

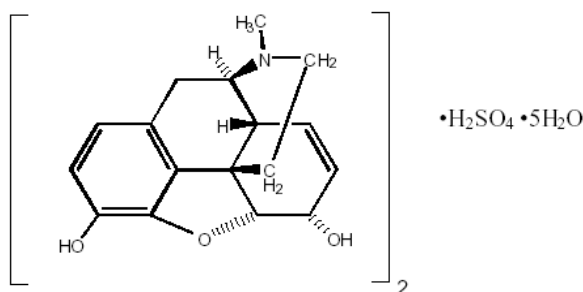
PRODUCT INFORMATION**DEPODUR®****10 mg/mL Modified Release Suspension for Injection
(For Epidural Use Only)****NAME OF DRUG**

Morphine sulfate

Molecular Formula: $C_{34}H_{40}N_2O_{10}S \cdot 5H_2O$

Molecular Weight: 758.83

CAS Registry Number: 6211-15-0

**DESCRIPTION**

DepoDur is an extended-release formulation of morphine sulfate for epidural injection. Morphine sulfate is also known as 7, 8-didehydro-4, 5 α -epoxy-17-methylmorphinan-3, 6 α -diol sulfate (2:1) (salt) pentahydrate.

DepoDur is a sterile, non-pyrogenic, white to off-white homogeneous suspension presented in a ready-to-use single dose vial, containing 10 mg of morphine sulfate encapsulated in multivesicular lipid-based particles (DepoFoam™ matrix) as 1 mL in normal saline. The median diameter of the lipid-based particles is in the range of 17 to 23 μ m. DepoDur also contains cholesterol, triolein, tricaprylin, dioleoylphosphatidylcholine, dipalmitoylphosphatidylglycerol, sodium chloride, diluted (10%) hydrochloric acid and water for injections.

Morphine base has a pKa of 7.9, with an octanol/water partition coefficient of 1.42 at physiologic pH 7.4. At this pH, morphine's tertiary amino group is mostly ionized, making the molecule water-soluble. The pH of DepoDur is in the range of 5.0 to 8.0.

DepoDur contains no antimicrobial agent. DepoDur is for single use in one patient only. Discard any residue.

PHARMACOLOGY**Pharmacodynamic Properties**

Pharmacotherapeutic group: Natural opium alkaloid

ATC Code: N02A 01

Epidural administration of morphine sulfate results in analgesia without attendant loss of motor, sensory, or sympathetic function. As compared to systemic administration of morphine at comparable doses, epidurally administered morphine results in improved analgesia with increased duration.

DepoDur is an extended-release formulation of the active ingredient morphine sulfate designed for epidural administration. After the administration of DepoDur into the epidural space, morphine sulfate is released from the multivesicular liposomes over a period of time. Morphine released from DepoDur is absorbed both neuraxially and systemically.

Morphine acts as an agonist at opioid receptors in the central nervous system (CNS), particularly mu and, to a lesser extent, kappa receptors. In addition to analgesia, the widely diverse effects of morphine include respiratory depression, drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

The effects described below are common to all morphine-containing products.

Effects on the Central Nervous System (CNS): The principal therapeutic action of morphine is analgesia. Other therapeutic effects of morphine include anxiolysis, euphoria and feelings of relaxation. Although the precise mechanism of the analgesic action is unknown, specific CNS opioid receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. As with all drugs in the opioid class, morphine can cause respiratory depression, in part by a direct effect on the brainstem respiratory centres. Morphine and related opioids depress the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose; however, when asphyxia is present during opioid overdose, marked mydriasis occurs.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle: Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone can be increased to the point of spasm, often resulting in constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System: In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine, like other opioids, produces peripheral vasodilatation that may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes and sweating.

Pharmacokinetic Properties

Epidural administration of DepoDur results in both systemic absorption of morphine sulfate and absorption of morphine sulfate through the meninges into the intrathecal space. The relative absorption systemically versus intrathecally is unknown for both morphine sulfate injection and for DepoDur.

Systemic Absorption of Morphine from DepoDur

In clinical studies, DepoDur was 89% bioavailable compared to morphine sulfate injection.

Based on systemic AUC, DepoDur appears to exhibit dose proportionality over a dose range of 5 to 20 mg. In contrast, systemic C_{max} did not exhibit dose-proportionality and tended to increase by an amount less than the proportional change in dose (Table 1).

Table 1: Morphine Plasma Pharmacokinetic Parameters (Mean, SD) Following Epidural Administration of Morphine Sulfate Injection and DepoDur

	Morphine Sulfate Injection 5 mg (n=26)	DepoDur 5 mg (n=14)	DepoDur 10 mg (n=36)	DepoDur 15 mg (n=71)	DepoDur 20 mg (n=63)
PK Parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/mL)	20.0 (10.1)	9.4 (5.7)	20.0 (9.5)	18.6 (10.4)	26.4 (18.6)
AUC _{0-∞} (ng•hr/mL)	51.7 (34.8)	41.0 (10.6)	124.9 (98.1)	131.6 (73.7)	185.9 (81.4)
$t_{1/2}$ (hr)	5.8 (16.9)	4.2 (2.1)	16.2 (19.7)	20.0 (20.6)	23.9 (25.4)

Distribution, Metabolism and Excretion of Morphine Sulfate

After morphine sulfate has been released from DepoDur and is absorbed systemically, its distribution, metabolism and excretion are the same as other morphine formulations. DepoDur is intended for single dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 1 to 4 L/kg. Morphine is 20 to 35% reversibly bound to plasma proteins. Morphine also crosses the placental membranes and has been found in breast milk.

The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral sulfate. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%). M3G has no significant analgesic activity. M6G has been shown to have opiate agonist and analgesic activity in humans.

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the faeces. The mean adult plasma clearance is about 20–30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2 hours. In some studies involving longer periods of plasma sampling, a longer terminal half-life of morphine of about 15 hours was reported.

The Elderly and Paediatrics

Elderly patients (aged 65 years or older) may have increased sensitivity to DepoDur, as with other opiates. In elderly patients (over 65 years of age), the C_{max} was similar to that of patients 65 years of age or younger, but the clearance in elderly patients was reduced by approximately 13%.

The pharmacokinetics of DepoDur have not been studied in paediatric patients.

Hepatic Failure

Systemic morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these subjects, indicating diminished metabolic activity. DepoDur is intended for single-dose administration, therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic function.

Renal Insufficiency

Systemic morphine pharmacokinetics are altered in patients with renal failure. Clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. DepoDur is intended for single-dose administration, therefore accumulation of morphine or its metabolites is not expected even in patients with impaired renal function.

Interactions with Other Drugs

Test Dose Interaction:

Epidural administration of a 3-mL test dose (lignocaine 1.5% and adrenaline 1:200,000) may affect the release of morphine sulfate from DepoDur (see PRECAUTIONS). This interaction has been examined in patients who received epidural administration of 15 mg of DepoDur at various time intervals after the test dose (Table 2). The test groups included a no-test-dose group and 3-, 10- and 15-minute delays between test dose and DepoDur administration. Additionally, saline flush after the test dose was assessed. The serum concentration of morphine was measured as a biomarker.

Table 2: Impact of Test Dose Administration on Peak Serum Morphine Concentration of DepoDur

Minutes Between Test Dose and DepoDur Administration	N	Mean t_{max} hr (SD)	Mean C_{max} ng/mL (SD)	Median C_{max} ng/mL	Min–Max ng/mL
No test dose	6	2.5 (2.1)	11.5 (7.4)	10.2	4.1–23.5
Flush + 3	8	0.2 (0.04)	30.2 (8.5)	31.4	15.8–40.1
Flush + 10	7	0.6 (0.7)	15.6 (9.3)	13.3	7.4–34.0
Flush + 15	8	0.5 (0.3)	11.4 (6.4)	11.4	2.0–20.0
No Flush + 3	8	0.4 (0.7)	25.6 (10.1)	22.6	15.2–45.4

Serum morphine C_{max} was equivalent to that of the no-test-dose group if a 0.9% normal saline catheter flush was given and DepoDur was administered 15 minutes after the test dose.

CLINICAL TRIALS

The efficacy of DepoDur was demonstrated in four clinical trials comprised of 876 patients undergoing surgical procedures such as hip arthroplasty, prostatectomy, colon resection and caesarean section. In these clinical trials, efficacy was assessed for at least 48 hours and safety for up to 30 days after DepoDur administration.

Please note that some doses used in clinical trials are greater than that approved for use (see DOSAGE AND ADMINISTRATION).

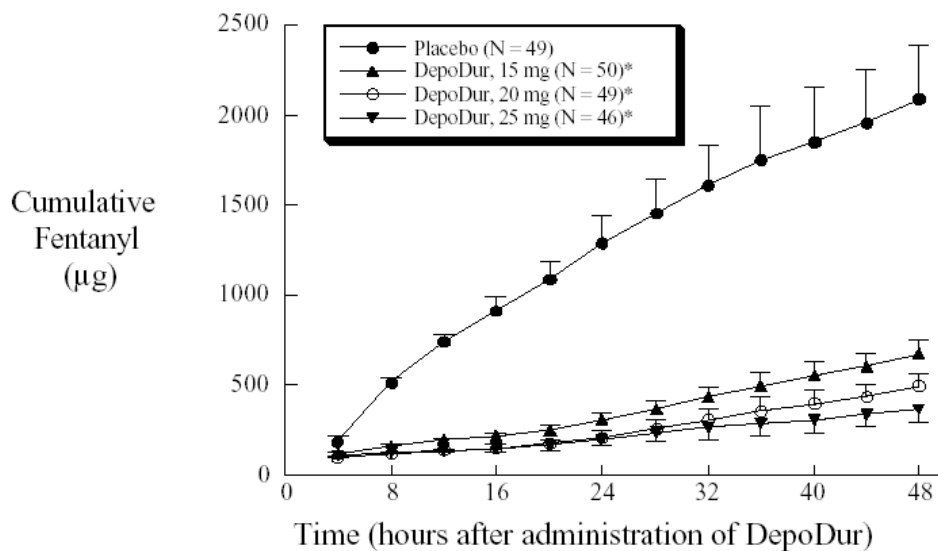
Hip Arthroplasty

Two randomised, double-blind, placebo-controlled, parallel-group, dose-ranging studies evaluated the safety and efficacy of DepoDur in 314 patients undergoing hip arthroplasty. The mean age of patients was 59 years (range 18 to 88 years). Study medication was administered approximately 30 minutes before surgery. Post-operatively, patients self-administered intravenous fentanyl via patient-controlled analgesia (PCA) to maintain satisfactory analgesia.

In one study (N=194), single epidural administration of DepoDur provided superior analgesic efficacy compared to placebo (epidural saline injection followed by IV fentanyl PCA), as measured by decreased fentanyl use (Figure 1) and Visual Analog Scores (VAS) (Figure 2). The second clinical study in hip arthroplasty revealed similar results.

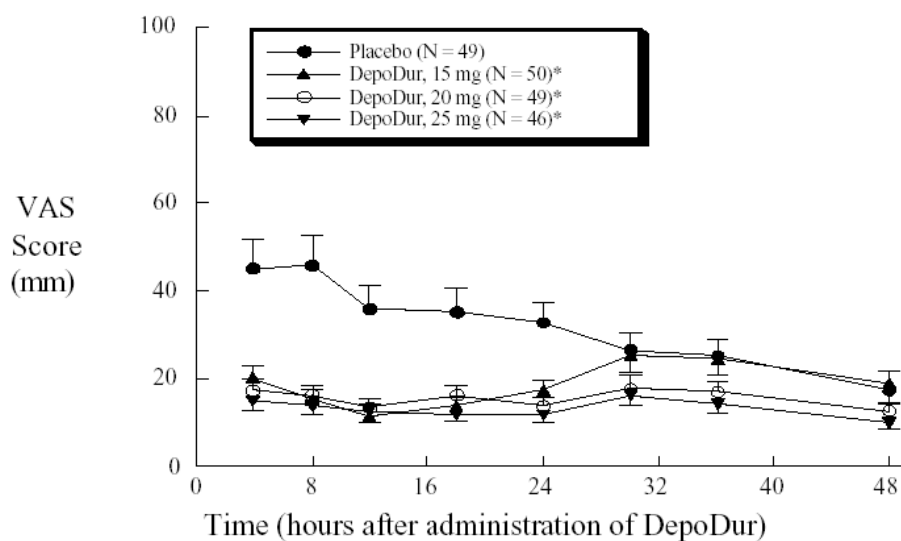
In another clinical study in this surgical model, up to 70% of patients receiving DepoDur did not require IV PCA post-operatively.

Figure 1: Cumulative Fentanyl Usage Over 48 Hours (Mean, SE)



* $P < 0.05$ compared with placebo at all time points after 4 hours

Figure 2: Pain Intensity Scores Over 48 hours (Mean, SE)



* $P < 0.05$ compared with placebo based on AUC over 48 hours

Lower Abdominal Surgery

A randomised, double-blind, parallel-group study evaluated the safety and efficacy of single epidural doses of ≥ 10 mg DepoDur compared to 5 mg DepoDur or 5 mg morphine sulfate in 487 patients undergoing lower abdominal surgery (i.e. surgery via an abdominal incision below umbilicus). Study medication was administered approximately 30 minutes prior to surgery. Post-operatively, patients self-administered intravenous fentanyl via patient-controlled analgesia (PCA) to maintain satisfactory analgesia. A dose response was observed, demonstrating a reduction in IV fentanyl use over the 48-hour period.

Caesarean Section

A randomised, double-blind, parallel-group study evaluated the safety and efficacy of single epidural doses of DepoDur compared to epidural morphine sulfate injection (5 mg) in 75 patients undergoing elective caesarean section under intrathecal anaesthesia. Note that this 5 mg dose of morphine sulfate injection is higher than the commonly used dose (2-3 mg) of morphine sulfate injection for post-caesarean section analgesia. Study medication was administered following delivery and clamping of the umbilical cord. At the investigator's discretion, patients were permitted to receive paracetamol with codeine or intravenous morphine sulfate as an intermittent bolus or via PCA pump, post-operatively. DepoDur 10 mg resulted in reduced use of rescue medication and improved post-operative analgesia based on AUC analysis of VAS pain scores at rest (R) and with activity (A), compared to morphine sulfate on average over the 48-hour period following elective caesarean section (Table 3).

Table 3: Caesarean Section: Total Opioid Use, Pain VAS at Rest and with Activity

Efficacy Parameters	Morphine Sulfate	DepoDur
	Injection	
	5 mg	10 mg
Opioid use (mg, morphine equivalents*) 0-48 h, median [#]	38.2	19.0
Opioid use (mg, morphine equivalents*) 24-48 h, median [^]	16.3	9.0
VAS-R AUC 0.48 h, mean \pm SD [#]	1186 \pm 939	454 \pm 334
VAS-a AUC 0.48 h, mean \pm SD [^]	2086 \pm 875	1235 \pm 775

* Median; [#] $p < 0.05$; [^] $p < 0.001$

Knee Arthroplasty

A randomised, double-blind, active-controlled, parallel group, dose-ranging study evaluated the safety and efficacy of high doses of DepoDur compared with intravenous morphine administered via PCA. DepoDur was administered approximately 30 minutes prior to surgery. Post-operatively, patients randomised to DepoDur self-administered intravenous hydromorphone to maintain satisfactory analgesia. A dose response was observed, demonstrating a reduction in pain scores and IV opioid consumption over a 48-hour period. DepoDur treatment was associated with a decrease in the use of post-operative opioids for pain control.

INDICATIONS

For the relief of post-operative pain following major orthopaedic, abdominal, or pelvic surgery via the lumbar epidural route at a maximum recommended dose of 10 mg. Appropriate monitoring must be maintained for at least 48 hours – see PRECAUTIONS.

CONTRAINDICATIONS

DepoDur is only for epidural administration. Intravenous, intramuscular, and intrathecal administrations are contraindicated.

DepoDur is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product.

DepoDur is contraindicated in patients receiving concurrent epidural anaesthesia, as local anaesthetics may cause the modified release mechanism to fail, resulting in overdose (see PRECAUTIONS – *Interactions with other drugs*).

DepoDur must not be given concurrently with long acting opioids during the first 48 hours following DepoDur administration.

DepoDur, like all opioids, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, or upper airway obstruction.

DepoDur causes vasodilatation that may exacerbate hypotension and hypoperfusion and, therefore, is contraindicated in circulatory shock.

DepoDur, like all opioids, is contraindicated in any patient who has or is suspected of having paralytic ileus.

Any contraindications for an epidural injection preclude the administration of DepoDur.

DepoDur should not be used in patients with suspected or known head injury or increased intracranial pressure.

DepoDur is contraindicated in patients undergoing day surgery.

PRECAUTIONS

Due to the risk of severe adverse events when the epidural route of administration is employed, patients must be monitored in a fully equipped and staffed environment for at least 48 hours after administration. The action of DepoDur persists for up to 48 hours. In some individuals in clinical trials, action continued beyond 48 hours, and thus monitoring should continue until all opioid side effects are resolved. Sedation and respiratory depression must be assessed at regular and frequent intervals with continuous close monitoring for at least 48 hours and full resuscitative facilities, personnel, drugs, equipment and protocols for managing respiratory depression must

be immediately available whether or not the patient undergoes surgery. Delayed respiratory depression is a potentially life threatening complication following epidural administration of opioids and has been reported in patients who have received DepoDur. Delayed and secondary peaks in morphine concentrations after DepoDur administration could impact on patient safety and thus ongoing monitoring is required.

DepoDur should only be administered by or under the direction of a physician experienced in epidural administration of opioids, and only where there are immediate facilities for resuscitation, including staff trained in airway management and artificial ventilation. The facility must be equipped to resuscitate patients with severe opioid overdose, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.

Respiratory depression can occur with DepoDur. Four percent of the patients who received DepoDur required treatment with narcotic antagonists for respiratory depression. Ninety percent of events of respiratory depression started within the first 24 hours after dosing with DepoDur. However, the incidence of respiratory depression starting after 48 hours, potentially related to DepoDur, was 0.6% (5 of 900 patients). Patients at increased risk of respiratory depression such as those with impaired respiratory drive, sleep apnoea, concomitant sedation, the elderly, debilitated patients and those suffering from conditions accompanied by hypoxia or hypercapnia, may require monitoring for periods longer than 48 hours.

Extreme care must be taken if DepoDur is given and surgery is subsequently cancelled or changed to a more minor procedure, or if alternative or additional analgesic techniques are used. If the surgical procedure is cancelled after the administration of DepoDur, the risk of respiratory depression may be increased, and patients should be monitored with a high level of vigilance. Respiratory depression can be severe if surgical pain is limited or absent.

No clinical studies have evaluated the safety of administration of DepoDur into the intrathecal space. DepoDur is intended for administration by the epidural route only. However, cases of intrathecal administration of DepoDur have been reported during post-marketing experience. In all cases, symptoms of prolonged respiratory depression were observed requiring narcotic antagonist (naloxone) administration or ventilatory support.

Systemic opioids may increase the risk of serious adverse events including respiratory depression. Particular caution is necessary with opioid agents of an intermediate or prolonged duration of action. Concurrent parenteral administration of long acting opioids such as morphine and hydromorphone must not be given if additional analgesic is needed during the first 48 hours following DepoDur administration. Short acting agents, such as non-opioid analgesics or opioid agents with a short duration of action, may be more suitable if analgesic supplements are needed. Close monitoring is mandatory.

There is no efficacy or safety clinical data pertaining to surgeries above the diaphragm for DepoDur.

Prior to drug administration, the physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, current and anticipated anticoagulant therapy, etc.) that call for special evaluation of the benefit versus risk potential.

Use with caution in opioid-dependent patients and in patients with decreased pulmonary function, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, sleep apnoea, and adrenocortical insufficiency.

DepoDur, like all other opioids, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs such as phenothiazines or general anaesthetics. DepoDur may produce orthostatic hypotension and syncope in ambulatory patients.

Seizures may result from high doses of morphine. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

The use of epidural opioid analgesia has been associated with disturbances of micturition, especially in males with prostatic hypertrophy. Early recognition of urinary retention and prompt intervention is indicated.

In addition, DepoDur may cause hypotension, paralytic ileus, urinary retention, biliary colic, somnolence, pruritis, nausea, and vomiting.

Administration of opioids with or without coadministration of other sedative or hypnotic drugs can worsen airway obstruction in patients with obstructive sleep-apnoea syndrome. Patients who are obese are at particular risk for this syndrome, which may be undiagnosed prior to administration.

Use in Hepatic or Renal Disease

After morphine sulfate has been released from DepoDur and is absorbed systemically, its distribution, metabolism and excretion are expected to be the same as other morphine formulations. DepoDur is intended for single-dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

Use in Biliary Surgery or Disorders of the Biliary Tract

Morphine is released into the systemic circulation after epidural administration. Therefore, smooth muscle hypertonicity may result in biliary colic.

DepoDur should be used with caution in patients with biliary tract disease, including acute pancreatitis, as morphine may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

Post-Surgical Ambulation

Patients with reduced circulating blood volume, impaired myocardial function or those receiving sympatholytic drugs should be monitored for the possible occurrence of orthostatic hypotension, a frequent complication in single-dose epidurally administered morphine analgesia.

Special Precautions for Storage

Store in a refrigerator (2-8°C). Protect DepoDur from freezing. Do not administer DepoDur if it is suspected that the vial has been frozen. Freezing may adversely affect the modified release mechanism of DepoDur. Each carton of DepoDur contains a freeze indicator that is visible through the top of the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb has changed from clear to pink or purple, the product should be destroyed.

Effects on Fertility

In a dominant lethal study, morphine treatment at 10 mg/kg/day (IP) in male mice over three consecutive days was associated with an increase in chromosomal aberration frequency in spermatocytes. In rats, decreased plasma and testicular levels of luteinising hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring, and decreased fertility in female offspring were observed. The clinical significance of these findings is not known.

Use in Pregnancy - Category C

DepoDur should not be administered to women during pregnancy, though it may be used during delivery by caesarean section, if administered after delivery of the baby and clamping of the umbilical cord.

Literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities generally in the presence of maternal toxicity. Morphine was not teratogenic in the rat or rabbit, but exposure to morphine during pregnancy in these species and/or hamsters is associated with reductions in embryofetal viability and foetal/neonatal growth, and reduced growth and behavioural abnormalities of the offspring.

DepoDur should only be given to pregnant women when the benefits clearly outweigh the potential risks to the foetus.

Use in Lactation

In studies of epidural administration of morphine sulfate injection, small amounts of morphine were detected in breast milk. Breastfeeding is not recommended while a patient is receiving morphine.

Paediatric Use

The safety and effectiveness of DepoDur in paediatric patients below the age of 18 years has not yet been established.

Use in the Elderly

DepoDur was studied in clinical trials of 876 subjects; 222 were 65 years of age and older, and 43 of these patients were 75 years of age and over. The efficacy and opioid adverse event profiles in these elderly patients, at the same or lower dose of DepoDur, were similar to those in younger adults (see DOSAGE AND ADMINISTRATION). However, elderly patients (65 years of age or older) may have increased sensitivity to morphine. Comorbid conditions may predispose the elderly population to serious adverse events such as respiratory depression, ileus, hypotension and myocardial infarction.

In general, caution should be exercised in the selection of the dose of DepoDur for an elderly patient. Dosing normally should be at the low end of the range. The maximum recommended dose is 10 mg, which should be reduced to 7.5 mg or less in the elderly (65 years of age or older).

DepoDur should be administered to elderly patients (65 years of age or older) after careful evaluation of their underlying medical condition and consideration of the risks associated with DepoDur. Provision for vigilant perioperative monitoring should be arranged for elderly patients receiving DepoDur.

Carcinogenicity

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted.

Genotoxicity

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of in-vitro studies showed that morphine is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. However, 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 spermatocytes.

Interactions with Other Drugs**Local Anaesthetics:**

A time interval of at least 15 minutes should elapse following a 3 mL lignocaine 1.5% with adrenaline 1:200,000 epidural test dose. Clinical studies have demonstrated that administration of DepoDur 3 minutes after a 3 mL test dose (lignocaine 1.5% and adrenaline 1:200,000) increases peak serum morphine concentrations. Flushing the epidural catheter and increasing the interval between the test dose and DepoDur administration to at least 15 minutes minimises this pharmacokinetic interaction. Please see the dosage recommendations in respect of this interaction and note the contraindication in patients receiving concurrent epidural anaesthesia.

If used in conjunction with subarachnoid block then the DepoDur should be administered at a level different to that of dural puncture. This may be achieved by passage of an epidural catheter or separate epidural injection. If there has been an inadvertant dural puncture and if DepoDur is still to be administered, then it must be at a different level.

Other than the interactions with a lignocaine plus adrenaline test-dose or with a bupivacaine or lignocaine/adrenaline therapeutic dose of local anaesthetic, no other pharmacokinetic drug-drug interactions have been examined in vivo. In vitro studies suggest a similar interaction could be expected with other amide local anaesthetics. No in vitro or in vivo studies have been performed with ester local anaesthetics. Known drug-drug interactions involving morphine are pharmacodynamic, not pharmacokinetic.

 α_2 Agonists:

Concurrent systemic or spinal administration of α_2 agonists (e.g. clonidine) may potentiate opioid analgesia. Pharmacodynamic and pharmacokinetic interactions between DepoDur and neuraxially or systemically administered α_2 agonists were not evaluated. Therefore, concomitant use of these drugs should not be attempted.

CNS Depressants:

The concurrent use of other central nervous system (CNS) depressants including sedatives, hypnotics, general anaesthetics, droperidol, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use with caution and in reduced dosages in patients taking these agents.

Monoamine Oxidase Inhibitors (MAOIs):

MAOIs markedly potentiate the action of morphine. DepoDur should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Effects on Ability to Drive and Use Machines

DepoDur, in common with other opioids, has CNS depressant effects. Effects on the ability to drive or operate machinery have not been studied, but it is expected to have a major influence on the ability to drive or operate machines within 48 hours of administration. Patients should not drive or use heavy machinery until all adverse CNS effects have fully worn off.

ADVERSE EFFECTS

The most common adverse events (greater than 10%) reported during therapy in patients treated with DepoDur were nausea, pruritus, pyrexia, vomiting, hypotension, anaemia, headache, constipation, decreased oxygen saturation, urinary retention, and dizziness. Adverse events occurring in 5-10% of study patients were flatulence, tachycardia, insomnia, and hypoxia. Other less common side effects (seen in 2-5% of patients receiving DepoDur) included somnolence, abdominal distension, hypoaesthesia, hypertension, respiratory depression, oliguria, bradycardia, anxiety, back pain, increased sweating, dyspepsia, bladder spasm, rigors, hypercapnia, dyspnoea, hypokalaemia, ileus paralytic, paraesthesia, and decreased haematocrit.

Of the patients treated with DepoDur in clinical trials, 4% exhibited signs of respiratory depression requiring treatment with narcotic antagonists. In clinical trials, 90% of respiratory depression occurred within 24 hours after administration of DepoDur. Delayed respiratory depression, which may be of sudden onset and is potentially life threatening, occurred up to 48 hours post dosing in approximately 2% of patients who have received DepoDur. Onset of respiratory depression occurred in 0.6% of patients after more than 48 hours.

During post-marketing experience, central nervous system (CNS) depression, including obtunded feeling, non-arousable condition, unresponsiveness, confusion, and lethargy, has been reported following epidural administration of DepoDur. In most of these cases with CNS depression, there was concomitant administration of different narcotics or hypnotic/sedative medications in the post-operative period.

During post-marketing experience, severe respiratory depression, involving apnoea or respiratory arrest, and cardiac arrest, have been reported following the administration of labeled doses of DepoDur.

DOSAGE AND ADMINISTRATION**Adults and the Elderly**

DepoDur is only for epidural administration. Intravenous, intramuscular, and intrathecal administrations are contraindicated. Experience of DepoDur in clinical trials has been limited to patients assessed as ASA grade I to III. DepoDur is not recommended in patients graded ASA IV or V. DepoDur may be administered peri-operatively via needle or catheter at the lumbar or lower thoracic levels. Administration of DepoDur at the mid-thoracic level or higher has not been studied. DepoDur may be administered undiluted or diluted up to 5-mL total volume with preservative-free 0.9% normal saline.

The maximum dose recommended is 10 mg, which should be reduced to 7.5 mg or less in the elderly (>65 years).

Continuous monitoring and observation of the patient for at least 48 hours following administration of DepoDur is mandatory in order to identify possible respiratory depression, which may be delayed, profound and of sudden onset (see PRECAUTIONS and ADVERSE EFFECTS). The minimum level of monitoring includes pulse oximetry, cardiac ECG monitoring and continuous observation and/or monitoring of respiratory rate, in a suitable environment with appropriately trained staff. During this period, full resuscitation facilities must be immediately available, including staff trained in airway management and artificial ventilation. A single dose of DepoDur should be considered to be equivalent to a continuous epidural infusion of morphine, and attendant monitoring requirements must reflect this, in line with relevant guidelines.

NB Continuous, close monitoring of patients for at least 48 hours after receiving DepoDur is mandatory irrespective of whether planned surgery was subsequently cancelled or modified.

For operations associated with less severe pain and/or where freedom from the usual side effects of morphine is a priority and in the elderly, frail or debilitated, lower doses may suffice. The maximum recommended dose in elderly patients (≥ 65 years) is 7.5 mg or less (see PRECAUTIONS).

DepoDur has been administered to women undergoing caesarean section following clamping of the umbilical cord. DepoDur should not be administered to women for vaginal labour and delivery. For caesarean section, the recommended dose of DepoDur is 10 mg. However DepoDur is contraindicated in patients who have received epidural local anaesthetics for analgesia during labour (see CONTRAINDICATIONS and PRECAUTIONS – *Interactions with other drugs*)

DepoDur should only be administered by or under the direction of a physician experienced in epidural administration of opioids, and only where there are immediate facilities for resuscitation, including staff trained in airway management and artificial ventilation. Such facilities for patient monitoring should be available for at least 48 hours.

Before administration of DepoDur, the physician must ensure that the needle or catheter is properly placed in the epidural space. Techniques to exclude misplacement of the needle or catheter include aspiration to check that blood or cerebrospinal fluid cannot be aspirated and administration of a test dose of local anaesthetic with adrenaline. If a test dose is administered, in order to minimise a pharmacokinetic interaction of DepoDur, the epidural catheter should be flushed with 1 mL of preservative-free 0.9% normal saline, and DepoDur should be administered after an interval of at least 15 minutes (see PRECAUTIONS – *Interactions with other drugs*).

The use of concomitant systemic opioids may increase the risk of serious adverse events (see CONTRAINDICATIONS and PRECAUTIONS).

Do not mix DepoDur with any other medications. Once DepoDur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Do not use an in-line filter during administration of DepoDur.

Vials of DepoDur should be gently inverted to re-suspend the particles immediately prior to withdrawal from the vial. Avoid aggressive agitation. No further reconstitution or dilution is required, but DepoDur may be diluted up to 5-mL total volume with preservative-free 0.9% normal saline using standard aseptic techniques.

DepoDur is a sterile agent; however, it does not contain any bacteriostatic agents. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours. Do not heat-sterilise or gas-sterilise.

Discard any unused portion in a manner appropriate for opioids.

Protect DepoDur from freezing. Do not administer DepoDur if it is suspected that the vial has been frozen (see PRECAUTIONS –*Special precautions for storage and STORAGE*).

DepoDur contains less than 1 mmol sodium (23 mg) per 10 mL.

Children

Safety and efficacy in children have not been demonstrated.

Instruction for Handling and Disposal

DepoDur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to health care workers.

Each vial of DepoDur contains a potent opioid that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.

Incompatibilities

Do not mix DepoDur with any other medications. Once DepoDur has been administered, no other medication should be administered into the epidural space for at least 48 hours.

OVERDOSAGE

Overdosage of morphine is characterized by respiratory depression, with or without concomitant CNS depression. In severe overdosage, apnoea, circulatory collapse, cardiac arrest and death may occur. The conditions that might cause an overdosage situation may vary from patient-to-patient. A DepoDur dose that is given within the labeled dosing guidelines may be found to be a dose higher than could be tolerated for an individual patient. During post-marketing experience, spontaneous cases of apnoea, respiratory arrest, and cardiac arrest have been reported after administration of labeled DepoDur doses (see ADVERSE EFFECTS). Since respiratory arrest may result either through direct depression of the respiratory centre or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The opioid antagonist, naloxone, is a specific antidote. An initial dose of 0.04 to 2 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. Doses at the lower end of this range may reverse unwanted effects including (non-delayed) respiratory depression without reversing the analgesia produced by epidural morphine. Higher doses may also reverse analgesia. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of opioid-induced, or partial opioid-induced, toxicity should be questioned. Intramuscular or subcutaneous administration of naloxone may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of DepoDur, repeated administration or continuous infusion of naloxone may be necessary. Patients should be closely observed for evidence of recurrence of respiratory depression and for delayed respiratory depression.

For further advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

STORAGE

Store at 2°C - 8°C (refrigerate - do not freeze) in the outer carton. Do not administer DepoDur if it is suspected that the vial has been frozen. See PRECAUTIONS. Avoid aggressive shaking.

A freeze indicator that is visible through the top of the carton indicates if the product has been frozen. It is important that the freeze indicator is inspected before removal of a vial from the carton. Vials from this carton should only be used if the solution in the bulb of the freeze indicator is clear. If the solution in the bulb has changed from clear to pink or purple, the product should be destroyed.

DepoDur may be held at room temperature below 25°C for up to 30 days in sealed, intact (unopened) vials. Vials stored at room temperature may be separated from the carton, but should not be returned to a refrigerator. Discard vials that have been stored at room temperature for over 30 days.

Vials for single use in one patient only.

PRESENTATION

DepoDur is supplied in a 10 mg/mL single-dose glass vial (Ph.Eur. type I amber glass), closed with an ethylenetetrafluoroethylene (ETFE) stopper and sealed with an aluminium flip-off seal, in cartons of 5 vials.

As a convenience to the hospital pharmacist, each carton of DepoDur includes pharmacy stickers noting when each vial has been removed from refrigeration and advising to resuspend just prior to use.

NAME AND ADDRESS OF THE SPONSOR

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Australia

Website: www.orphan.com.au

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POISONS SCHEDULE

S8

DATE OF APPROVAL

Product Information approved by the TGA on 24th December 2007.