs, and rabbits. Exencephaly, cryptorchid testes, and axial skeletal fusions were observed in morphine treated CF-1 mice given doses of 200-400 mg/kg IP on gestation days 8 or 9 (Iuliucci and Gautieri, 1971). These effects were also observed after subcutaneous morphine injections in another study; morphine produced exencephaly at doses of 300 mg/kg and greater given on gestation day 8, and axial skeletal fusions at doses of 100 mg/kg and greater on gestation day 9 in CF-1 albino mice (Harpel and Gautieri, 1968). Continuous subcutaneous infusion of morphine sulfate at 0.15 – 15 mg/kg/d using inplantations of miniature infusion pumps in pregnant mice on gestation days 7 through 10 resulted in fetal exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and

malformed xiphoid (Ciociola and Gautieri, 1982). Additional embryotoxic effects of morphine observed in mice in one or more of these studies include decreased crown-rump length, decreased fetal body weights, and partial fetal resorptions. The relative contribution of maternal toxicity (e.g., decreased maternal food consumption, decreased body weights, and hypoxia) to the observed toxicity in the fetal mice could not be determined.

Reproductive toxicology studies in rats administered morphine by oral, IP, and SC injection were reported in the literature. Morphine sulfate decreased fetal viability, body weights and postnatal viability, and increased the sensitivity to morphine-induced analgesia in the male offspring of pregnant rats given doses of 12.5 mg/kg/day and greater when administered in a morphine-admixed liquid diet on gestation day 5 through postpartum day 2 in rats (Eriksson and Ronnback, 1989). In that study, there were no surviving offspring at doses greater than 25 mg/kg/day PO. Daily prenatal exposure to morphine in the maternal drinking water at 0.4 g/L on gestation days 0 through 21 resulted in faster acquisition of morphine self-administration behavior in the offspring of the morphine treated rats (Glick *et al.*, 1977).

Intraperitoneal administration of morphine sulfate in rats at sequentially increasing doses from 5 mg/kg/day to 40 mg/kg/day beginning several weeks before mating through mating, gestation and 10 days into the postpartum period, altered several reproductive parameters in both the dams and offspring (Siddiqui *et al.*, 1997). In that study, abnormal estrus cycles, increased gestational length and increased number of stillbirths were observed in the morphine-treated, but not in the saline control-treated maternal rats. In the offspring, morphine treatment decreased body weights at birth and body weight gain during development, delayed sexual maturation, altered mating behavior at adulthood, and decreased plasma estradiol, ovarian estradiol, progesterone, and hypothalamic norepinephrine. Zagon and McLaughlin (1977a and 1977b) observed decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights at birth and during the neonatal period, brain lengths, and cerebral and cerebellar widths, increased neonatal mortality, and cyanotic and hypothermic infants after morphine sulfate administration at 80 mg/kg/day IP from 5 days before mating through gestation and lactation. Similar effects were observed in a study by Siddiqui *et al* (1995) in rats given 40 mg/kg/day IP morphine sulfate beginning several weeks before mating through the 10th day postpartum. Additionally, decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis were reported in the male offspring.

Sixteen literature reports of studies on reproductive toxicology of morphine by the subcutaneous route in rats were submitted by the sponsor (see Johannesson and Becker, 1972; Sobrian, 1977; Kirby, 1982; Vathy *et al.*, 1983; Fujinaga and Mazze, 1988; Vathy and Katay, 1992; Koyuncuoglu and Aricioglu, 1993; Ramsey *et al*,. 1993; Vathy *et al.*, 1994; Vathy *et al.*, 1995; Gagin and Shavit, 1996; Hol *et al.*, 1996; Niesink *et al.*, 1996; Gagin *et al.*, 1997 a and 1997b; Shavit *et al.*, 1998). Morphine doses of 10-70 mg/kg SC, by injection or perfusion pumps, were studied in paradigms ranging from dosing during

various gestation periods of organogenesis (e.g., gestation days 5-12, 11-18, etc.), to dosing from pre-mating through gestation day 15. An early study by Sobrian (1977) showed that subcutaneous morphine administered to pregnant rats at 40 mg/kg/d from 5 days before mating through gestation day 15 resulted in decreased fetal viability and body weights, and increased neonatal mortality and postnatal spontaneous motor activity. Morphine treatment during gestational periods of organogenesis resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: increased pre- and post-natal mortality, inter-litter variability for vaginal opening, increased incidence of enlarged cerebral ventricles, and increased hypothalamic norepinephrine in males, decreased body weights, growth of spinal cord components, female hypothalamic norepinephrine, and immune function. Also observed in the offspring of dams administered subcutaneous morphine were enhanced analgesic responses and social play behavior, enhanced adult feminine sexual behavior, partial feminization in copulatory behavior of male offspring, and altered development of norepinephrine and dopamine neurotransmitter systems in the hypothalamus, preoptic area, striatum and cerebellum. Overall, the NOAEL for fetal toxicity in rats was 10 mg/kg/day SC (associated with a maternal plasma level of 200 ng/ml). No teratogenicity was found at up to 70 mg/kg/day SC morphine in the rats (plasma level 668-676 ng/ml, Johannesson and Becker, 1972). Pregnancy rates were reduced at doses at and above 35 mg/kg/day SC. Maternal toxicity including clinical signs, decreased food consumption and body weights, and hypoxia, and the effects of maternal withdrawal from repeated dosing with morphine may have contributed to the observed embryotoxic effects.

In reproductive toxicology studies on embryo-fetal development in hamsters, morphine sulfate produced exencephaly and/or cranioschisis at subcutaneous doses of 88 mg/kg/day and greater on gestation day 8 (Geber and Schramm, 1975) and altered sexual behavior in male offspring when given intraperitoneally at 10 mg/kg/day from 4 days before mating through lactation (Johnston *et al.*, 1996). There appeared to be a ceiling effect in the study by Geber and Schramm (1975); the fetal abnormalities increased with increasing dose from 35 to 222 mg/kg/day, but there were no further increases in the incidence of malformations in the dose range of 222 to 322 mg/kg/day. The study by Johnston et al. (1994) showed enhanced feminine sexual behavior, indicated by adoption of lordotic posture, as well as increased masculine sexual behavior (mounts, genital groomings and intromissions) in the male offspring of morphine-treated dams compared to the untreated and saline-treated controls.

In a study on the effects of chronic *in utero* opioid exposure on neonatal ventilation in guinea pigs, morphine sulfate administered at doses of 1.5-15 mg/kg/day SC from gestation day 32 until parturition decreased maternal body weights and offspring birth weights, and increased neonatal minute ventilation, central respiratory drive, and locomotor activity in the early postnatal period (Hunter *et al.*, 1997). The hyperventilation and increased locomotor activity suggested a withdrawal syndrome, and subsided after the first neonatal week.

Subcutaneous morphine at doses of 50-100 mg/kg/day SC for 7 days in rabbits, given daily from pre-mating through gestation resulted in dose-dependent decreases in maternal

and fetal body weights, maternal food consumption, fetal crown-rump lengths, and lung weights, and increased fetal liver, kidney, heart and interscapular fat pad weights (Raye *et al.*, 1977). When administered to rabbits at doses of 10-40 mg/kg four times each day on gestation days 6-14, morphine decreased both maternal and fetal body weights and increased the abortion rate in a dose related manner (Roloff *et al.*, 1975). However, there were no differences between the morphine-treated and control fetal rabbits in indices of lung maturity (i.e., deflation limb of the pressure/volume curve, phospholipid content of tracheal washings).

CONCLUSIONS

The published literature reports of studies on the mutagenic potential and reproductive toxicology of morphine summarized above, were submitted and found adequate to support the safety and labeling of the proposed drug product. Carcinogenicity studies have not been conducted, and may be completed as a Phase IV commitment. Changes to the proposed label are recommended as described under RECOMMENDATIONS below. The recommended changes supercede those described in the original Pharmacology and Toxicology review dated January 2, 2001.

RECOMMENDATIONS

External Recommendations to the Sponsor:

The following changes to the label are recommended:

Carcinogenicity/Mutagenicity/Impairment of Fertility

[redacted] Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. [redacted]. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies [redacted] showed that morphine is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with [redacted] murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma cell line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids [redacted] Some of the *in vivo* clastogenic effects reported with morphine in mice, may be directly related to increases in glucocorticoid levels produced by morphine in this species [redacted]

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue, and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted——— in the absence of maternal toxicity——— In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. ——— Morphine—was not a significant teratogen in the rat ———exposure levels significantly beyond that normally encountered in clinical practice. In one study however, decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days prior to mating. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg. In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

———exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. ——— ———decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring. Behavioral abnormalities———chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal,

and altered responsiveness to morphine persisting into adulthood.

[redacted]

[redacted] controlled studies of chronic *in utero* morphine exposure in women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2, and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

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