

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

FINAL PRINTED LABELING

- 1 AVINZA™
2 (morphine sulfate extended-release capsules)
3 CII
4 R_x 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

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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.

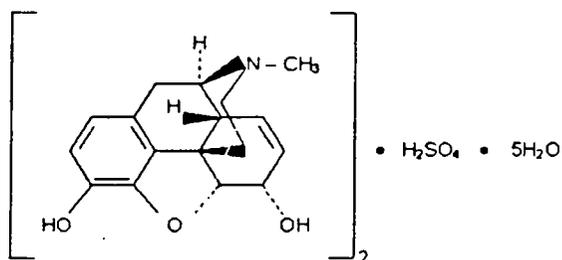
11 Chemically, morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17-methyl-morphinan-
12 3,6 alpha-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758.

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_a 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

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

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

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.

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

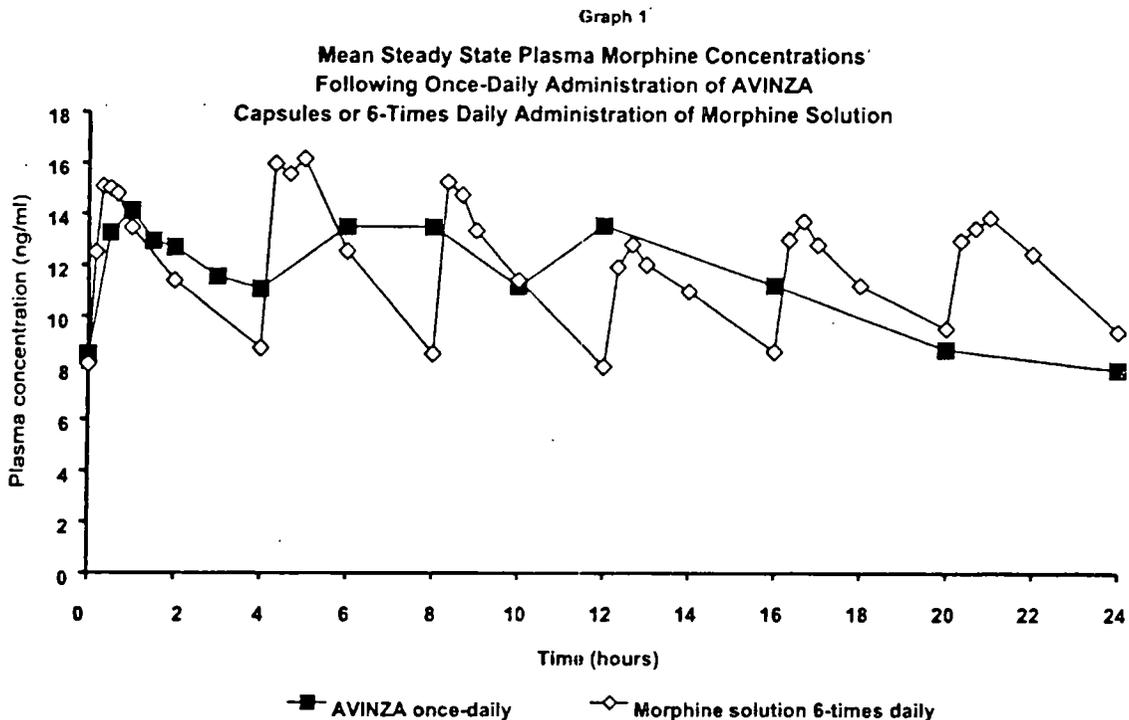
87 **Absorption**

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.



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).

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113

114

Table 1
Pharmacokinetic Data
Mean ± SD

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

115

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

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.

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**

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

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.

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

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.

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**

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.

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

- 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.

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.

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.

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

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 CO₂ 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.

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

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

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.

- 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

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.**

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

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

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

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

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

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.

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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 parenteral 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.

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

752 R_x 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.  élan

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

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PATIENT INFORMATION

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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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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

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- Only use AVINZA the way your healthcare provider recommends.

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

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

800

801

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

802

803

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

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- you have severe asthma or severe lung problems.

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

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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.

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

831

- trouble breathing or lung problems

832

- recent head injury or concussion

833

- liver or kidney problems

834

- adrenal gland problems, such as Addison's disease

835

- convulsions or seizures

836

- alcoholism

837

- hallucinations or other severe mental problems

838

- past or present substance abuse or drug addiction

839

840

If you are pregnant or plan to become pregnant, talk with your healthcare provider.

841

AVINZA may not be right for you. Tell your healthcare provider if you are breast feeding.

842

Morphine will pass through the milk and may harm the baby.

843

844

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.

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How Should You Take AVINZA?

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- **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.

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- **Try to take AVINZA at the same time each day.**

856

- **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.**

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- **AVINZA capsules may be opened and the entire bead contents sprinkled on a small amount of applesauce immediately prior to eating.**

861

862

- **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.

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- **In case of overdose, call your local emergency number or poison control center right away.**

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- **Regularly review your pain symptoms with your healthcare provider.**

- 869
- 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.
- 870
- 871
- 872
- If you are instructed to stop taking AVINZA, flush the unused capsules down the toilet.
- 873

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

- 875
- **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.
- 876
- 877
- 878
- **Do not drink alcohol while using AVINZA. It may increase the chance of having dangerous side effects.**
- 879
- **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.
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887 **Call Your Healthcare Provider Or Get Medical Help Right Away If**

- 888
- your breathing slows down or becomes difficult
 - you feel faint, dizzy, confused, or have any other unusual symptoms
- 889
- 890

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

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893 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**.

894

895

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897 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.

898

899

900 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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904

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

906

907

908 Distributed by: Ligand Pharmaceuticals Inc.
909 San Diego, CA 92121-1117, USA
910 March 20, 2002
911

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Compton
3/20/02 08:02:18 PM
CSO

**APPEARS THIS WAY
ON ORIGINAL**