

From: Jennifer Altier
To: Lisa Miller
Sent: 9/10/2012 9:40:00 PM
Subject: Presentations and Objection Handler
Attachments: NSM Objection Handling Tool_LAM edits 09 10 12.docx; NSM Presentation - 4 strengths.pptx; NSM Presentation - Marketing Presentation.pptx

Hi Lisa,

Please find attached both of my revised presentations from today, along with the updated objection handler. Could you please add the job numbers to the presentations and circulate to PRC for review?

Thanks,
Jennifer

Jennifer Altier
Marketing Director

Description:
C:\Documents and Settings\JALTIER\Applicat Data\Microsoft\Signatures

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Exhibit: 009
Allergan - ALTIER
Date: 8/2/18
Reporter: Amanda Miller, CRR

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PLAINTIFFS TRIAL
EXHIBIT
P-03750_00001

ACTAVIS0389758

P-03750 _ 00001



**Responding to Customer Objections That May Arise During a
KADIAN® (Morphine Sulfate Extended-Release) Capsules Presentation**

| Objection | Why is Actavis introducing the new strengths now? Is this just to make money now that the other strengths have generic competition? | Will generic versions of the new dosage strengths be available? | What is the managed care coverage for the new strengths? | What are you doing to make sure pharmacies have these new strengths in stock? |
|--------------------|---|---|---|--|
| Sales Tools | Detail Aid | Co-Pay Cards | FormTrak® | Pharmacy Flyer |
| Corporate Position | <ul style="list-style-type: none"> Actavis is introducing these new strengths to address a gap in our available dosage strengths and to address the need of prescriber and patients. Given the environment surrounding opioids and the need to provide the least amount of opioid required to manage the patients' pain, the new strengths allow you to have additional dosing flexibility while not requiring you to increase the level of opioid more than is required. | <ul style="list-style-type: none"> The company is launching these new strengths as branded only; however, the new strengths are covered under the KADIAN® co-pay card program, which provides patients with the first \$50 of their co-pay – no patient payment upfront. | <ul style="list-style-type: none"> The new strengths are covered under the same tiers as the other KADIAN® branded strengths. I can provide you with a spreadsheet (FormTrak®) that details the managed care coverage for KADIAN®. | <ul style="list-style-type: none"> My job is to work with the pharmacy to make sure they understand the need to stock the new dosage strengths. If you provide me with the names of the pharmacies where the majority of your patients fill their prescriptions, I will visit those pharmacies to let them know that prescriptions for these strengths will be coming in from you. |

Continued

**Responding to Customer Objections That May Arise During a
KADIAN® (Morphine Sulfate Extended-Release) Capsules Presentation**

| | | | | |
|--------------------|---|---|---|--|
| Objection | You are comparing different formulations in the graphs. It compares KADIAN® BID to Morphine Solution q4h. I would expect KADIAN® to have a better PK profile." | Morphine is morphine. They're both sustained release formulations and are fine my patients | There was little to no difference in time to remedication in patients taking KADIAN® BID versus morphine sulfate BID. | Why was there a higher % of patients needing rescue medication who took KADIAN® BID compared to patients taking it QD? Shouldn't taking the drug BID have them needing less rescue medication?" |
| Sales Tools | Detail Aid (refer to top left chart on page 6) | Detail Aid (refer to top two charts on page 6) | Detail Aid (refer to chart on page 7) | Detail Aid (refer to chart on page 7) |
| Corporate Position | <ul style="list-style-type: none"> The same active ingredient (morphine sulfate) is being compared across the three arms, but the excipients and formulations differ between products, which can affect release and sustained availability of morphine in these products Morphine sulfate ER tablets show more significant fluctuations (spikes and valleys) despite similar BID dosing Morphine solution fluctuates significantly throughout the 12 hour period | <p>Release time says they are not the same:</p> <ul style="list-style-type: none"> Most morphine preparations release 50% of active ingredient Morphine (within the first 30 min). KADIAN® pellets are designed to release a small amount of morphine in the stomach, and most of the morphine is slowly released in the intestine. 50% of the morphine in KADIAN® is released over an 8h period. <p>The PK says they are not the same:</p> <ul style="list-style-type: none"> KADIAN® PK studies show a sustained level of plasma morphine concentrations over the dosing period. Other morphine formulations show greater fluctuations in plasma morphine concentrations. <p>The sustained reduction in VAS Pain scores with KADIAN® reflects the consistent release of morphine.</p> <p>The decreased need for rescue medication also reflects the efficacy of KADIAN®.</p> | <ul style="list-style-type: none"> The active ingredient, morphine, is a highly effective analgesic and one would expect similar levels of pain relief. The differences between the formulations reside in the fluctuations across the dosing period. | <ul style="list-style-type: none"> KADIAN® dosed either BID or QD was demonstrated to be bioequivalent. This is reflected in level of overall pain control (evidenced by VAS and VRS for pain), and the similar number of patients requiring rescue medication, the number of doses of rescue medication as well as the amount of rescue medication. The differences between BID and QD KADIAN® for these parameters were very small and not significant. |

Responding to Customer Objections That May Arise During a KADIAN® (Morphine Sulfate Extended-Release) Capsules Presentation

| Objection | This data doesn't relate to my clinical practice. Most of my patients take morphine sulfate TID or QID and they get adequate pain control with that dosing regimen | Why did a higher % of physicians report marked or moderate pain control for their patients taking KADIAN® QD versus KADIAN® BID? Shouldn't it be the other way around? | There was little to no difference in VRS scores for patients taking KADIAN® versus morphine sulfate. Why is this?" | Why are the mean VAS scores lower for patients taking KADIAN®QD versus BID? Shouldn't a patient taking it BID have better pain scores?" |
|-------------|--|---|--|---|
| Sales Tools | Detail Aid (refer to pages 6 & 7) | Detail Aid (refer to page 7) | Detail Aid (refer to page 7) | Detail Aid (refer to page 7) |
| Messages | <ul style="list-style-type: none"> The level of pain control is excellent and comparable between the treatment groups as reflected by the VAS pain score and VRS pain intensity and pain control scores More patients receiving KADIAN® rated their Global Assessment of Pain Control as "good" or "very good" than those receiving BID ER Morphine (the difference was significant for the QD KADIAN® group) Similarly, more physicians reported their Global Assessment of Pain Control as either "marked" or "moderate efficacy" for patients receiving QD or BID KADIAN®, than the BID ER morphine comparator, although these differences were not statistically significant Patients receiving BID ER Morphine required an additional 23% more morphine per day than either KADIAN® BID (14.9%) or KADIAN® QD (17.3%) These values were numerically less for KADIAN® vs. ER morphine, but not significantly different between the treatment groups | <ul style="list-style-type: none"> The differences are not statistically significant between treatment groups. Global Pain Assessments take into consideration more than just pain. It considers the effects pain has on the patient's life including, but not limited to their function, quality of relationships and activities of daily living. The differences are significant in the % of patients reporting improvement in their global assessments. This may reflect the dosing frequency and its impact on the patient, and/or perceptions of a QD being better than a BID medication. | <ul style="list-style-type: none"> It is important to focus on the entire picture related to IR morphine, which was used as rescue medication. Although differences between BID treatment groups was small relative to the time to remedication and not statistically significant, what is interesting and important to note is that the total amount of rescue medication required was less for patients receiving KADIAN®. Patients receiving BID ER Morphine required an additional 23% more morphine per day than either KADIAN® BID (14.9%) or KADIAN® QD (17.3%). These values were numerically less for KADIAN® vs. ER morphine, but not significantly different between the treatment groups. | <ul style="list-style-type: none"> The mean VAS Pain is 17.9 for once-daily KADIAN®, 20.8 for twice-daily KADIAN® and 23.5 for twice-daily ER Morphine. These values indicate that pain level for these patients is rated as mild, and as such is well controlled across all three treatment groups. The strong analgesic effects of morphine are clear in this study. These differences are very similar and not statistically different. |



KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

KADIAN[®]

New Strengths Launch

Jennifer Altier
September 13, 2012



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New Dosage Strengths



- We are here to launch 4 new dosage strengths for KADIAN®:
 - 40mg
 - 70mg
 - 130mg
 - 150mg

KADIAN® 100mg, 130mg, 150mg, and 200mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established

Background



- KADIAN[®] launched 16 years ago
- Generic competition (along with an Actavis AG) launched November 2011
- Watson to acquire Actavis in November 2012

Why launch 4 new strengths of KADIAN[®] now?



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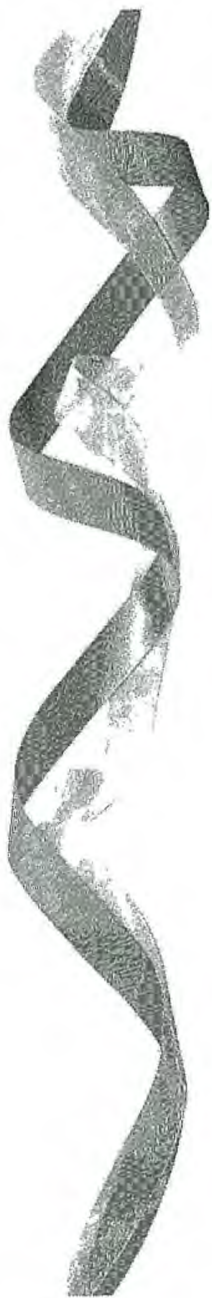
Rationale for new strengths



- APS guidelines – “start low and go slow”:
 - In patients who are opioid naïve, or have modest previous opioid exposure, opioids should be started at a low dose and titrated slowly, to decrease risk of opioid-related adverse events
- Prescriber challenges: Balancing the need to manage pain with the risks of abuse

Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain, February 2009

There is a need to give the patient the optimum dose they need – no more, no less



Gap Analysis



- 8 dosage strengths left gaps, especially when dosing BID

| Dose | BID |
|-------------|-------------|
| 30mg | 60mg |
| 40mg | 80mg |
| 50mg | 100mg |

| Dose | BID |
|-------------|--------------|
| 60mg | 120mg |
| 70mg | 140mg |
| 80mg | 160mg |

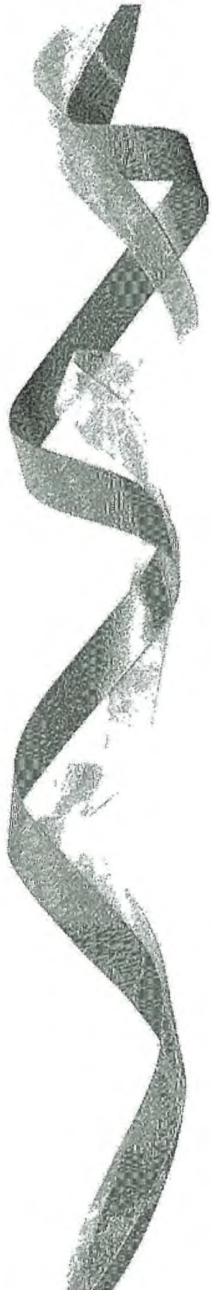
- 40 mg gap is large, especially at lower doses
- The new 40mg and 70mg doses fill that gap
- 130mg and 150mg provide additional titration options between the 100mg and 200mg
 - KADIAN® 100mg, 130mg, 150mg, and 200mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established



Corporate Commitment



- By introducing these new dosage strengths, Actavis is leading the way by providing physicians with the most dosing and administration options for their patients
- No changes to existing dosage strengths (no strengths will be withdrawn)
- Physicians can make the choice whether to incorporate the new strengths into their prescribing behavior
- KADIAN remains the lowest solid oral dosage form (10mg)



KADIAN[®]

Marketing Update

Jennifer Altier
September 13, 2012



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Agenda



- Market Research Update
- What's New with KADIAN®?
 - Clinical Data
 - 4 New Strengths
- Launch Strategy
- Obstacle Handling



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Market Research Feedback



In a recent market research survey, called-on physicians reported the following perceptions of KADIAN[®] attributes:

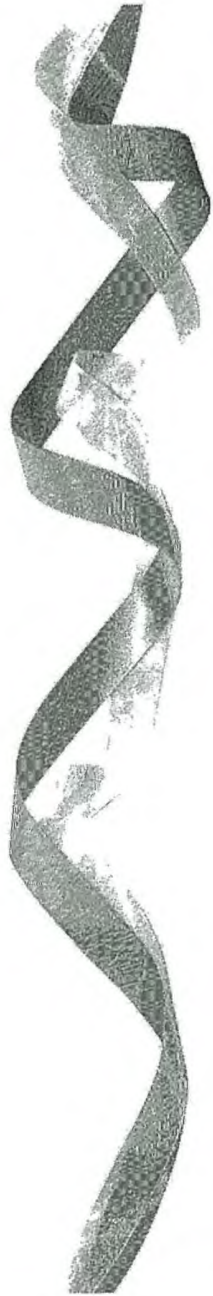
- 12-24 hour pain control
- Easy to titrate due to broad range of dosage strengths
- Low dose (10mg) good for elderly patients
- Perception of low abuse potential
- Less tolerability issues than generic morphine sulfate
- Capsules allow for administration by G-Tube or added to food



What's New with KADIAN®?



- Clinical data – not new, but we haven't discussed it lately
- Much has changed in the long acting opioid environment since this data was initially released, so it is important to remind healthcare professionals about the KADIAN® profile



Updated claims



- KADIAN[®] Patients:
 - Experience sustained morphine release with less fluctuations vs. morphine sulfate
 - Report improved management of pain vs. morphine sulfate
 - Require less rescue medication vs. morphine sulfate



What's New with KADIAN®?



- 4 new dosage strengths: 40mg, 70mg, 130mg and 150mg

| Dose | BID |
|-------------|-------------|
| 30mg | 60mg |
| 40mg | 80mg |
| 50mg | 100mg |

| Dose | BID |
|-------------|--------------|
| 60mg | 120mg |
| 70mg | 140mg |
| 80mg | 160mg |

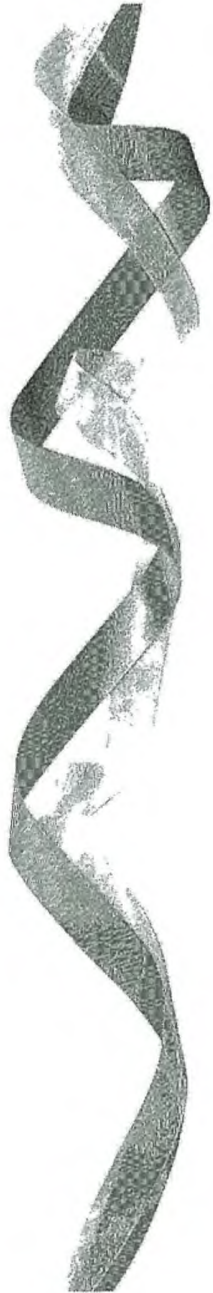
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What's New with KADIAN®?



- Updated branding
 - All of the new detail pieces have the updated branding – a gold ribbon has been added to the green ribbon
- Updated PI
 - New labeling as previously discussed



Launch Strategy



- Phase I – Pharmacy Stocking
 - Rob has detailed the “push” initiatives, including the wholesaler programs and PharmAlerts sent to Retail Pharmacies
 - We need you to provide the “pull”



Phase I HCP Sales Calls



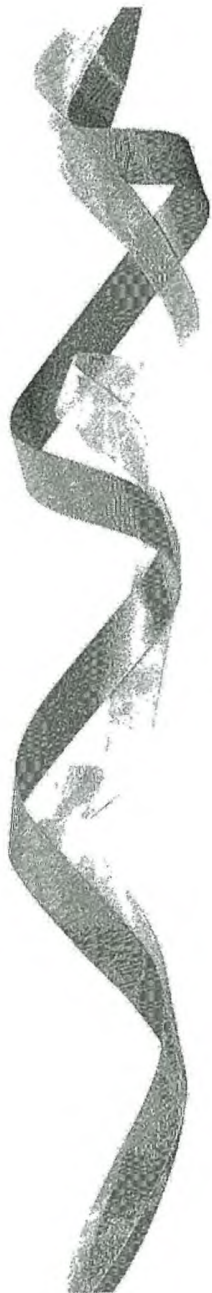
- Starting Monday, Sept 17th:
 - Mornings: Call on healthcare professionals and let them know we are launching 4 new strengths: (40mg, 70mg, 130mg, 150mg).
 - New strength tactics are still in production – you will need to speak to the benefits with limited visuals – use pharmacy flyer)
 - Ask physicians what key pharmacies will need to be stocked with the new strengths (where will their patients be going to fill their prescriptions)



Phase I Pharmacy Sales Calls



- Afternoon: Pharmacy Sales Calls
 - Relay conversations with local physicians – who will be prescribing, they will be sending patients to this pharmacy, etc.
 - Provide Pharmacy Flyer – highlight offer details, create sense of urgency for stocking
 - Utilize 867 pharmacy data to target pharmacies as well – internal spreadsheet detailing where current strengths of KADIAN® are stocked (will ultimately include 4 new strengths as well)
 - Continue through one call cycle and continue to follow up with pharmacies as physicians report stocking issues




Phase II – HCP Detail

KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

NOW AVAILABLE

4 NEW Strengths
to Expand Your
Titration Choices:
40 mg • 70 mg • 130 mg • 150 mg

KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

Please see Boxed WARNING on page 2, Important Safety Information on pages 2-4, and accompanying Full Prescribing Information and Medication Guide.

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Detail Aid Page 2

KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

KADIAN[®]
Morphine Sulfate Extended-Release Capsules

| | |
|------------------------------------|-------------------------------------|
| KADIAN [®] 10 mg Capsules | KADIAN [®] 70 mg Capsules |
| KADIAN [®] 20 mg Capsules | KADIAN [®] 80 mg Capsules |
| KADIAN [®] 30 mg Capsules | KADIAN [®] 100 mg Capsules |
| KADIAN [®] 40 mg Capsules | KADIAN [®] 130 mg Capsules |
| KADIAN [®] 50 mg Capsules | KADIAN [®] 150 mg Capsules |
| KADIAN [®] 60 mg Capsules | KADIAN [®] 200 mg Capsules |

KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg
70mg-80mg-100mg-130mg-150mg-200mg

Rx only

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

KADIAN[®] contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN[®]. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving KADIAN[®] for signs of misuse, abuse, and addiction during treatment.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of KADIAN[®], even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and KADIAN[®] should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of KADIAN[®] or following a dose increase. Instruct patients to swallow KADIAN[®] capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure

Accidental consumption of KADIAN[®], especially in children, can result in a fatal overdose of morphine.

Important Safety Information

Contraindications

KADIAN[®] is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus, and hyperalgesia to morphine.

KADIAN[®] 100 mg, 130 mg, 150 mg, and 200 mg capsule strengths ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. Ingestion of these capsules or the contents within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.

Warnings and Precautions

KADIAN[®] contains morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing KADIAN[®] in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Misuse or abuse of KADIAN[®] by crushing, chewing, snorting or injecting the dissolved product poses a significant risk that could result in overdose and death. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN[®]. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use. Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Respiratory depression is the primary risk of KADIAN[®] and if not immediately recognized and treated, may lead to respiratory arrest and death. Serious, life-threatening, or fatal respiratory depression can occur at any time during the use of KADIAN[®]. Closely monitor patients for respiratory depression when initiating therapy with KADIAN[®] and following dose increases. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists.

Instruct patients that KADIAN[®] should only be used by the patient to whom KADIAN[®] is prescribed. Inappropriate use may result in fatal respiratory depression. KADIAN[®] must be kept in a secure place, and out of reach of children. Accidental consumption of KADIAN[®], especially in children, can result in a fatal overdose of morphine.

Please see Boxed WARNING on this page, Important Safety Information on pages 2-4, and accompanying Full Prescribing Information and Medication Guide.

2



Detail Aid Page 3

KADIAN[®]

Morphine Sulfate
Extended-Release Capsules

10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

Important Safety Information (continued)

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN[®] is essential. Overestimating the KADIAN[®] dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance as compared to younger, healthier patients. Monitor patients closely particularly when initiating and titrating KADIAN[®] and when KADIAN[®] is given concomitantly with other drugs that depress respiration.

Monitor patients with significant chronic obstructive pulmonary disease or *cor pulmonale*, substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, particularly when initiating therapy and titrating with KADIAN[®]. In these patients, even usual therapeutic doses of KADIAN[®] may decrease respiratory drive to the point of apnea. Consider the use of alternative non-opioid analgesics in these patients if possible.

Hypotension, profound sedation, coma, or respiratory depression may result if KADIAN[®] is used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of KADIAN[®] in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression, and the patient's use, if any, of alcohol or other drugs that cause CNS depression. Start with a lower KADIAN[®] dose than usual and monitor patients for signs of sedation and respiratory depression. Also consider using a lower dose of the concomitant CNS depressant.

KADIAN[®] may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating KADIAN[®]. In patients with circulatory shock, KADIAN[®] should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Monitor patients taking KADIAN[®] who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with KADIAN[®]. KADIAN[®] may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of KADIAN[®] in patients with impaired consciousness or coma.

KADIAN[®] is contraindicated in patients with paralytic ileus, and its use should be avoided in patients with other gastrointestinal obstructions. The morphine in KADIAN[®] may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Droids may cause increases in the serum amyloid.

Morphine may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures. Monitor patients with a history of seizure disorders for worsening/worsened seizure control during KADIAN[®] therapy.

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and buprenorphin) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including KADIAN[®]. Mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing KADIAN[®], gradually taper the dose. Do not abruptly discontinue KADIAN[®].

KADIAN[®] may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of KADIAN[®] and know how they will react to the medication.

Drug Interactions

Concomitant use of alcohol with KADIAN[®] can result in increased plasma levels of morphine and result in a potentially fatal overdose of morphine.

KADIAN[®] should be used with great caution and in reduced dosage in patients who are concurrently receiving other CNS depressants including sedatives, hypnotics, general anesthetics, tranquilizers, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. Additive effects may be expected when KADIAN[®] is used concomitantly with CNS depressant drugs, and reduced doses of KADIAN[®] (or the other drug(s)) should be considered.

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and buprenorphin) may reduce the analgesic effect of KADIAN[®] or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist analgesics in patients receiving KADIAN[®].

Opioids may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression. Monitor patients receiving KADIAN[®] concomitantly with muscle relaxants for increased respiratory depression.

continued

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Important Safety Information (continued)

Monoamine Oxidase inhibitors (MAOIs) may potentiate the effects of morphine. KADIAN[®] should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

There is an isolated report of confusion and severe respiratory depression in a hemodialysis patient who was concurrently administered morphine and cimetidine. Monitor patients receiving KADIAN[®] concomitantly with cimetidine for increased respiratory and CNS depression.

Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatic.

Anticholinergics used concurrently with opioid analgesics may result in urinary retention and/or severe constipation. Monitor patients receiving KADIAN[®] concomitantly with anticholinergic drugs for signs of urinary retention or reduced gastric motility.

P-Glycoprotein (PGP) inhibitors may increase the absorption/exposure of morphine by two fold. Monitor patients receiving KADIAN[®] concurrently with a PGP inhibitor for respiratory and CNS depression.

Adverse Reactions

The most serious adverse events associated with KADIAN[®] and other opioid analgesics are respiratory depression, chronic pulmonary disease, increased intracranial pressure, interactions with other CNS depressants, hypotensive effect, gastrointestinal effects and seizures.

The most frequent ($\geq 5\%$ of patients) adverse reactions with KADIAN[®] therapy are constipation, nausea, somnolence, dizziness and anxiety.

Special Populations

KADIAN[®] is in Pregnancy Category C. It is not known if morphine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Chronic maternal use of morphine during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts. KADIAN[®] should be given to a pregnant woman ONLY if clearly needed.

KADIAN[®] is not recommended for use in women during and immediately prior to labor. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression.

Caution should be used when KADIAN[®] is administered to a nursing mother due to the potential for serious adverse reactions in nursing infants. Take into account the importance of KADIAN[®] to the mother.

The safety and effectiveness of KADIAN[®] in patients less than 18 years of age has not been established.

Use caution when selecting a dose of KADIAN[®] in elderly patients aged 65 years or older. Dosing should be initiated at the low end of the dosing range. Monitor patients closely for respiratory and central nervous system depression.


Indications and Usage

KADIAN[®] is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

- KADIAN[®] is not for use:
 - As an as-needed (prn) analgesic
 - For pain that is mild or not expected to persist for an extended period of time
 - For acute pain
 - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time
- KADIAN[®] 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Please see Boxed WARNING on page 2, Important Safety Information on pages 2-4, and accompanying Full Prescribing Information and Medication Guide.




KADIAN[®] (morphine sulfate extended-release) Capsules—
your choice for the treatment of moderate to severe pain
when a continuous around-the-clock opioid analgesic is
needed for an extended period of time

KADIAN[®] Patients
experience sustained morphine release with less
fluctuations vs. morphine sulfate.¹²

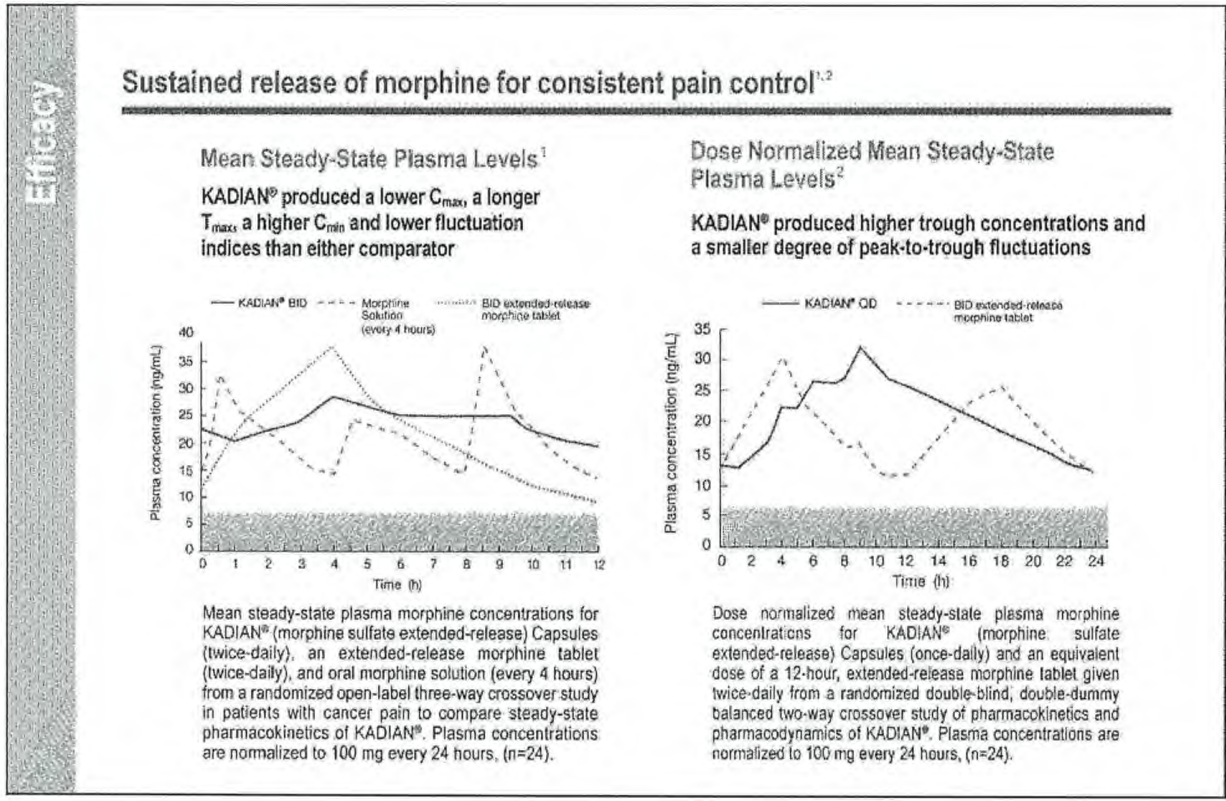
KADIAN[®] Patients
report improved management of pain vs. morphine sulfate.¹³

KADIAN[®] Patients
require less rescue medication vs. morphine sulfate.⁷

Respiratory depression is the primary risk of KADIAN[®]. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses), Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage (10)* section of Full Prescribing Information].

KADIAN[®] 
Morphine Sulfate
Extended-Release Capsules
10mg-20mg-30mg-40mg-50mg-60mg
70mg-80mg-100mg-130mg-150mg-200mg

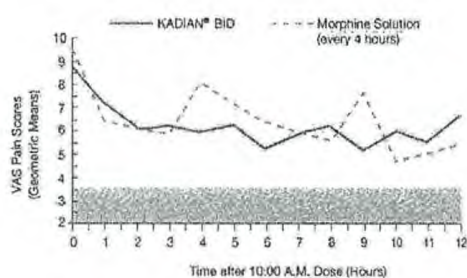
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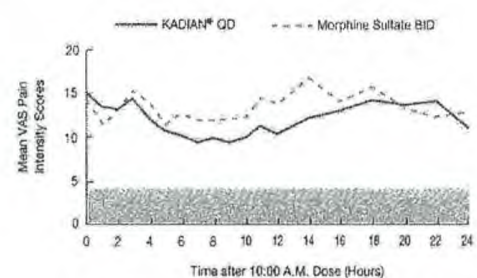
Improved management of pain vs. morphine sulfate^{1,2}

Improved Pain Scores vs. Morphine Solution When Dosed Twice-Daily¹



Steady-state Visual Analog Scale (VAS) pain score on Day 7 of treatment for KADIAN[®] (morphine sulfate extended-release) Capsules (twice-daily) and oral morphine solution (every 4 hours) from a randomized, double-blind, double-dummy crossover study comparing the efficacy and safety of KADIAN[®] in the management of moderate to severe cancer pain. VAS scores are presented as geometric means, (n=24).

Improved Pain Scores vs. Morphine Sulfate When Dosed Once-Daily²



Comparison of Visual Analog Scale (VAS) scores for pain intensity for KADIAN[®] (morphine sulfate extended-release) Capsules (once-daily) and morphine sulfate (twice-daily) in a randomized double-blind, double-dummy two-period crossover comparison of KADIAN[®] in patients with moderate to severe cancer pain. VAS scores are presented as a linear scale running from 0 to 100, (n=29).

Please see **Boxed WARNING** on page 2, **Important Safety Information** on pages 2-4, and accompanying **Full Prescribing Information and Medication Guide**.



KADIAN[®] (morphine sulfate extended-release) Capsules are efficacious and well tolerated for the management of moderate to severe chronic pain, with demonstrated dosing flexibility of either twice-daily or once-daily dosing

Less Rescue Medication Required vs. Morphine Sulfate¹

| Efficacy Parameter | Treatment ^a | | |
|--|-------------------------------------|--------------------------------------|------------------------------------|
| | KADIAN [®] once-daily (54) | KADIAN [®] twice-daily (45) | Morphine sulphate twice-daily (53) |
| Primary Parameters | | | |
| Mean total rescue medication (mg) | 25.1 | 22.0 | 27.7 |
| Mean total rescue medication (% IRM) ^b | 17.3% | 14.9% | 23.1% |
| Mean time to remediation (h) ^c | 16.0 ^d | 9.1 | 8.7 |
| Total number of rescue doses | 55 | 47 | 61 |
| 0 to 12 h | 38 (68%) | 33 (70%) | 47 (77%) |
| 12 to 24 h | 18 (32%) | 14 (30%) | 14 (23%) |
| Mean pain intensity - VAS ^e | 17.9 | 20.8 | 23.5 |
| Mean pain intensity - VRS ^f | 0.9 | 0.9 | 0.9 |
| Mean pain control - VRS ^f | 0.8 | 0.8 | 0.9 |
| Secondary Parameters | | | |
| Patient Global Assessment of Pain Control - mean % of patients rating "good" or "very good" ^g | 89% ^h | 76% | 68% |
| Physician Global Assessment of Pain Control - % of investigators rating "marked" or "moderate efficacy" ^g | 94% | 87% | 85% |

a. 172 randomized, numbers in table denote number of randomized subjects per arm who completed it; percentages of the four treated daily doses of immediate-release morphine (IRM) taken during the lead-in period and designated as IRM; c. Indicates times to administration of first dose of rescue medication in patients who took rescue medication, and times to administration of the next scheduled dose of study drug in patients who did not take rescue medication; d. Statistically significant difference between the KADIAN[®] once-daily group and the KADIAN[®] twice-daily and morphine sulfate twice-daily groups (p<0.01 by ANOVA); e. Visual Analog Scale (VAS); 0 = no pain, 100 = worst possible pain; f. Verbal Rating Scale (VRS); 0 = none, 1 = mild, 2 = moderate, 3 = severe; g. Verbal Rating Scale (VRS); 0 = complete, 1 = partial, acceptable; h. Statistically significant difference between the KADIAN[®] once-daily and morphine sulfate twice-daily (p<0.05 by Fisher's exact test)

KADIAN[®] contains morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing KADIAN[®] in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.





Dosing / Administration

**KADIAN® (morphine sulfate extended-release) Capsules
Provide the Most Dosing Strengths**



Capsules are not shown at actual size.

- 12 dosing strengths—the most of any long-acting opioid
- Lowest solid oral dose morphine/morphine equivalent (10 mg)
- Provides 10 mg dose increments from 10 mg to 80 mg
- Supports once- and twice-daily dosing to help achieve adequate pain management with reliable morphine delivery and bioavailability
- KADIAN® 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN® are essential. Overestimating the KADIAN® dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with KADIAN® (see *Warnings and Precautions* section of accompanying Full Prescribing Information).

Consider the following factors when selecting an initial dose of KADIAN®: Total daily dose, potency, and any prior opioid the patient has been taking previously; Reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration); Patient's degree of opioid experience and opioid tolerance; General condition and medical status of the patient; Concurrent medication; Type and severity of the patient's pain.

Please see **Boxed WARNING** on page 2, **Important Safety Information** on pages 2-4, and accompanying **Full Prescribing Information** and **Medication Guide**.



Expanded dosing strengths for individualized titration and tapering

| Twice-daily Dosing (mg) | Daily Dose (mg) | Twice-daily Dosing (mg) | Daily Dose (mg) |
|-------------------------|-----------------|-------------------------|-----------------|
| 10 mg | 20 mg | 50 mg | 100 mg |
| 20 mg | 40 mg | 60 mg | 120 mg |
| 30 mg | 60 mg | 70 mg | 140 mg |
| 40 mg | 80 mg | 80 mg | 160 mg |

* 130 mg and 150 mg capsules provide additional titration options between 100 mg and 200 mg dosages

Three Administration Options

| | | |
|---|---|---|
| <p>As a capsule</p>  <p>Capsule can be swallowed whole.</p> | <p>Sprinkle dosing</p>  <p>Capsule is not opened at room temperature. Capsule can be opened and the contents sprinkled on applesauce for patients who have difficulty swallowing.*</p> | <p>G-tube dosing</p>  <p>Contents of capsule can be syringed in water and administered through a 18 French gastrostomy tube.**</p> |
|---|---|---|

*The store should be room temperature and used immediately.
**The non-proprietary KADIAN[®] pellets through a nasogastric tube should not be attempted.

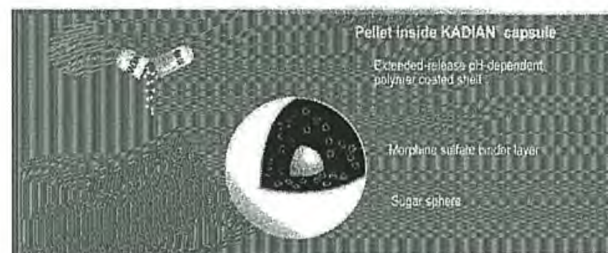
Accidental consumption of KADIAN[®], especially in children, can result in a fatal overdose of morphine. Instruct patients to swallow KADIAN[®] capsules intact or to sprinkle the capsule contents on applesauce and swallow without chewing. The pellets in the capsules are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals.

Discontinuation of KADIAN[®]:
When a patient no longer requires therapy with KADIAN[®], use a gradual downward titration, of the dose every two to four days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue KADIAN[®].



Pellet Technology

KADIAN[®] (morphine sulfate extended-release) Capsules utilize polymer-coated pellet technology to provide reliable morphine delivery



Pellet and capsule are not shown at actual size.

- Distinctive pellet composition releases morphine steadily into the bloodstream for up to 24 hours*
- Extended-release coating initiates slow release in the stomach and continues release once in the duodenal space
- Can be administered without regards to meals

Misuse or abuse of KADIAN[®] by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN[®]. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use. Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Please see Boxed WARNING on page 2, Important Safety Information on pages 2-4, and accompanying Full Prescribing Information and Medication Guide.

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KADIAN[®] is not metabolized through the cytochrome P450 (CYP450) pathway

- Opioids are metabolized through different pathways, including the cytochrome P450 pathway, glucuronidation, sulfation, and demethylation.¹
- The CYP450 pathway is not involved in hepatic metabolism of the morphine contained within KADIAN[®] (morphine sulfate extended-release) Capsules.⁴
- Major pathways of morphine metabolism in the liver include glucuronidation (up to 65% of metabolites), sulfation (up to 30% of metabolites), and demethylation (less than 5% of metabolites).²

Potential drug-drug interactions however do exist. Opioids including KADIAN[®] potentially demonstrate the following drug-drug interactions and patients using these medications concomitantly should be closely monitored: alcohol, CNS depressant drugs, mixed agonist/antagonist analgesics, skeletal muscle relaxants, monoamine oxidase inhibitors, cimetidine, diuretics, anticholinergics, p-glycoprotein inhibitors (see Important Safety Information - Drug Interactions).

In clinical trials in patients with chronic cancer pain, the most common adverse events $\geq 5\%$ reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%).

In a four-week open-label safety study in subjects with chronic, non-malignant pain, the most common adverse events reported by the 1418 enrolled patients were constipation (12%), nausea (9%), and somnolence (3%). Other less common side effects occurring in less than 3% of patients were vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue, and rash.

The following serious adverse reactions have been reported for morphine sulfate: respiratory depression, chronic pulmonary disease, head injuries and increased intracranial pressure, interactions with other CNS depressants, hypotensive effect, gastrointestinal effects, and seizures.



Detail Aid Back Cover

KADIAN[®] 
 Morphine Sulfate
 Extended-Release Capsules
 10mg-20mg-30mg-40mg-50mg-60mg
 70mg-80mg-100mg-130mg-150mg-200mg

KADIAN[®] (morphine sulfate extended-release) Capsules—your choice for the treatment of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time

- Sustained release of morphine for consistent pain control^{1,2}
- Improved management of pain vs. morphine sulfate^{1,3}
- Less rescue medication required vs. morphine sulfate¹
- 12 dosing strengths—the most of any long-acting opioid including the lowest solid oral dose morphine/morphine equivalent
- Expanded dosing strengths for individualized titration and tapering with 10 mg dose increments from 10 mg to 80 mg
- Distinctive pellet composition releases morphine steadily into the bloodstream for up to 24 hours⁴
- The most frequent (25% of patients) adverse reactions with KADIAN[®] therapy are constipation, nausea, somnolence, dizziness and anxiety

KADIAN[®]
 Morphine Sulfate Extended-Release Capsules



| | |
|------------------------------------|-------------------------------------|
| KADIAN [®] 10 mg Capsules | KADIAN [®] 70 mg Capsules |
| KADIAN [®] 20 mg Capsules | KADIAN [®] 80 mg Capsules |
| KADIAN [®] 30 mg Capsules | KADIAN [®] 100 mg Capsules |
| KADIAN [®] 40 mg Capsules | KADIAN [®] 130 mg Capsules |
| KADIAN [®] 50 mg Capsules | KADIAN [®] 150 mg Capsules |
| KADIAN [®] 60 mg Capsules | KADIAN [®] 200 mg Capsules |



For further information, please visit www.KADIAN.com or call 1-888-496-3082. Please see accompanying Full Prescribing Information and Medication Guide. KADIAN[®] is a registered trademark of Actavis Elizabeth LLC.

References:
 1. KADIAN[®] data on file at Country Dr., Chevy Chase, MD. 2. Hershberg, et al. *Journal of Clinical Pharmacy and Therapeutics*. 2004; 29(1): 1-10. 3. Hershberg, et al. *Journal of Clinical Pharmacy and Therapeutics*. 2004; 29(1): 1-10. 4. Hershberg, et al. *Journal of Clinical Pharmacy and Therapeutics*. 2004; 29(1): 1-10.



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Rx only

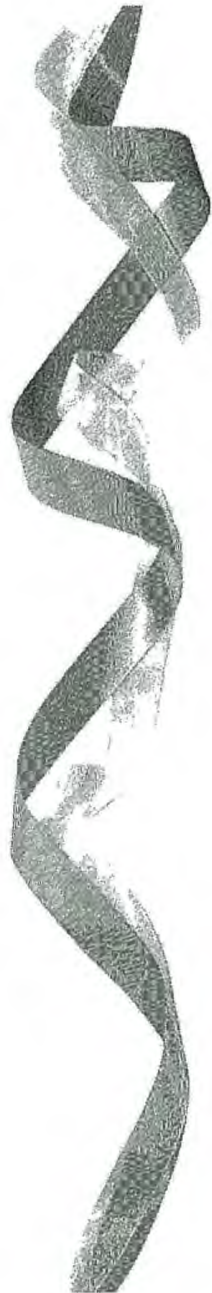
WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential
 KADIAN[®] contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN[®]. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving KADIAN[®] for signs of misuse, abuse, and addiction during treatment.

Life-Threatening Respiratory Depression
 Respiratory depression, including fatal cases, may occur with use of KADIAN[®], even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and KADIAN[®] should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of KADIAN[®] or following a dose increase. Instruct patients to swallow KADIAN[®] capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure
 Accidental consumption of KADIAN[®], especially in children, can result in a fatal overdose of morphine.

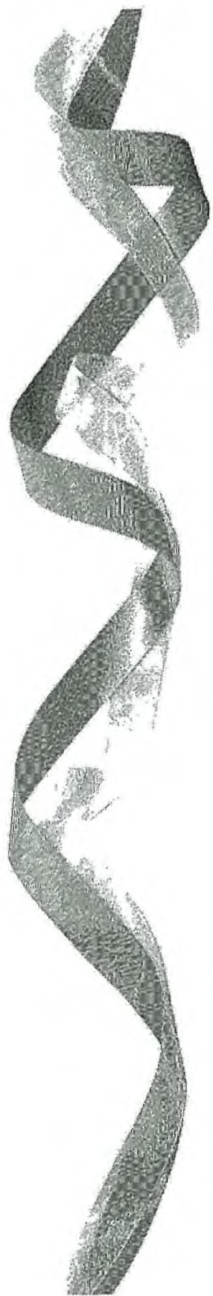
KADIAN[®] 
 Morphine Sulfate
 Extended-Release Capsules
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 70mg-80mg-100mg-130mg-150mg-200mg



Tactics and Timing



- Pharmacy Flyers: 150 flyers arriving at your house this week (sample at your table)
- 867 pharmacy data – internal spreadsheet will be provided on an weekly basis
- Co-Pay Cards with updated strengths : 20 packs (200 cards) arriving to your house by the end of next week
 - Card still works for Actavis AG but not printed on materials
 - Thank you for your feedback on this and other tactics



Tactics and Timing



Other tactics in development:

- Detail Aid
- Dosing Guide
- Conversion Guide
- Table top exhibit panels – in production for fall meetings



Objection Handling: Physicians



- Objection: Why is Actavis introducing the new strengths now? Is this just to make money now that the other strengths have generic competition?
- Corporate Position:
 - *Actavis is introducing these new strengths to address a gap in our available dosage strengths and to address the need of prescribers and patients.*
 - *Given the environment surrounding opioids and the need to provide the least amount of opioid required to manage the patient's pain, the new strengths allow you to have additional dosing flexibility while not requiring you to increase the level of opioid more than is required.*

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Objection Handling: Physicians



- Objection: Will generic versions of the new dosage strengths be available?
- Corporate Position:
 - *The company is launching these new strengths as branded only; however, the new strengths are covered under the KADIAN[®] co-pay card program, which provides patients with the first \$50 of their co-pay – no patient payment upfront.*



Objection Handling: Physicians



- Objection: What is the managed care coverage for the new strengths?
- Corporate Position:
 - *The new strengths are covered under the same tiers as the other KADIAN® branded strengths. I can provide you with a spreadsheet (FormTrak®) that details the managed care coverage for KADIAN®.*



Objection Handling: Physicians



- Objection: What are you doing to make sure pharmacies have these new strengths in stock?
- Corporate Position: *My job is to work with the pharmacy to make sure they understand the need to stock the new dosage strengths. If you provide me with the names of the pharmacies where the majority of your patients fill their prescriptions, I will visit those pharmacies to let them know that prescriptions for these strengths will be coming in from you.*



Objection Handling: Physicians



- Objection: I don't want to use the new strengths.
- Corporate Position:
 - *That's fine. None of the existing dosage strengths are being withdrawn, so you can prescribe them as you always have for your patients.*



Objection Handling: Pharmacist



- Objection: I don't want to stock additional strengths of KADIAN® (too expensive, already stock multiple dosage strengths)
- Corporate Position
 - *This morning, when I with Dr. Smith, he told me that he would be writing these new strengths and sending his patients here to get them filled.*
 - *Actavis is offering 5% off invoice between now and October 15, 2012 when you buy just one bottle of each new strength*
 - *You may return full bottles after 4 months on initial orders only*
 - *Now is the time to order – won't you please order today?*

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Questions?

Thank you!