

AVINZA™ (morphine sulfate) Extended-Release Capsules 30mg, 60mg, 90mg and 120mg  
New Drug Application # 21-260  
ELAN PHARMACEUTICAL RESEARCH CORPORATION

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- 1 **AVINZA™**  
2 **(morphine sulfate extended-release capsules)**  
3 **CII**  
4 **R<sub>x</sub> Only**

**WARNING:**

**AVINZA capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.**

5  
6  
7 **DESCRIPTION**

8 AVINZA (morphine sulfate extended-release capsules) 30, 60, 90, and 120 mg contain  
9 both immediate release and extended release beads of morphine sulfate for once daily  
10 oral administration.

11 Chemically, morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17-methyl-morphinan-  
12 3,6 alpha-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758.

13 Morphine sulfate occurs as white, feathery, silky crystals; cubical masses of crystal; or  
14 white crystalline powder. It is soluble in water and slightly soluble in alcohol, but is  
15 practically insoluble in chloroform or ether. The octanol:water partition coefficient of  
16 morphine is 1.42 at physiologic pH and the pK<sub>a</sub> is 7.9 for the tertiary nitrogen (the  
17 majority is ionized at pH 7.4).

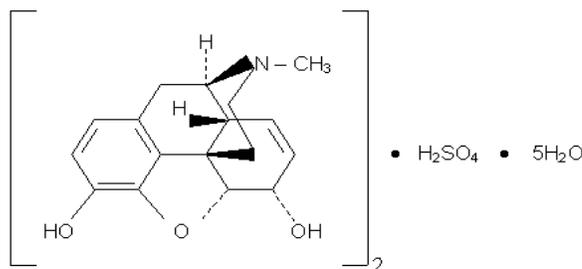
18 Each AVINZA Capsule contains either 30, 60, 90, or 120 mg of morphine sulfate, USP  
19 and the following inactive ingredients: ammonio-methacrylate copolymers, NF

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20 , fumaric acid, NF, povidone, USP, sodium lauryl sulfate, NF, sugar starch spheres,  
21 NF, and talc, USP. The capsule shell contains black ink, gelatin, titanium dioxide,  
22 D&C yellow No. 10 (30 mg), FD&C green No. 3 (60 mg), FD&C red No. 40 (90 mg),  
23 FD&C red No. 3 (120 mg), and FD& C blue No. 1 (120 mg).

24 Structure:



25

26 AVINZA uses the proprietary SODAS® (Spheroidal Oral Drug Absorption System)  
27 technology, to produce the extended release component of AVINZA, which combined  
28 with an immediate release component achieves the desired release profile  
29 characteristics of AVINZA capsules. Within the gastrointestinal tract, due to the  
30 permeability of the ammonio methacrylate copolymers of the beads, fluid enters the  
31 beads and solubilizes the drug. This is mediated by fumaric acid, which acts as an  
32 osmotic agent and a local pH modifier. The resultant solution then diffuses out in a  
33 predetermined manner which prolongs the *in vivo* dissolution and absorption phases  
34 (See Pharmacokinetics).

35

### 36 CLINICAL PHARMACOLOGY

37 Morphine, a pure opioid agonist, is relatively selective for the mu receptor, although it  
38 can interact with other opioid receptors at higher doses. In addition to analgesia, the

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39 widely diverse effects of morphine include drowsiness, changes in mood, respiratory  
40 depression, decreased gastrointestinal motility, nausea, vomiting and alterations of the  
41 endocrine and autonomic nervous system.

42 **Effects on the Central Nervous System (CNS):** The principal therapeutic action of  
43 morphine is analgesia. Other therapeutic effects of morphine include anxiolysis,  
44 euphoria and feelings of relaxation. Although the precise mechanism of the analgesic  
45 action is unknown, specific CNS opiate receptors and endogenous compounds with  
46 morphine-like activity have been identified throughout the brain and spinal cord and  
47 are likely to play a role in the expression and perception of analgesic effects. In  
48 common with other opioids, morphine causes respiratory depression, in part by a  
49 direct effect on the brainstem respiratory centers. Morphine and related opioids  
50 depress the cough reflex by direct effect on the cough center in the medulla.  
51 Antitussive effects may occur with doses lower than those usually required for  
52 analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign  
53 of opioid overdose; however, when asphyxia is present during opioid overdose,  
54 marked mydriasis occurs.

55 **Effects on the Gastrointestinal Tract and on Other Smooth Muscle:** Gastric, biliary  
56 and pancreatic secretions are decreased by morphine. Morphine causes a reduction  
57 in motility and is associated with an increase in tone in the antrum of the stomach and  
58 duodenum. Digestion of food in the small intestine is delayed and propulsive  
59 contractions are decreased. Propulsive peristaltic waves in the colon are decreased,  
60 while tone is increased to the point of spasm. The end result may be constipation.  
61 Morphine can cause a marked increase in biliary tract pressure as a result of spasm of

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62 the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary  
63 bladder.

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

#### 70 **Pharmacodynamics**

71 Morphine concentrations are not predictive of analgesic response, especially in  
72 patients previously treated with opioids. The minimum effective concentration varies  
73 widely and is influenced by a variety of factors, including the extent of previous opioid  
74 use, age, and general medical condition. Effective doses in tolerant patients may be  
75 significantly higher than in opioid-naïve patients.

76 In all patients, the dose of morphine should be titrated on the basis of clinical  
77 evaluation of the patient and to achieve a balance between therapeutic and adverse  
78 effects.

#### 79 **Pharmacokinetics**

80 AVINZA consist of two components, an immediate release component that rapidly  
81 achieves plateau morphine plasma concentrations and an extended release  
82 component that maintains plasma concentrations throughout the 24 hour dosing  
83 interval. The amount of morphine absorbed from AVINZA following oral  
84 administration, is similar to that absorbed from other oral morphine formulations.

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85 The oral bioavailability of morphine is less than 40% and shows large inter-individual  
86 variability due to extensive pre-systemic metabolism.

87 **Absorption**

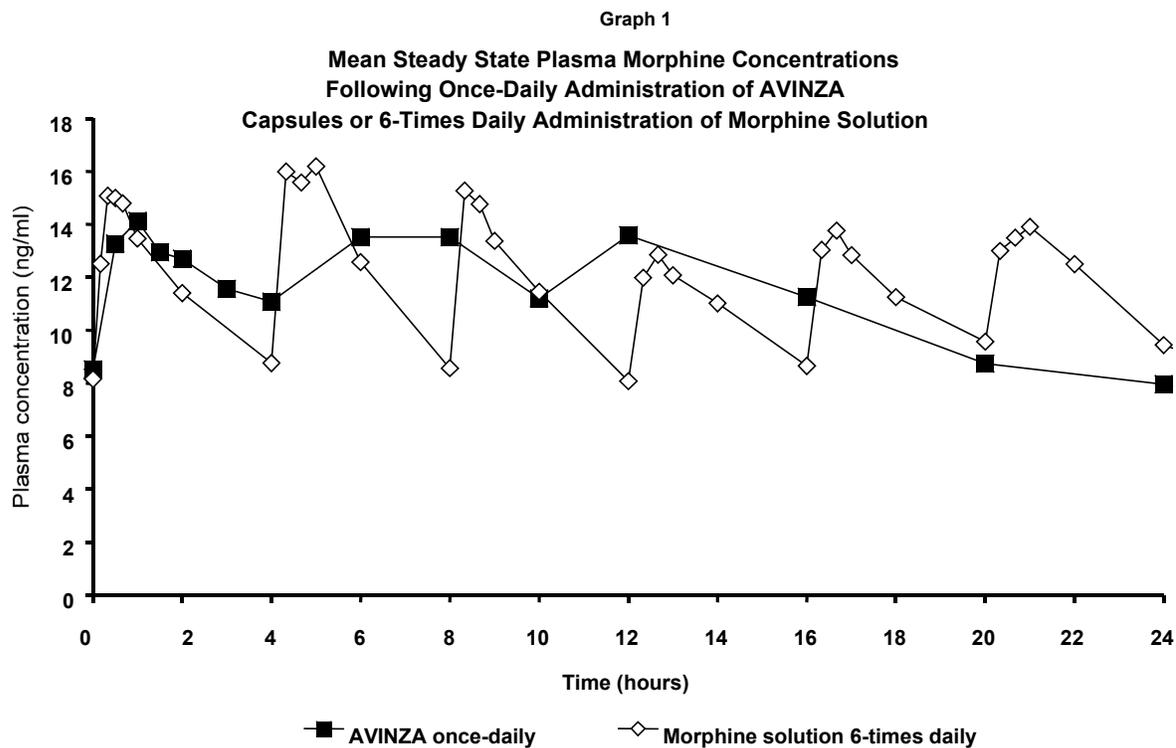
88 Following single-dose oral administration of a 60 mg dose of AVINZA under fasting  
89 conditions, morphine concentrations of approximately 3 to 6 ng/ml were achieved  
90 within 30 minutes after dosing and maintained for the 24-hour dosing interval. The  
91 pharmacokinetics of AVINZA were shown to be dose-proportional over a single oral  
92 dose range of 30 to 120 mg in healthy volunteers and a multiple oral dose range of at  
93 least 30 to 180 mg in patients with chronic moderate to severe pain.

94 **Food Effects:** When a 60mg dose of AVINZA was administered immediately following  
95 a high fat meal, peak morphine concentrations and AUC values were similar to those  
96 observed when the dose of AVINZA was administered in a fasting state, although  
97 achievement of initial concentrations were delayed by approximately 1 hour under fed  
98 conditions. Therefore, AVINZA can be administered without regard to food. When the  
99 contents of AVINZA were administered by sprinkling on applesauce, the rate and  
100 extent of morphine absorption were found to be bioequivalent to the same dose when  
101 administered as an intact capsule.

102 **Steady State:** When dosed once-daily, AVINZA steady state pharmacokinetics are  
103 characterized by a plateau-like plasma concentration profile. Steady state plasma  
104 concentrations of morphine are achieved 2 to 3 days after initiation of once-daily  
105 administration of AVINZA.

106 AVINZA 60 mg Capsules (once-daily) and 10 mg morphine oral solution (6 times daily)  
107 were equally bioavailable.

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108

109 A once-daily dose of AVINZA provided similar  $C_{max}$ ,  $C_{min}$ , and AUC values and peak-  
 110 trough fluctuations ( $\% FL$ ,  $C_{max}-C_{min}/C_{av}$ ) compared to 6-times daily administration of  
 111 the same total daily dose of morphine oral solution (Table 1).

112

113

114

**Table 1**  
**Pharmacokinetic Data**  
**Mean  $\pm$  SD**

Parameter	AVINZA Capsules Once-Daily	Morphine Oral Solution 6-Times Daily
AUC (ng/ml.h)	273.25 $\pm$ 81.24	279.11 $\pm$ 63.00
$C_{max}$ (ng/ml)	18.65 $\pm$ 7.13	19.96 $\pm$ 4.82
$C_{min}$ (ng/ml)	6.98 $\pm$ 2.44	6.61 $\pm$ 2.15
% FL	106.38 $\pm$ 78.14	116.22 $\pm$ 26.67

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116 **Distribution**

117 Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal  
118 tract, lungs, spleen and brain. Although the primary site of action is the CNS, only  
119 small quantities cross the blood-brain barrier. Morphine also crosses the placental  
120 membranes and has been found in breast milk. The volume of distribution of  
121 morphine is approximately 1 to 6 L/kg, and morphine is 20 to 35% reversibly bound to  
122 plasma proteins.

123 **Metabolism**

124 The major pathway of morphine detoxification is conjugation, either with D-glucuronic  
125 acid to produce glucuronides or with sulfuric acid to produce morphine-3-etheral  
126 sulfate. While a small fraction (less than 5%) of morphine is demethylated, virtually all  
127 morphine is converted by hepatic metabolism to the 3- and 6-glucuronide metabolites  
128 (M3G and M6G; about 50% and 15%, respectively). M6G has been shown to have  
129 analgesic activity but crosses the blood-brain barrier poorly, while M3G has no  
130 significant analgesic activity.

131 **Excretion**

132 Most of a dose of morphine is excreted in urine as M3G and M6G, with elimination of  
133 morphine occurring primarily as renal excretion of M3G. Approximately 10% of the  
134 dose is excreted unchanged in urine. A small amount of the glucuronide conjugates  
135 are excreted in bile, with minor enterohepatic recycling. Seven to 10% of administered  
136 morphine is excreted in the feces.

137 The mean adult plasma clearance is approximately 20 to 30 ml/min/kg. The effective  
138 terminal half-life of morphine after IV administration is reported to be approximately 2

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139 hours. In some studies involving longer periods of plasma sampling, a longer terminal  
140 half-life of morphine of about 15 hours was reported.

#### 141 **Special Populations**

142 **Geriatric:** Elderly patients (aged 65 years or older) may have increased sensitivity to  
143 morphine. AVINZA pharmacokinetics have not been studied specifically in elderly  
144 patients.

145 **Nursing Mothers:** Low levels of morphine sulfate have been detected in maternal  
146 milk. The milk: plasma morphine AUC ratio is about 2.5:1. The amount of morphine  
147 delivered to the infant depends on the plasma concentration of the mother, the amount  
148 of milk ingested by the infant, and the extent of first pass metabolism.

149 **Pediatric:** The pharmacokinetics of AVINZA have not been studied in pediatric  
150 patients below the age of 18. The range of dose strengths available may not be  
151 appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is  
152 **NOT** a suitable alternative for these patients.

153 **Gender:** A gender analysis of pharmacokinetic data from healthy subjects taking  
154 AVINZA indicated that morphine concentrations were similar in males and females.

155 **Race:** There may be some pharmacokinetic differences associated with race. In one  
156 published study, Chinese subjects given intravenous morphine had a higher clearance  
157 when compared to Caucasian subjects (1852 +/- 116 ml/min compared to 1495 +/- 80  
158 ml/min).

159 **Hepatic Failure:** Morphine pharmacokinetics have been reported to be significantly  
160 altered in patients with cirrhosis. Clearance was found to decrease with a  
161 corresponding increase in half-life. The M3G and M6G to morphine plasma AUC  
162 ratios also decreased in these subjects, indicating diminished metabolic activity.

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163 **Renal Insufficiency:** Morphine pharmacokinetics are altered in patients with renal  
164 failure. Clearance is decreased and the metabolites, M3G and M6G may accumulate  
165 to much higher plasma levels in patients with renal failure as compared to patients with  
166 normal renal function.

167 **Drug-Drug Interactions:** Known drug-drug interactions involving morphine are  
168 pharmacodynamic, not pharmacokinetic (See PRECAUTIONS, DRUG  
169 INTERACTIONS).

### 170 **Clinical Studies**

171 AVINZA was studied in over 140 healthy volunteers and 560 patients with chronic,  
172 moderate to severe pain who participated in 6 pharmacokinetic studies, 4 clinical  
173 studies and 3 studies which provided both pharmacokinetic and clinical data. The  
174 patient population included those who were either receiving chronic opioid therapy or  
175 had a prior sub-optimal response to acetaminophen and/or NSAID therapy, as well as  
176 patients who previously received intermittent opioid analgesic therapy. In the  
177 controlled clinical studies, patients were followed from 7 days to up to 4 weeks, and in  
178 the open label studies, patients were followed for up to 6 to 12 months.

179 AVINZA was studied in a double-blind, placebo-controlled, fixed-dose, parallel group  
180 trial in 295 patients with moderate to severe pain due to osteoarthritis. These patients  
181 had either a prior sub-optimal response to acetaminophen, NSAID therapy, or  
182 previously received intermittent opioid analgesic therapy. Thirty-milligrams AVINZA  
183 capsules administered once-daily, either in the morning or the evening, were more  
184 effective than placebo in reducing pain.

### 185 **TABLE 2**

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Placebo	Avinza QAM*	Avinza QPM*
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Overall

LS Mean	-36.23	-75.26	-75.39
Std. Error	11.482	11.305	11.747

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186 \*P<0.05; REPEATED MEASURES ANALYSIS

187 This study was not designed to assess the effects of AVINZA on the course of the  
188 osteoarthritis.

189

190 **INDICATIONS AND USAGE**

191 AVINZA capsules are a modified-release formulation of morphine sulfate intended for  
192 once daily administration indicated for the relief of moderate to severe pain requiring  
193 continuous, around-the-clock opioid therapy for an extended period of time.

194 AVINZA is **NOT** intended for use as a prn analgesic.

195 The safety and efficacy of using AVINZA in the postoperative setting has not been  
196 evaluated. AVINZA is not indicated for postoperative use. If the patient has been  
197 receiving the drug prior to surgery resumption of the pre-surgical dose may be  
198 appropriate once the patient is able to take the drug by mouth. Physicians should  
199 individualize treatment, moving from parenteral to oral analgesics as appropriate. (See  
200 American Pain Society guidelines.)

201

202 **CONTRAINDICATIONS**

203 AVINZA is contraindicated in patients with known hypersensitivity to morphine,  
204 morphine salts, or any components of the product. AVINZA, like all opioids, is  
205 contraindicated in patients with respiratory depression in the absence of resuscitative  
206 equipment and in patients with acute or severe bronchial asthma.

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

209 **WARNINGS**

210 AVINZA must be swallowed whole (not chewed, crushed, or dissolved) or AVINZA  
211 may be opened and the entire bead contents sprinkled on a small amount of  
212 applesauce immediately prior to ingestion. **THE CAPSULES MUST NOT BE**  
213 **CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE**  
214 **AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.** (See Box  
215 Warning, CLINICAL PHARMACOLOGY)

216 **THE DAILY DOSE OF AVINZA MUST BE LIMITED TO A MAXIMUM OF 1600**  
217 **MG/DAY. AVINZA DOSES OF OVER 1600 MG/DAY CONTAIN A QUANTITY OF**  
218 **FUMARIC ACID THAT HAS NOT BEEN DEMONSTRATED TO BE SAFE, AND**  
219 **WHICH MAY RESULT IN SERIOUS RENAL TOXICITY.**

220 **Misuse, Abuse and Diversion of Opioids**

221 Morphine is an opioid agonist and a Schedule II controlled substance. Such drugs are  
222 sought by drug abusers and people with addiction disorders. Diversion of Schedule II  
223 products is an act subject to criminal penalty.

224 Morphine can be abused in a manner similar to other opioid agonists, legal or illicit.

225 This should be considered when prescribing or dispensing AVINZA in situations where  
226 the physician or pharmacist is concerned about an increased risk of misuse, abuse, or  
227 diversion.

228 Abuse of AVINZA by crushing, chewing, snorting, or injecting the dissolved product will  
229 result in the immediate release of the entire daily dose of the opioid and pose a

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230 significant risk to the abuser that could result in overdose and death. Intravenous  
231 abuse of a water extract of AVINZA may lead to serious pulmonary complications due  
232 to the extraction of talc along with morphine sulfate.

233 (see **DRUG ABUSE AND ADDICTION**).

234 Concerns about abuse, addiction, and diversion should not prevent the proper  
235 management of pain. Healthcare professionals should contact their State  
236 Professional Licensing Board, or State Controlled Substances Authority for information  
237 on how to prevent and detect abuse or diversion of this product.

238

#### 239 **Interactions with Alcohol and Drugs of Abuse**

240 Morphine may be expected to have additive effects when used in conjunction with  
241 alcohol, other opioids, or illicit drugs that cause central nervous system depression.

242

#### 243 **Impaired Respiration**

244 Respiratory depression is the chief hazard of all morphine preparations. Respiratory  
245 depression occurs more frequently in elderly or debilitated patients and in those  
246 suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway  
247 obstruction, in whom even moderate therapeutic doses may significantly decrease  
248 pulmonary ventilation.

249 Morphine should be used with extreme caution in patients with chronic obstructive  
250 pulmonary disease or cor pulmonale and in patients having a substantially decreased  
251 respiratory reserve (e.g. severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing  
252 respiratory depression. In such patients, even usual therapeutic doses of morphine  
253 may increase airway resistance and decrease respiratory drive to the point of apnea.

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254 **Head Injury and Increased Intracranial Pressure**

255 The respiratory depressant effects of morphine with carbon dioxide retention and  
256 secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in  
257 the presence of head injury, other intracranial lesions, or a pre-existing increase in  
258 intracranial pressure. Morphine produces effects which may obscure neurologic signs  
259 of further increases in intracranial pressure in patients with head injuries. Morphine  
260 should only be administered under such circumstances when considered essential and  
261 then with extreme care.

262 **Hypotensive Effect**

263 AVINZA, like all morphine products, may cause severe hypotension in an individual  
264 whose ability to maintain blood pressure has already been compromised by a depleted  
265 blood volume or concurrent administration of drugs such as phenothiazines or general  
266 anesthetics (See also PRECAUTIONS, Drug Interactions). AVINZA may produce  
267 orthostatic hypotension and syncope in ambulatory patients.

268 AVINZA is an opioid analgesic which should be administered with caution to patients  
269 in circulatory shock, as vasodilation produced by the drug may further reduce cardiac  
270 output and blood pressure.

271 **Gastrointestinal Obstruction**

272 AVINZA should not be administered to patients with gastrointestinal obstruction,  
273 especially paralytic ileus because AVINZA, like all morphine preparations, diminishes  
274 propulsive peristaltic waves in the gastrointestinal tract and may prolong the  
275 obstruction.

276

277 **PRECAUTIONS**

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278

279 **General**

280 AVINZA is intended for use in patients requiring continuous around-the-clock  
281 treatment with an opioid analgesic. It is not appropriate as a prn treatment for pain.  
282 As with any opioid, it is critical to adjust the dose of AVINZA for each individual patient,  
283 taking into account the patient's prior experience with analgesics. (see DOSAGE AND  
284 ADMINISTRATION).

285 **Use in Pancreatic/Biliary Tract Disease**

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

289 **Special Risk Groups**

290 AVINZA should be administered cautiously and in reduced dosages in patients with  
291 severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic  
292 hypertrophy, or urethral stricture, and in elderly or debilitated patients (see Geriatric  
293 Use and Pharmacokinetics, Special Populations)

294 Caution should be exercised in the administration of morphine to patients with CNS  
295 depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure  
296 disorders.

297 **Driving and Operating Machinery**

298 Patients should be cautioned that AVINZA could impair the mental and/or physical  
299 abilities needed to perform potentially hazardous activities such as driving a car or  
300 operating machinery.

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301 Patients should also be cautioned about the potential combined effects of AVINZA with  
302 other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics  
303 and alcohol (See PRECAUTIONS, Drug Interactions).

#### 304 **Tolerance and Physical Dependence**

305 Tolerance is the need for increasing doses of opioids to maintain a defined effect such  
306 as analgesia (in the absence of disease progression or other external factors).

307 Physical dependence is manifested by withdrawal symptoms after abrupt  
308 discontinuation of a drug or upon administration of an antagonist. Physical  
309 dependence and tolerance are not unusual during chronic opioid therapy.

310 The opioid abstinence or withdrawal syndrome is characterized by some or all of the  
311 following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia,  
312 and mydriasis. Other symptoms also may develop, including: irritability, anxiety,  
313 backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia,  
314 vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

315 In general, opioids should not be abruptly discontinued (see **DOSAGE AND**  
316 **ADMINISTRATION: Cessation of Therapy**).

#### 317 **Information for Patients**

318 Patients receiving AVINZA ( morphine sulfate extended-release capsules) should be  
319 given the following instructions by the physician:

- 320 1. Patients should be advised that AVINZA capsules contain morphine and should be  
321 taken once daily.
- 322 2. AVINZA must be swallowed whole (not chewed, crushed, or dissolved) or AVINZA  
323 may be opened and the entire bead contents sprinkled on a small amount of

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- 324 applesauce immediately prior to ingestion. **The beads must NOT be chewed,**  
325 **crushed, or dissolved due to the risk of exposure to a potentially toxic dose**  
326 **of morphine.**
- 327 3. The dose of AVINZA should not be adjusted without consulting with a physician or  
328 other health care professional.
- 329 4. Patients should be advised that AVINZA may impair mental and/or physical ability  
330 required for the performance of potentially hazardous tasks (e.g. driving, operating  
331 machinery). Patients started on AVINZA or patients whose dose has been  
332 adjusted should refrain from any potentially dangerous activity until it is established  
333 that they are not adversely affected.
- 334 5. Patients should be advised that AVINZA, should not be combined with alcohol or  
335 other CNS depressants (e.g. sleep medications, tranquilizers). A physician should  
336 be consulted if other medications are currently being used or are added in the  
337 future.
- 338 6. Women of childbearing potential who become, or are planning to become  
339 pregnant, should consult a physician prior to initiating or continuing therapy with  
340 AVINZA.
- 341 7. If patients have been receiving treatment with AVINZA for more than a few weeks  
342 and cessation of therapy is indicated, they should be counseled on the importance  
343 of safely tapering the dose and that abruptly discontinuing the medication could  
344 precipitate withdrawal symptoms. The physician should provide a dose schedule  
345 to accomplish a gradual discontinuation of the medication.

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346 8. Patients should be advised that AVINZA is a potential drug of abuse. They should  
347 protect it from theft. It should never be given to anyone other than the individual for  
348 whom it was prescribed.

349 9. Patients should be instructed to keep AVINZA in a secure place out of the reach of  
350 children. When AVINZA is no longer needed, the unused capsules should be  
351 destroyed by flushing down the toilet.

352 As with other opioids, patients taking AVINZA should be advised of the potential for  
353 severe constipation; appropriate laxatives, and/or stool softeners as well as other  
354 appropriate treatments should be initiated from the onset of opioid therapy.

### 355 **Drug Interactions**

356 **CNS Depressants:** The concurrent use of other central nervous system (CNS)  
357 depressants including sedatives, hypnotics, general anesthetics, antiemetics,  
358 phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory  
359 depression, hypotension, profound sedation, or coma. Use with caution and in  
360 reduced dosages in patients taking these agents.

361 **Muscle Relaxants:** Morphine may enhance the neuromuscular blocking action of  
362 skeletal muscle relaxants and produce an increased degree of respiratory depression.

363 **Mixed Agonist/Antagonist Opioid Analgesics:** Mixed agonist/antagonist analgesics  
364 (i.e. pentazocine, nalbuphine and butorphanol) should NOT be administered to  
365 patients who have received or are receiving a course of therapy with a pure opioid  
366 agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce  
367 the analgesic effect and/or may precipitate withdrawal symptoms.

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368 **Monoamine Oxidase Inhibitors (MAOIs):** MAOIs markedly potentiate the action of  
369 morphine. AVINZA should not be used in patients taking MAOIs or within 14 days of  
370 stopping such treatment.

371 **Cimetidine:** Concomitant administration of morphine and cimetidine has been  
372 reported to precipitate apnea, confusion and muscle twitching in an isolated report.  
373 Patients should be monitored for increased respiratory and CNS depression when  
374 receiving cimetidine concomitantly with AVINZA.

375 **Food:** AVINZA can be administered without regard to food (See Pharmacokinetics,  
376 Food Effects).

377 **Carcinogenicity/Mutagenicity/Impairment of Fertility**

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

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391 **Pregnancy**

392 **Teratogenic Effects (Pregnancy Category C)**

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

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414 who attempted suicide by taking an overdose of morphine and other medication during  
415 the first trimester of pregnancy.

#### 416 **Nonteratogenic Effects**

417 Published literature has reported that exposure to morphine during pregnancy is  
418 associated with reduction in growth and a host of behavioral abnormalities in the  
419 offspring of animals. Morphine treatment during gestational periods of organogenesis  
420 in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related  
421 embryotoxicity and neonatal toxicity in one or more studies: decreased litter size,  
422 embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar  
423 weights, lengths or widths at birth and during the neonatal period, delayed motor and  
424 sexual maturation, and increased neonatal mortality, cyanosis and hypothermia.

425 Decreased fertility in female offspring, and decreased plasma and testicular levels of  
426 luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule  
427 shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring  
428 were also observed. Behavioral abnormalities resulting from chronic morphine  
429 exposure of fetal animals included altered reflex and motor skill development, mild  
430 withdrawal, and altered responsiveness to morphine persisting into adulthood.

431 Controlled studies of chronic *in utero* morphine exposure in pregnant women have not  
432 been conducted. Infants born to mothers who have taken opioids chronically may  
433 exhibit withdrawal symptoms, reversible reduction in brain volume, small size,  
434 decreased ventilatory response to CO<sub>2</sub> and increased risk of sudden infant death  
435 syndrome. Morphine sulfate should be used by a pregnant woman only if the need for  
436 opioid analgesia clearly outweighs the potential risks to the fetus.

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437 **Labor and Delivery**

438 Opioids cross the placenta and may produce respiratory depression and psycho-  
439 physiologic effects in neonates. AVINZA is not recommended for use in women during  
440 and immediately prior to labor, when use of shorter acting analgesics or other  
441 analgesic techniques are more appropriate. Occasionally, opioid analgesics may  
442 prolong labor through actions which temporarily reduce the strength, duration and  
443 frequency of uterine contractions. However this effect is not consistent and may be  
444 offset by an increased rate of cervical dilatation, which tends to shorten labor.  
445 Neonates whose mothers received opioid analgesics during labor should be observed  
446 closely for signs of respiratory depression. A specific opioid antagonist, such as  
447 naloxone or nalmefene, should be available for reversal of opioid-induced respiratory  
448 depression in the neonate.

449 **Neonatal Withdrawal Syndrome**

450 Chronic maternal use of opioids during pregnancy may cause newborns to suffer from  
451 neonatal withdrawal syndrome (NWS) following birth. Manifestations of this syndrome  
452 include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor,  
453 vomiting, diarrhea, weight loss, and failure to gain weight. The time and amount of the  
454 mother's last dose, and the rate of elimination of the drug from the newborn may affect  
455 the onset, duration, and severity of the disorder. When severe symptoms occur,  
456 pharmacologic intervention may be required.

457 **Nursing Mothers**

458 Low levels of morphine sulfate have been detected in human milk. Breast-feeding  
459 infants might experience withdrawal symptoms upon cessation of AVINZA  
460 administration to the mother. Because of the potential for nursing infants to

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461 experience adverse reactions, a decision should be made whether to discontinue  
462 nursing or discontinue AVINZA, taking into account the benefit of the drug to the  
463 mother.

#### 464 **Pediatric Use**

465 Safety and effectiveness of AVINZA in pediatric patients below the age of 18 have not  
466 been established. The range of dose strengths available may not be appropriate for  
467 treatment of very young pediatric patients. Sprinkling on applesauce is **NOT** a suitable  
468 alternative for these patients.

#### 469 **Geriatric Use**

470 Of the total number of subjects in clinical studies of AVINZA, there were 168 patients  
471 age 65 and over, including 64 patients over the age of 74, 100 of whom were treated  
472 with AVINZA. Subgroup analyses comparing efficacy were not possible given the  
473 small number of subjects in each treatment group. No overall differences in safety  
474 were observed between these subjects and younger subjects. In general, caution  
475 should be exercised in the selection of the starting dose of AVINZA for an elderly  
476 patient usually starting at the low end of the dosing range. As with all opioids, the  
477 starting dose should be reduced in debilitated and non-tolerant patients (See  
478 CLINICAL PHARMACOLOGY, Special Populations, Geriatric and PRECAUTIONS,  
479 Special Risk Groups).

#### 480 **ADVERSE REACTIONS**

481 In controlled and open label clinical studies, 560 patients with chronic malignant or  
482 non-malignant pain were treated with AVINZA. The most common serious adverse  
483 events reported with administration of AVINZA were vomiting, nausea, death,  
484 dehydration, dyspnea, and sepsis. (Deaths occurred in patients treated for pain due to

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485 underlying malignancy). Serious adverse events caused by morphine include:  
486 respiratory depression, apnea, and to a lesser degree, circulatory depression,  
487 respiratory arrest, shock and cardiac arrest.

#### 488 **Adverse Events**

489 The common adverse events seen on initiation of therapy with morphine are dose-  
490 dependent and are typical opioid related side effects. The most frequent of these  
491 include constipation, nausea and somnolence. The frequency of these events depends  
492 upon several factors including the clinical setting, the patient's level of opioid  
493 tolerance, and host factors specific to the individual. These events should be  
494 anticipated and managed as part of opioid analgesia therapy.

495 The most common adverse events (seen in greater than 10%) reported by patients  
496 treated with AVINZA during the clinical trials at least once during therapy were  
497 constipation, nausea, somnolence, vomiting, and headache. Adverse events  
498 occurring in from 5-10% of study patients were peripheral edema, diarrhea, abdominal  
499 pain, infection, urinary tract infection, accidental injury, flu syndrome, back pain, rash,  
500 sweating, fever, insomnia, depression, paresthesia, anorexia, dry mouth, asthenia and  
501 dyspnea. Other less common side effects expected from opioid analgesics, including  
502 morphine, or seen in fewer than 5% of patients taking AVINZA in the clinical trials  
503 were:

504 *Body as a Whole:* malaise, withdrawal syndrome.

505 *Cardiovascular System:* bradycardia, hypertension, hypotension, palpitations,  
506 syncope, tachycardia.

507 *Digestive System:* biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver  
508 function tests, rectal disorder, thirst.

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509 *Hemic and Lymphatic System:* anemia, thrombocytopenia.

510 *Metabolic and Nutritional Disorders:* edema, weight loss.

511 *Musculoskeletal:* skeletal muscle rigidity.

512 *Nervous System:* abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia,

513 confusion, convulsions, coma, delirium, euphoria, hallucinations, lethargy,

514 nervousness, abnormal thinking, tremor, vasodilation, vertigo.

515 *Respiratory System:* hiccup, hypoventilation, voice alteration.

516 *Skin and Appendages:* dry skin, urticaria.

517 *Special Senses:* amblyopia, eye pain, taste perversion.

518 *Urogenital System:* abnormal ejaculation, dysuria, impotence, decreased libido,

519 oliguria, urinary retention.

520

## 521 **DRUG ABUSE AND ADDICTION**

522 **AVINZA is a mu-agonist opioid and is a Schedule II controlled substance.**

523 **Morphine, like other opioids used in analgesia, can be abused and is subject to**  
524 **criminal diversion.**

525 Drug addiction is characterized by compulsive use, use for non-medical purposes, and

526 continued use despite harm or risk of harm. Drug addiction is a treatable disease,

527 utilizing a multi-disciplinary approach, but relapse is common.

528 “Drug seeking” behavior is very common in addicts and drug abusers. Drug-seeking

529 tactics include emergency calls or visits near the end of office hours, refusal to

530 undergo appropriate examination, testing or referral, repeated “loss” of prescriptions,

531 tampering with prescriptions and reluctance to provide prior medical records or contact

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532 information for other treating physician(s). “Doctor shopping” to obtain additional  
533 prescriptions is common among drug abusers and people suffering from untreated  
534 addiction.

535

536 Abuse and addiction are separate and distinct from physical dependence and  
537 tolerance. Physicians should be aware that addiction may not be accompanied by  
538 concurrent tolerance and symptoms of physical dependence. The converse is also  
539 true. In addition, abuse of opioids can occur in the absence of true addiction and is  
540 characterized by misuse for non-medical purposes, often in combination with other  
541 psychoactive substances. Careful record-keeping of prescribing information, including  
542 quantity, frequency, and renewal requests is strongly advised.

543

544 Proper assessment of the patient, proper prescribing practices, periodic re-evaluation  
545 of therapy, and proper dispensing and storage are appropriate measures that help to  
546 limit abuse of opioid drugs.

547

548 **AVINZA is intended for oral use only. Abuse of the crushed capsule poses a**  
549 **hazard of overdose and death. This risk is increased with concurrent abuse of**  
550 **alcohol and other substances. With parenteral abuse, the capsule excipients,**  
551 **especially talc, can be expected to result in local tissue necrosis, infection,**  
552 **pulmonary granulomas, and increased risk of endocarditis and valvular heart**  
553 **injury. Parenteral drug abuse is commonly associated with transmission of**  
554 **infectious diseases such as hepatitis and HIV.**

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555 **AVINZA OVERDOSAGE**

556 **Symptoms**

557 Acute overdose with morphine is manifested by respiratory depression, somnolence  
558 progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin,  
559 constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension,  
560 and death.

561 **Treatment**

562 Primary attention should be given to re-establishment of a patent airway and institution  
563 of assisted or controlled ventilation when overdose of an extended-release formulation  
564 such as AVINZA has been ingested. Elimination or evacuation of gastric contents may  
565 be necessary in order to eliminate unabsorbed drug. Before attempting treatment by  
566 gastric emptying or activated charcoal, care should be taken to secure the airway.  
567 Pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory  
568 depression resulting from opioid overdose. Since the duration of reversal is expected  
569 to be less than the duration of action of AVINZA, the patient must be  
570 carefully monitored until spontaneous respiration is reliably re-established. AVINZA,  
571 as with other controlled delivery preparations in overdose situations, may continue to  
572 release morphine for 36 to 48 hours or longer following ingestion, and management of  
573 an overdose should be monitored accordingly. If the response to opioid antagonists is  
574 sub-optimal or only brief in nature, additional antagonist should be administered as  
575 directed by the manufacturer of the product.  
576 Opioid antagonists should not be administered in the absence of clinically significant  
577 respiratory or circulatory depression secondary to morphine overdose. Such agents  
578 should be administered cautiously to persons who are known, or suspected to be

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579 physically dependent on AVINZA. In such cases, an abrupt or complete reversal of  
580 opioid effects may precipitate an acute abstinence syndrome.

581 **Opioid-Tolerant Individuals:** In an individual physically dependent on opioids,  
582 administration of the usual dose of the antagonist will precipitate an acute withdrawal  
583 syndrome. The severity of the withdrawal symptoms experienced will depend on the  
584 degree of physical dependence and the dose of the antagonist administered. Use of  
585 an opioid antagonist should be reserved for cases where such treatment is clearly  
586 needed. If it is necessary to treat serious respiratory depression in the physically  
587 dependent patient, administration of the antagonist should be initiated with care and  
588 titrated with smaller than usual doses.

589 Supportive measures (including oxygen, vasopressors) should be employed in the  
590 management of circulatory shock and pulmonary edema as indicated. Cardiac arrest  
591 or arrhythmias may require cardiac massage or defibrillation.

## 592 **DOSAGE AND ADMINISTRATION**

593 **AVINZA MUST BE SWALLOWED WHOLE (NOT CHEWED, CRUSHED, OR**  
594 **DISSOLVED) OR AVINZA MAY BE OPENED AND THE ENTIRE BEAD CONTENTS**  
595 **SPRINKLED ON A SMALL AMOUNT OF APPLESAUCE IMMEDIATELY PRIOR TO**  
596 **INGESTION. THE BEADS MUST NOT BE CHEWED, CRUSHED, OR DISSOLVED**  
597 **DUE TO RISK OF ACUTE OVERDOSE. INGESTING CHEWED OR CRUSHED**  
598 **AVINZA BEADS WILL LEAD TO THE RAPID RELEASE AND ABSORPTION OF A**  
599 **POTENTIALLY TOXIC DOSE OF MORPHINE.**

600 **The daily dose of AVINZA must be limited to a maximum of 1600 mg/day.**

601 **AVINZA doses of over 1600 mg/day contain a quantity of fumaric acid that has**

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602 **not been demonstrated to be safe, and which may result in serious renal**  
603 **toxicity. (See Warnings).**

604 **The 60, 90, and 120mg capsules are for use only in opioid tolerant patients.**

605 All doses are intended to be administered once daily. As with any opioid drug product,  
606 it is necessary to adjust the dosing regimen for each patient individually, taking into  
607 account the patient's prior analgesic treatment experience. In the selection of the  
608 initial dose of AVINZA, attention should be given to the following:

- 609 1. the total daily dose, potency and specific characteristics of the opioid the patient  
610 has been taking previously;
- 611 2. the reliability of the relative potency estimate used to calculate the equivalent  
612 morphine dose needed;
- 613 3. the patient's degree of opioid tolerance;
- 614 4. the general condition and medical status of the patient;
- 615 5. concurrent medications;
- 616 6. the type and severity of the patient's pain.

617 The following dosing recommendations, therefore, can only be considered suggested  
618 approaches to what is actually a series of clinical decisions over time in the  
619 management of the pain of each individual patient.

#### 620 **Conversion from Other Oral Morphine Formulations to AVINZA**

621 Patients receiving other oral morphine formulations may be converted to AVINZA by  
622 administering the patient's total daily oral morphine dose as AVINZA once-daily.

623 AVINZA should not be given more frequently than every 24 hours. As with conversion  
624 from any oral morphine formulation to another, supplemental pain medication may be

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625 required until the response to the patient's daily AVINZA dosage has stabilized (up to 4  
626 days).

627 **Conversion from Parenteral Morphine or Other Non-Morphine Opioids**  
628 **(Parenteral or Oral) to AVINZA**

629 There is inter-patient variability in the potency of opioid drugs and opioid formulations.  
630 Therefore, a conservative approach is advised when determining the total daily dose  
631 of AVINZA. It is better to underestimate a patient's 24-hour oral morphine dose and  
632 make available rescue medication than to overestimate the 24-hour oral morphine  
633 dose and manage an adverse experience or overdose. The following general points  
634 should be considered regarding opioid conversions.

635 *Parenteral to oral morphine ratio:* Anywhere from 3 to 6 mg of oral morphine may be  
636 required to provide pain relief equivalent to 1 mg of parenteral morphine. Based on  
637 this rationale, a reasonable starting dose of AVINZA would be approximately three  
638 times the previous daily parenteral morphine requirement.

639 *Other parenteral or oral non-morphine opioids to oral morphine sulfate:* Physicians  
640 and other health care professionals are advised to refer to published relative potency  
641 information, keeping in mind that conversion ratios are only approximate. In general, it  
642 is safest to administer half of the estimated daily morphine requirement as the initial  
643 AVINZA dose once per day and then manage insufficient pain relief by  
644 supplementation with immediate-release morphine or other short-acting analgesics.  
645 (See Individualization of Dosage).

646 **Individualization of Dosage**

647 Physicians should individualize treatment using a progressive plan of pain  
648 management such as outlined by the World Health Organization, the American Pain

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649 Society and the Federation of State Medical Boards Model Guidelines. Health care  
650 professionals should follow appropriate pain management principles of careful  
651 assessment and ongoing monitoring. AVINZA (morphine sulfate) is on the third step  
652 of the WHO three step analgesic ladder and is of most benefit when a constant level of  
653 opioid analgesia is used as a platform from which break-through pain is managed.  
654 Once acceptable pain relief is no longer achieved from combinations of non-opioid  
655 medications (NSAIDs and acetaminophen) and intermittent usage of moderate or  
656 strong opioids, conversion to a 24-hour oral morphine equivalent is warranted.  
657 The dose may be titrated as frequently as every other day to control analgesia. In the  
658 event that break-through pain occurs, AVINZA may be supplemented with a small  
659 dose (5-15% of the total daily dose of morphine) of a short-acting analgesic.  
660 When AVINZA is chosen as the initial opioid for patients who do not have a proven  
661 tolerance to opioids, patients should be treated initially at a dose of 30 mg once-daily  
662 (at 24-hour intervals). For opioid-naïve patients, the dose should be increased  
663 conservatively. For such patients, it is recommended that the dose of AVINZA be  
664 adjusted in increments not greater than 30 mg every 4 days. Some degree of  
665 tolerance may occur, requiring dosage adjustment until the achievement of a balance  
666 between analgesia and opioid side effects. When necessary, the total dose of  
667 AVINZA should be increased until pain relief is reached or clinically significant opioid-  
668 related adverse reactions occur.

#### 669 **Alternative Methods of Administration**

670 AVINZA beads sprinkled over applesauce were found to be bioequivalent to AVINZA  
671 capsules swallowed whole under fasting conditions in a study of healthy volunteers.  
672 Absorption of the beads sprinkled on other foods has not been tested. This method of

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673 administration may be beneficial for patients who have difficulty swallowing whole  
674 capsules or tablets.

- 675 1. Sprinkle the entire contents of the capsule(s) onto a small amount of  
676 applesauce. The applesauce should be at room temperature or cooler. Use  
677 immediately (See also CLINICAL PHARMACOLOGY, Food Effects).
- 678 2. Swallow mixture without chewing or crushing beads.
- 679 3. Rinse mouth and swallow to ensure all beads have been ingested.
- 680 4. Patients should consume the entire portion and should not divide applesauce  
681 into separate doses.

#### 682 **Conversion from AVINZA to Other Pain Control Therapies**

683 It is important to remember that the persistence of AVINZA-derived plasma morphine  
684 concentrations may be in excess of 36 hours when making a conversion to other pain  
685 control therapies.

#### 686 **Conversion from AVINZA to Other Controlled-Release Oral Morphine**

##### 687 **Formulations**

688 For a given dose, the same total amount of morphine is available from AVINZA as  
689 from oral morphine solution or controlled-release morphine tablets. The extended  
690 duration of release of morphine from AVINZA results in reduced maximum and  
691 increased minimum plasma morphine concentrations than with shorter acting  
692 morphine products. Conversion from AVINZA to the same total daily dose of another  
693 controlled-release morphine formulation could lead to either excessive sedation at  
694 peak serum levels or inadequate analgesia at trough serum levels. Dosage  
695 adjustment with close observation is recommended.

696

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697

## 698 **Conversion from AVINZA to Parenteral Opioids**

699 When converting from AVINZA to parenteral opioids, it is best to calculate an  
700 equivalent parenteral dose and then initiate treatment at half of this calculated value.

701 As an example, an estimated total 24-hour parenteral morphine requirement of a  
702 patient receiving AVINZA is one-third of the dose of AVINZA. This is because the oral  
703 bioavailability of morphine is one-third that of parenteral morphine. This estimated  
704 dose should then be divided in half, and this last calculated dose is the total daily  
705 dose. This value should be further divided by six if the desire is to dose with  
706 parenteral morphine every four hours.

707 Consider a patient taking 360 mg of AVINZA daily. First, divide by 3, to account for  
708 differences in bioavailability between oral and parental morphine. This new figure, 120  
709 mg, is the estimated total 24-hour requirement of parenteral morphine. Dividing by 2,  
710 the result gives the total daily dose of 60 mg. If it is decided to administer the drug at  
711 four-hour intervals, then administer 10 mg (60 divided by 6) every four hours.

712 Although this approach may require a dosage increase in the first 24 hours for many  
713 patients, this method is recommended, as it is less likely to result in overdose.

714 Overdose is more likely to occur when administering an equivalent dose of parenteral  
715 morphine without titration. Provision for break-through pain should be made.

716

## 717 **Cessation of Therapy**

718 When the patient no longer requires therapy with AVINZA capsules, doses should be  
719 tapered gradually to prevent signs and symptoms of withdrawal in the physically  
720 dependent patient.

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721

722 **SAFETY AND HANDLING**

723 AVINZA consist of hard gelatin capsules containing polymer-coated morphine sulfate  
724 beads that pose no known risk of handling to health care workers. All opioids are liable  
725 to diversion and misuse both by the general public and health care workers and should  
726 be handled accordingly.

727 **HOW SUPPLIED**

728 **30 mg Capsule:** size 3 capsule, yellow cap imprinted  and white, opaque body  
729 imprinted 30 mg and 505.

730 NDC 64365-505-01: Unit dose packaging, 25s (For Institutional Use Only).

731 NDC 64365-505-03: Bottles of 100 capsules.

732 **60 mg Capsule:** size 3 capsule, bluish green cap imprinted  and white, opaque  
733 body imprinted 60 mg and 506.

734 NDC 64365-506-01: Unit dose packaging, 25s (For Institutional Use Only).

735 NDC 64365-506-03: Bottles of 100 capsules.

736 **90 mg Capsule:** size 1 capsule, red cap imprinted  and white, opaque body  
737 imprinted 90 mg and 507.

738 NDC 64365-507-01: Unit dose packaging, 25s (For Institutional Use Only).

739 NDC 64365-507-02: Bottles of 100 capsules.

740 **120 mg Capsule:** size 1 capsule, blue violet cap imprinted  and white, opaque body  
741 imprinted 120 mg and 508.

742 NDC 64365-508-01: Unit dose packaging, 25s (For Institutional Use Only).

743 NDC 64365-508-02: Bottles of 100 capsules.

744

745 Store at 25°C (77°F); excursions permitted to 15-30° C (59-86°F). [see USP Controlled  
746 Room Temperature]

747 Protect from light and moisture.

748 Dispense in a tight, light-resistant container as defined in USP.

749

750 CAUTION: DEA Order Form Required.

751

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752 Rx Only.

753

754 Manufactured for:



755  
756

757 Ligand Pharmaceuticals Incorporated

758 San Diego, CA 92121

759 Medical Information Telephone Number: (800) 964-5836

760 By:



761

762 Elan Holdings, Inc.

763 Rev. 03/02

764 AVINZA is a registered trademark of Ligand Pharmaceuticals, Inc.

765 SODAS® is a registered trademark of Elan Corporation, plc.



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768 U. S. Patent No.: 6,066,339

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## PATIENT INFORMATION

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772

### AVINZA™ Schedule II

773

(morphine sulfate extended-release capsules)

774

AVINZA™ Capsules, 30 mg

775

AVINZA™ Capsules, 60 mg

776

AVINZA™ Capsules, 90 mg

777

AVINZA™ Capsules, 120 mg

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Carefully read this information and any additional information given to you by your healthcare provider or pharmacist before taking AVINZA™ (ah-VIN-zah) capsules. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. Share this information with members of your household.

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### What is AVINZA?

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787

AVINZA is a capsule that comes in several strengths (30 mg, 60 mg, 90 mg, and 120 mg) and contains the medicine morphine (MOR-feen), in an extended-release form. AVINZA treats moderate to severe pain that is expected to last for more than a few days. Each capsule contains enough medicine to last for 24 hours.

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### What You Need To Remember About AVINZA

794

795

- Only use AVINZA the way your healthcare provider recommends.

796

797

- Only use AVINZA for the condition for which it was prescribed.

798

799

- AVINZA is not for occasional ("as needed") use.

800

801

- AVINZA works best when taken at the same time once a day.

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- Do not crush, dissolve, or chew the contents (beads) of the capsules before swallowing. AVINZA works properly over 24 hours only when the capsules are swallowed whole. Alternatively, the bead contents of the capsule may be sprinkled on applesauce immediately prior to eating. If the beads are crushed, dissolved, or chewed, the entire 24 hour dose may be absorbed into your body all at once. This can lead to serious problems, including overdose and death.

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- Keep AVINZA out of the reach of children. Accidental overdose by a child is dangerous and may result in death.

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- Prevent theft and misuse. AVINZA contains morphine, a narcotic painkiller, that can be a target for people who abuse prescription medicines. Therefore, keep your capsules in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine may endanger other individuals and is against the law.

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AVINZA™ (morphine sulfate) Extended-Release Capsules 30mg, 60mg, 90mg and 120mg  
New Drug Application # 21-260  
ELAN PHARMACEUTICAL RESEARCH CORPORATION

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**Do not take AVINZA if your healthcare provider did not prescribe AVINZA for you or if:**

- **you have severe asthma or severe lung problems.**
- **you have had a severe allergic reaction to morphine. A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.**

**Your healthcare provider should know about all your medical conditions** before deciding if **AVINZA** is right for you and what dose is best. Only you and your healthcare provider can decide if **AVINZA** is right for you.

Tell your healthcare provider about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- recent head injury or concussion
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

**If you are pregnant or plan to become pregnant, talk with your healthcare provider. AVINZA** may not be right for you. **Tell your healthcare provider if you are breast feeding.** Morphine will pass through the milk and may harm the baby.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with **AVINZA**, especially if they cause drowsiness.

#### **How Should You Take AVINZA?**

- **Follow your healthcare provider's directions exactly.** Your healthcare provider may change your dose based on your reactions to the medicine. Do not change your dose unless your healthcare provider tells you to change it. Do not take **AVINZA** more often than prescribed.
- **Try to take AVINZA at the same time each day.**
- **Do not crush, dissolve, or chew** the contents (beads) of the capsules before swallowing. **If the capsule beads are not swallowed whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **AVINZA capsules may be opened and the entire bead contents sprinkled on a small amount of applesauce immediately prior to eating.**
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless instructed by your healthcare provider. If uncertain about your dosing, call your healthcare provider.
- **In case of overdose**, call your local emergency number or poison control center right away.
- **Regularly review your pain symptoms with your healthcare provider.**

AVINZA™ (morphine sulfate) Extended-Release Capsules 30mg, 60mg, 90mg and 120mg  
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- Consult your healthcare provider for instructions on how to stop taking this medicine slowly to avoid uncomfortable symptoms. You should not stop taking **AVINZA** all at once if you have been taking it for more than a few days.
  - If you are instructed to stop taking AVINZA, flush the unused capsules down the toilet.

#### 874 **What Should You Avoid While Taking AVINZA?**

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- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. **AVINZA** can make you drowsy.
  - **Do not drink alcohol while using AVINZA. It may increase the chance of having dangerous side effects.**
  - **Do not take other medicines without your healthcare provider's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you drowsy.

#### 887 **Call Your Healthcare Provider Or Get Medical Help Right Away If**

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- your breathing slows down or becomes difficult
  - you feel faint, dizzy, confused, or have any other unusual symptoms

#### 891 **What are the Possible Side Effects of AVINZA?**

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Some of the common side effects of **AVINZA** are constipation, nausea, drowsiness, and itching. Some of these side effects may decrease with continued use. These are not all the possible side effects of **AVINZA**.

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Constipation is a common side effect of opioids, including **AVINZA**. You may wish to discuss steps to prevent or relieve constipation with your healthcare provider.

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There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing an abuse problem or addiction again while using **AVINZA**. It is not known how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

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This leaflet summarizes the most important information about **AVINZA**. If you would like more information, talk with your healthcare provider or pharmacist.

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/s/

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Kimberly Compton  
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CSO