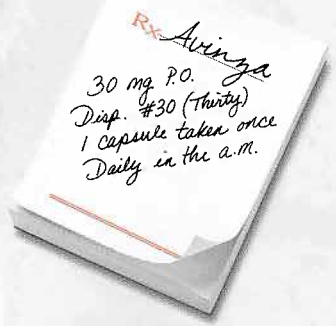
AVINZA®—
Get Patients Back to Active Living

- Proven efficacy with continuous 24-hour pain control[1]
- Significant improvement in physical and social function[1]
- Proven safety and tolerability[2]
- Simplified drug accountability



24-Hour Pain Relief Available in Multiple Dosing Strengths

30 mg | 60 mg | 90 mg | 120 mg

Capsules are shown at actual size.

Please see full Prescribing Information enclosed.
For questions regarding *AVINZA*, please call the *AVINZA* Information Service at 1-888-8-AVINZA.

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LIGAND PHARMACEUTICALS | Organon

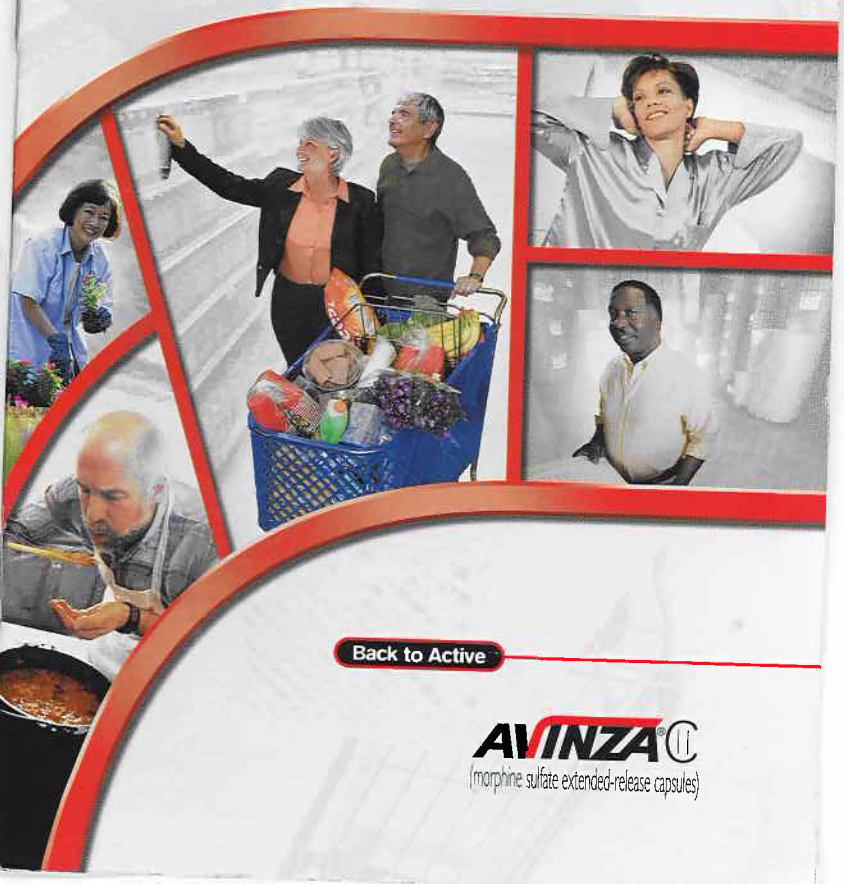
AVINZA®
(morphine sulfate extended-release capsules)

AVIN512-RCW 0106 AVI-3052

AVINZA® Treatment Guide

For Chronic Moderate-to-Severe Pain

Continuous 24-Hour Pain Relief To Get Back to Active Living



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AVINZA®
(morphine sulfate extended-release capsules)

AVINZA®— Proven Efficacy

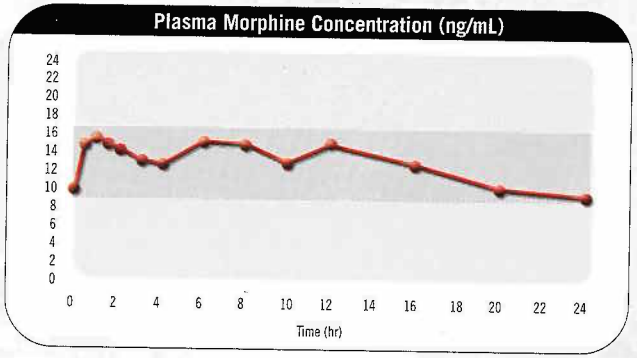
The Benefits of Continuous 24-Hour Pain Control and Long-Lasting Relief

*Double-blind, placebo-controlled, fixed-dose, parallel-group trial of 295 patients with moderate to severe pain due to osteoarthritis (OA) of hip and/or knee. Statistically significant reductions in pain were seen with *AVINZA* as compared to placebo. Results with *AVINZA* reflect average of AM and PM dosing.

- Simplified drug regimen and accountability
  - — One dose per day makes it easy to keep track of capsules and prescriptions for physicians, office staff, patients, and caregivers
- Reduces need for clock-watching
- Less interruption to daytime activities and nighttime rest

To Get Back to Active Living

Long Duration of Action[2]



- *AVINZA* has a unique delivery system that slowly and consistently releases over 24 hours
- More stable plasma concentration
- Pharmacokinetic profiles may or may not imply efficacy[2]

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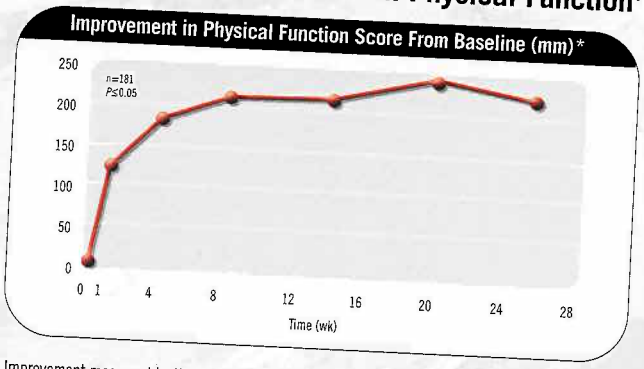
(morphine sulfate extended-release capsules)

AVINZA®— Improved Overall Function

Long-Lasting Improvements in Physical Function[1]



* Improvement measured by the Western Ontario and McMaster Universities (WOMAC) OA Index Pain Scale, a comprehensive, well-validated, self-administered questionnaire consisting of subsets of questions that are answered by the patients. Results with *AVINZA* reflect average of AM and PM dosing. Week 0 (baseline) is Week 4 of the double-blind trial. For some patients, titration occurred over the 26-week period to achieve optimal pain relief.

- Improvement seen as early as Week 1
- Sustained improvement over 6 months

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To Get Back to Active Living

Improvement in Daily Activities Includes†[1]

- Walking on a flat surface ✓
- Standing or sitting ✓
- Climbing stairs ✓
- Getting in and out of bed or bath ✓
- Ability to perform domestic duties ✓

† Results from a 26-week, open-label extension trial involving patients who successfully completed a 4-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel trial comparing the safety and efficacy of once-daily *AVINZA* 30 mg and twice-daily MS Contin® 15 mg. Upon entering the extension trial, patients were randomized to receive *AVINZA* 30 mg once daily in the morning (*AVINZA* QAM) or *AVINZA* 30 mg once daily in the evening (*AVINZA* QPM). If optimal pain relief was not achieved, the *AVINZA* dose was allowed to be increased.

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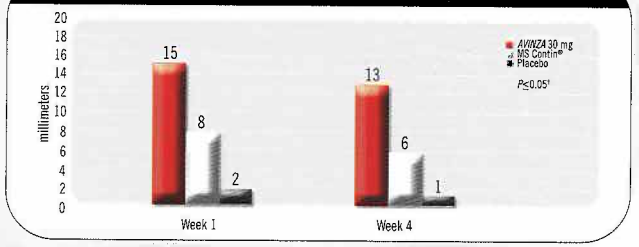
AVINZA®— Improved Sleep Quality

Improvement in Quality of Sleep[1]

Improvement in Sleep Scores From Baseline (0-100 mm)*



* Results from a 4-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel trial. Upon entering the trial, patients were randomized to 1 of 4 treatments: *AVINZA* 30 mg once daily in the morning (*AVINZA* QAM), *AVINZA* 30 mg once daily in the evening (*AVINZA* QPM), MS Contin® 15 mg twice daily, or placebo twice daily.

† *P* value for *AVINZA* vs placebo.

To Get Back to Active Living

Improved Quality of Sleep Includes[1]

- Sustained sleep improvement over 6 months
- Reduced need for sleep medication
- Increased ability to fall asleep
- Increased duration of sleep each night
- Less awakening at night

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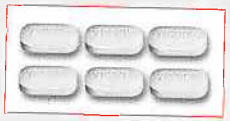
AVINZA®
(morphine sulfate extended-release capsules)

AVINZA®— Convenient Dosing

Continuous 24-Hour Pain Relief in A Single Daily Dose[3]

Vicodin®
(hydrocodone/acetaminophen CIII):
6 times a day[4]



30 mg* *AVINZA*
Once Daily[3]

* Equianalgesic ratio of morphine to hydrocodone is 1:1.5.[3] Rounded down to the nearest *AVINZA* dose.

Simplified drug regimen and accountability

- 30 Days = 30 Doses
- One dose per day makes it easy to keep track of capsules and prescriptions to physicians, office staff, patients, and caregivers

For Simplified Accountability

Individualization of Dosage[2]

- In all patients, the dose of *AVINZA* should be titrated to achieve a balance between therapeutic and adverse effects
- As with any opioid, it is critical to adjust the dose of *AVINZA* for each individual patient, taking into account the patient's prior analgesic treatment experience
- Practitioners should consider other factors when starting a patient on opioid therapy (eg, age, medical history, concomitant medications)
- *AVINZA* has been proven to be safe and well tolerated

AVINZA® (morphine sulfate extended-release capsules)

AVINZA®— Convenient Dosing

For Simplified Accountability

Dosing and Conversions

- All *AVINZA* doses are intended to be administered once daily. Treatment should be individualized using a progressive plan of pain management such as outlined by the
  - World Health Organization
  - American Pain Society
  - Federation of State Medical Boards Model Guidelines
- The following guidelines should be considered for reference only. As with any opioid, it is critical to adjust the dose of *AVINZA* for each individual patient. Because every patient responds differently to opioid drugs and formulations, a conservative approach is advised when determining the total daily dose of *AVINZA*
- 30 mg capsules are indicated for opioid-naïve patients. 60 mg, 90 mg, and 120 mg capsules are for use in opioid-tolerant patients only
- When selecting the initial dose of *AVINZA*, it's advisable to pay attention to
  - The patient's prior experience with analgesic treatment, including
    - The total daily dose, potency, and specific characteristics of the opioid previously taken
    - The reliability of the relative potency estimate used to calculate the equivalent morphine dose needed
  - The patient's degree of opioid tolerance
  - The general condition and medical status of the patient
  - Concomitant medications
  - The type and severity of the patient's pain

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AVINZA®— Convenient Dosing

For Simplified Accountability

Important: Conversion From Non-Morphine Opioids

In general, it is safest to administer half of the estimated daily morphine requirement as the initial *AVINZA* dose once per day, and then manage insufficient pain relief by supplementation with immediate-release morphine or other short-acting analgesics. Clinical judgment is advised when dosing for each individual patient.

Titration

In all patients, the dose of *AVINZA* should be titrated to achieve a balance between therapeutic and adverse effects.

Tolerance and Reassessment

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). As with all opioids, some degree of tolerance may occur, requiring a dosage adjustment. When it does, the total dose of *AVINZA* should be increased until pain relief is reached or clinically significant opioid-related adverse reactions occur.

Managing Side Effects

Common adverse events seen on initiation of therapy with *AVINZA* are dose dependent, and are typical opioid-related side effects, including constipation, nausea, and somnolence.

In general, *AVINZA* has been proven to be safe and well tolerated.

Physicians should start patients on a bowel regimen from the onset of therapy to manage opioid-induced constipation.

Discontinuation of *AVINZA* Therapy

In general, opioids should not be abruptly discontinued. Instead, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

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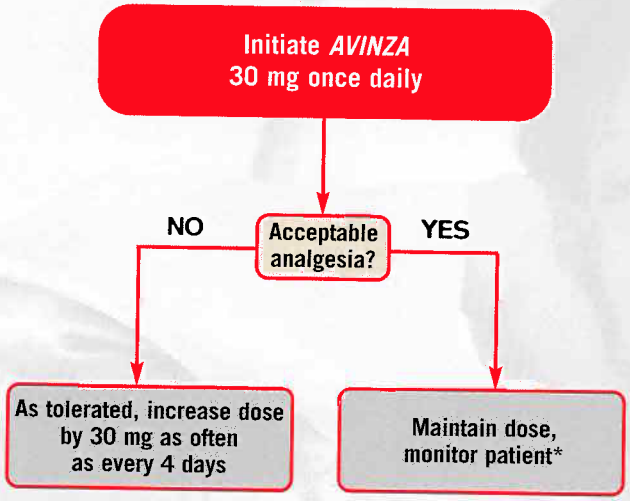
Titrating AVINZA®



Continually monitor the patient; manage adverse events as needed.

If breakthrough pain occurs, supplement with immediate-release medication (5% to 15% of total daily dose of morphine equivalent).

***For unacceptable side effects, reassess/reduce the dose.**

For Opioid-Naïve Patients

Individually Assess Each Patient and Titrate to the Optimal *AVINZA* Dose

- Assess patient's medical condition and *AVINZA* therapy objectives
- Initial dose: 30 mg once daily
- Administer at 24-hour intervals
- Do not increase dosing frequency
- Dose adjustment: no more than 30 mg every 4 days†

†Steady-state concentrations of morphine are achieved 2 to 3 days after initiation of once-daily *AVINZA*. In some cases, steady state may be reached in 4 to 5 days.

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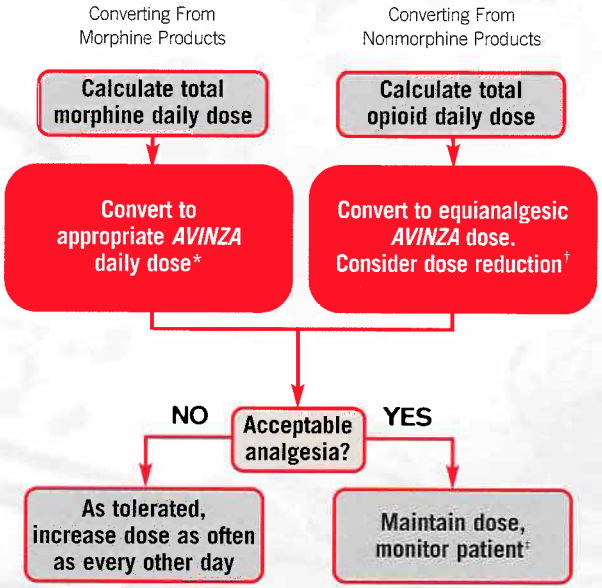
(morphine sulfate extended-release capsules)

Titrating *AVINZA*®

For Opioid-Tolerant Patients



Continually monitor the patient; manage adverse events as needed.

If breakthrough pain occurs, supplement with immediate-release medication (5% to 15% of total daily dose of morphine equivalent).

**From oral morphine:* The amount of morphine absorbed from *AVINZA* following oral administration is similar to that absorbed from other oral morphine formulations. *From intravenous (IV) morphine:* A reasonable starting dose of *AVINZA* would be approximately 3 times the daily IV morphine requirement. (3 mg to 6 mg of oral morphine may be required to provide pain relief equivalent to 1 mg of IV morphine.)

Individually Assess Each Patient and Titrate to the Optimal *AVINZA* Dose

- Assess patient's medical condition and *AVINZA* therapy objectives
- Review the product information of prior medication regarding conversion to other opioids
- Titration frequency: as often as every other day
- Dose should be taken at 24-hour intervals
- Do not increase dosing frequency
- Steady-state concentrations of morphine can be achieved 2 to 3 days after initiation of once-daily *AVINZA*. Therefore, it may take 3 to 4 days to see the clinical benefit of increased dosage

† *From oral nonmorphine opioids:* Use the equianalgesic table in the following section to determine the daily dose of *AVINZA* based on current opioid total daily dose. Due to interpatient variability and incomplete cross-tolerance, it is generally safest to administer half of the estimated daily morphine requirement as the initial *AVINZA* dose once per day, and then manage insufficient pain relief by supplementation with immediate-release morphine or other short-acting analgesics.

‡ **If excessive side effects occur, reduce the *AVINZA* dose and reassess.**

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(morphine sulfate extended-release capsules)

AVINZA®— Convenient Dosing

These tables should be considered for guidance only, providing the total daily cumulative equianalgesic dosing for various opioids.

Morphine Agents to *AVINZA*

Immediate Release	IV dose/day	Extended Release	*AVINZA**
5 mg q4h	10 mg	15 mg q12h	30 mg q24h
10 mg q4h	20 mg	30 mg q12h	60 mg q24h
15 mg q4h	30 mg	45 mg q12h	90 mg q24h
20 mg q4h	40 mg	60 mg q12h	120 mg q24h
25 mg q4h	50 mg	75 mg q12h	150 mg q24h
30 mg q4h	60 mg	90 mg q12h	180 mg q24h
35 mg q4h	70 mg	105 mg q12h	210 mg q24h
40 mg q4h	80 mg	120 mg q12h	240 mg q24h
45 mg q4h	90 mg	135 mg q12h	270 mg q24h
50 mg q4h	100 mg	150 mg q12h	300 mg q24h

Equianalgesic ratio is 1:1[5]

*Consider the need for dose reduction.

Morphine Products:

Immediate Release: MSIR®, Roxanol™

IV: Morphine sulfate (including Infumorph®, Duramorph®).

Extended Release: Kadian®, MS Contin®, Oramorph SR®

Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.

Equianalgesic Tables

These tables should be considered for guidance only, providing the total daily cumulative equianalgesic dosing for various opioids.

Oral Oxycodone Agents to *AVINZA*

Immediate Release	Controlled Release	*AVINZA**
5 mg q6h	10 mg q12h	30 mg q24h
10 mg q6h	20 mg q12h	60 mg q24h
15 mg q6h	30 mg q12h	90 mg q24h
20 mg q6h	40 mg q12h	120 mg q24h
25 mg q6h	50 mg q12h	150 mg q24h
30 mg q6h	60 mg q12h	180 mg q24h
35 mg q6h	80 mg q12h	240 mg q24h

Equianalgesic ratio is 1:1.5[5]

*Consider the need for dose reduction.

Oxycodone Products:

Immediate Release: Oxy IR®, Oxydose™, Oxyfast®, Roxicodone® Intensol, Roxicodone®, Endocet®, Percocet®, Roxicet™, Tylox®, Endodan®, Percodan®

Controlled Release: OxyContin®

For oxycodone combination products with acetaminophen, higher doses may exceed maximum recommended daily doses of acetaminophen (4 g).[6]

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Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.

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AVINZA®— Convenient Dosing

Hydromorphone Agents to *AVINZA*

Oral Hydromorphone	*AVINZA**
2 mg q4h	30 mg q24h
2 mg q6h	30 mg q24h
4 mg q4h	90 mg q24h
4 mg q6h	60 mg q24h
6 mg q4h	120 mg q24h
6 mg q6h	90 mg q24h
8 mg q4h	180 mg q24h
8 mg q6h	120 mg q24h
10 mg q4h	240 mg q24h
10 mg q6h	150 mg q24h

Equianalgesic ratio is 1:4.[5]

*Consider the need for dose reduction.

Oral Hydromorphone Products:
Dilaudid®, Dilaudid®-5.

Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.

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Equianalgesic Tables

Hydrocodone Agents to *AVINZA*

Oral Hydrocodone	*AVINZA**
5 mg q4h	30 mg† q24h
7.5 mg q4h	60 mg† q24h
7.5 mg q6h	30 mg† q24h
10 mg q4h	90 mg q24h
10 mg q6h	60 mg q24h
15 mg q4h	120 mg† q24h
15 mg q6h	90 mg q24h
20 mg q4h	180 mg q24h
20 mg q6h	120 mg q24h

Equianalgesic ratio is 1:1.5.[3]

*Consider the need for dose reduction.

Combination Oral Hydrocodone Products:
Anexsia®, Bancap® HC, Lorcet® 10/650, Lorcet® Plus, Lortab®, Lorcet®-HD, Norco® (Vicodin®, Vicodin HP®, Vicodin ES®), Zydone®

Rounded down to nearest *AVINZA* dose.
For hydrocodone combination products with acetaminophen, care should be taken not to exceed recommended daily doses of acetaminophen (4 g).[6]

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Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.

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AVINZA®— Convenient Dosing

Fentanyl Transdermal System to *AVINZA*

Fentanyl Transdermal System	*AVINZA**
25 mcg/h	60-90 mg q24h
50 mcg/h	90-180 mg q24h
75 mcg/h	180-270 mg q24h
100 mcg/h	270-360 mg q24h

*Consider the need for dose reduction.

AVINZA doses are suggested equianalgesic ranges based on American Pain Society recommendations.[5]

Fentanyl Transdermal System Product:
Duragesic®

Conservatively, 30 mg of *AVINZA* could be substituted for each 25 mcg/h fentanyl transdermal patch for initial conversion.

After patch removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations in healthy individuals.[7] *AVINZA* treatment can be initiated 18 hours following removal of the transdermal fentanyl patch, or as clinically indicated.

References: 1. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and open-label extension trial. *J Pain Symptom Manage.* 2002;23:278-291. **2.** *AVINZA* [prescribing information]. San Diego, Calif: Ligand Pharmaceuticals Inc.; Rev. 10/05. **3.** Brookoff D. Chronic pain: 2. The case for opioids. Available at: http://www.hosppract.com/issues/2000/09/brook.htm. Accessed December 29, 2005. **4.** Vicodin [prescribing information]. North Chicago, Ill: Abbott Laboratories; Rev. June 2002. **5.** American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain.* 5th ed. Glenview, Ill: American Pain Society; 2003. **6.** Gilman AG, consulting ed; Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill; 2001. **7.** Duragesic [package insert]. Titusville, NJ: Janssen Pharmaceutica Products, L.P.; 2003.

Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.

Equianalgesic Tables

Other Oral Medications to *AVINZA*

Oral Methadone	Oral Meperidine	*AVINZA**
	50 mg q4h	30 mg q24h
	100 mg q4h	60 mg q24h
5 mg q4h	150 mg q4h	90 mg q24h
	200 mg q4h	120 mg q24h
10 mg q4h		180 mg q24h
15 mg q4h		270 mg q24h

Equianalgesic ratio.[1] Equianalgesic ratio is 1:0.1[5] *Consider the need for dose reduction.

[1]The half-life of methadone varies from 15-40 hours and, with chronic administration, methadone accumulates in body tissue.[6] Use care when rotating patients from methadone to other opioids.[5]

Oral Methadone Products:
Dolophine® HCL, Methadose®, Methadone HCL, Methadone HCL Intensol™, Methadose®.

Oral Meperidine Products:
Demerol® HCL, Meperidine Hydrochloride.

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Note: Confirm the actual opioid dosage being taken per day to determine the total daily *AVINZA* dose.