From: Jennifer Altier
To: 'Tom Johnson' (tj@adwise.com)
Sent: 8/2/2012 5:27:37 AM
Subject: Slides for today's conference call
Attachments: KADIAN detail aid suggestions-revised_20120801.pptx; Kadian Detail Pieces - ABM Comments.pptx

Tom,

Please find attached the slide presentations we will be reviewing during our conference call at 10:00.

Thanks,
Jennifer

Jennifer Altier
Marketing Director

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

Actavis
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PLAINTIFFS TRIAL EXHIBIT
P-01078_00001


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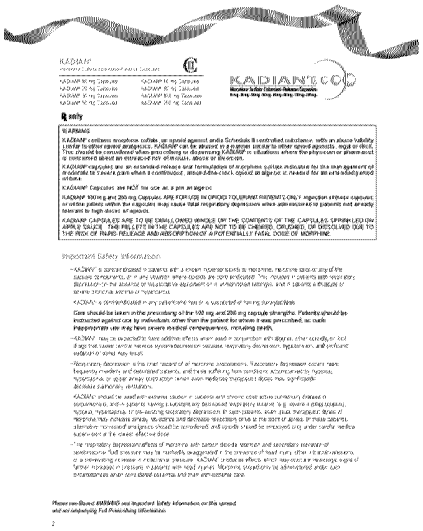
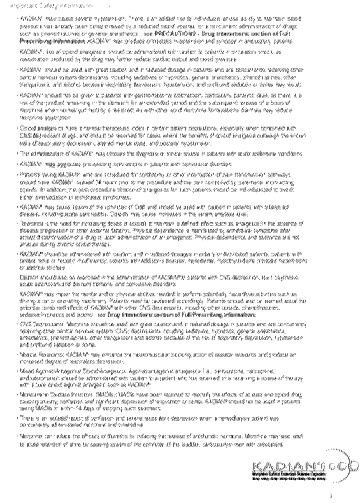
KADIAN®

Detail Aid Expansion

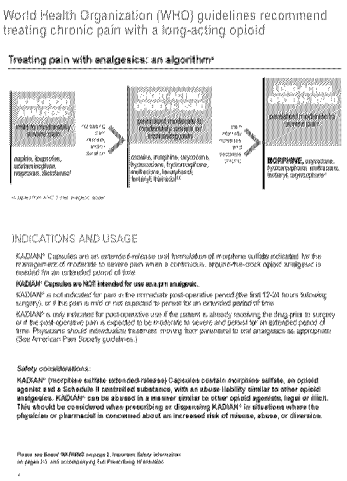
Ivan T. Shaw
02 August 2012

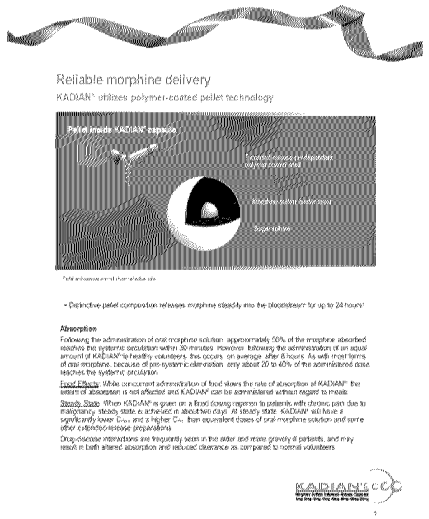
Current Detail Aid (08-09-10)





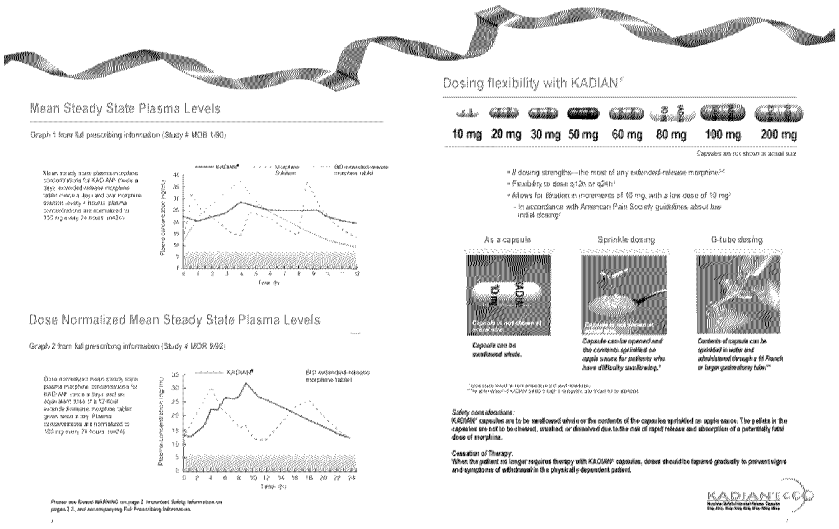
- Boxed warning and Important Safety Information (2-3)

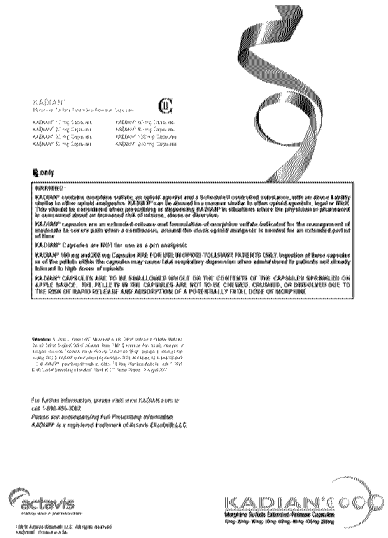




- WHO Guidelines (4)
- Indication and Usage (4)
- Reliable morphine delivery (5)

Current Detail Aid (08-09-10)





- Mean Steady State Plasma Levels (6)
- Dose Normalized Mean Steady State Plasma Levels (6)
- Dosing Flexibility with KADIAN (7)

- Boxed warning (8)
- Doses (8)

Updated detail aid

- Update information based on July 2012 revision to USPI
- Advise physicians on availability of new dosing strengths
- Include information not present in current detail aid

Discussion with Medical Affairs

- In today's environment there is still a place for opioids (pain relief is still required)
  - Multimodal approach to therapy
  - Treatment guidelines: lowest dose is recommended; Kadian provides lowest solid oral morphine/MED
  - Educational information is available through REMS
- Pellet technology: 2 stages
- PK – flat
  - Steady response
- Safety/efficacy spread
  - Study endpoints: redosing, rescue meds
  - AE Profile
  - Cytochrome p450 (CYP3A4)
- Dosing flexibility: 12 doses including 4 new strengths (titration story)
- Things to consider in opioid candidates
  - Background
  - Other medications
  - Kadian: drug-drug interactions (and where there are no interactions), pathways
- Summary – Kadian offers:
  - Lowest morphine/MED
  - Dosing flexibility: 12 doses, BID or QD, hard to swallow pts.
  - Actavis: committed to supporting appropriate opioid use (support of website, etc).

Proposed section flow

08-09-2010 Detail Aid

1. Boxed warning and Important Safety Information
2. WHO Guidelines
3. Indication and Usage
4. Reliable Morphine Delivery
5. Mean Steady State Plasma Levels
6. Dose Normalized Mean Steady State Plasma Levels
7. Dosing Flexibility
8. Boxed warning and Doses

Revised Detail Aid

1. Boxed warning and Important Safety Information
2. WHO Guidelines
3. Multimodal pain management
4. Indication and Usage
5. Dosing Flexibility
6. Reliable Morphine Delivery
7. Mean Steady State Plasma Levels
8. Dose Normalized Mean Steady State Plasma Levels
9. Clinical Efficacy
    1. BID and QD dosing
    2. Pivotal trials
10. Safety
    1. AEs
    2. Hepatic metabolism
    3. Drug-drug interactions
11. Methods of Administration
12. Boxed warning, Doses and REMS

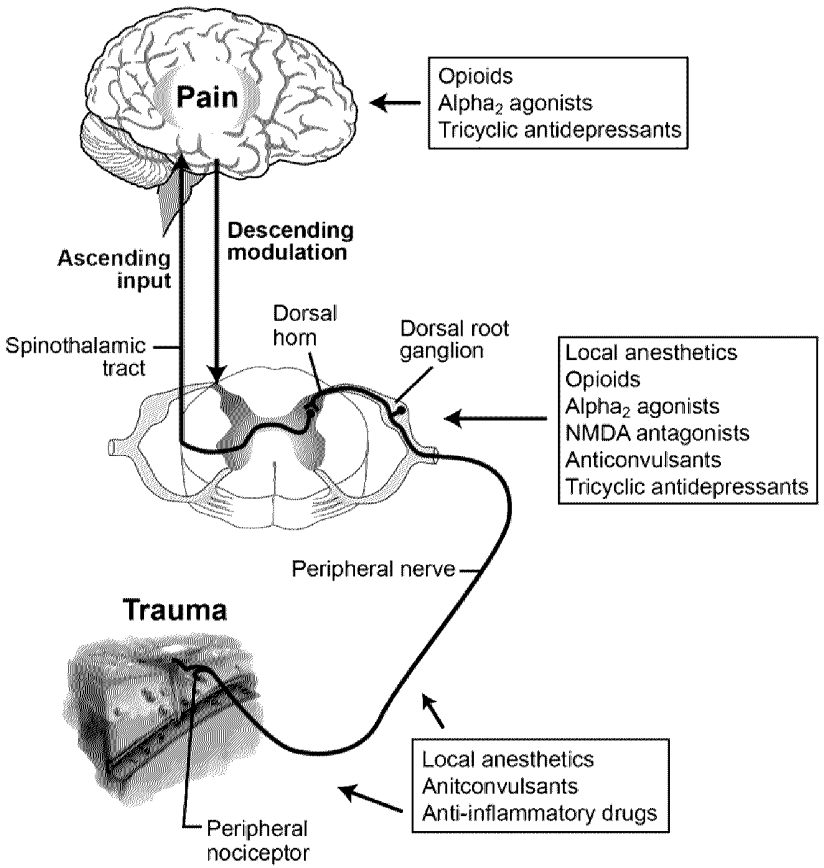
Boxed warning and ISI

- Revised boxed warning and ISI to be inserted in place of existing information
  - ISI will be revised to decrease word count after 03-Aug-2012 PRC review

WHO Guidelines

- Retain: WHO 3-step analgesic ladder

New: Multimodal management



Sherwood ER, Williams CG, Prough DS. Anethesiology principles, pain management, and conscious sedation. In: Townsend CM, Beauchamp RD, Evers BM, et al (eds). Townsend: Sabiston Textbook of Surgery, 18th ed. Saunders, Elsevier. 2007:456-463.

- New section to further expand WHO concept of an analgesic ladder
- Place/position for opioids as a valid option in multimodal management of chronic pain when their use is appropriate
  - Pain management pathway
  - mu receptor
- Things to consider for patients with moderate to severe pain
  - Patient background
  - Concomitant medications
  - Is the use of an opioid analgesic appropriate?

Indication and Usage

Old USPI (Feb 2010)

KADIAN□ Capsules are an extended-release oral formulation of morphine sulfate 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 (see CLINICAL PHARMACOLOGY).

KADIAN® Capsules are NOT intended for use as a prn analgesic.

KADIAN® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN□ is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

New USPI (Jul 2012)

KADIAN is 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:

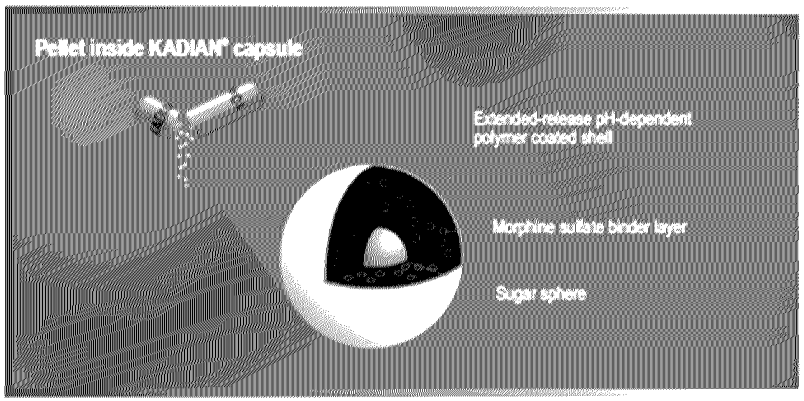
- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe 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.

Dosing flexibility

- KADIAN offers the lowest solid oral dose morphine/MED as per APS guidelines
  - APS guidelines (http://www.jpain.org/article/S1526-5900(08)00831-6/fulltext): "*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 effects.*"
- Dosing flexibility with 12 doses starting from 10 mg to 200 mg
  - Flexible titration and tapering as required for patient management
  - Permits dose modulation in 10 mg increments (up/down) with use of either a single capsule or two capsules
- BID or QD dosing as per patient management requirements
  - Pellet technology and bioavailability supports both
- Capsule ingestion or sprinkling or G-tube (link to Methods of Administration)

Reliable Morphine Delivery



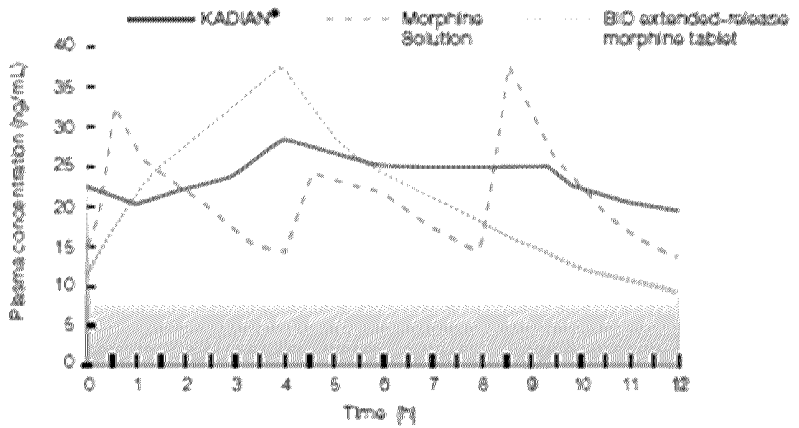
Pellet and capsule are not shown at actual size

Current Detail Aid lists

- Distinctive pellet composition
- Absorption
  - Food effects
  - Steady state

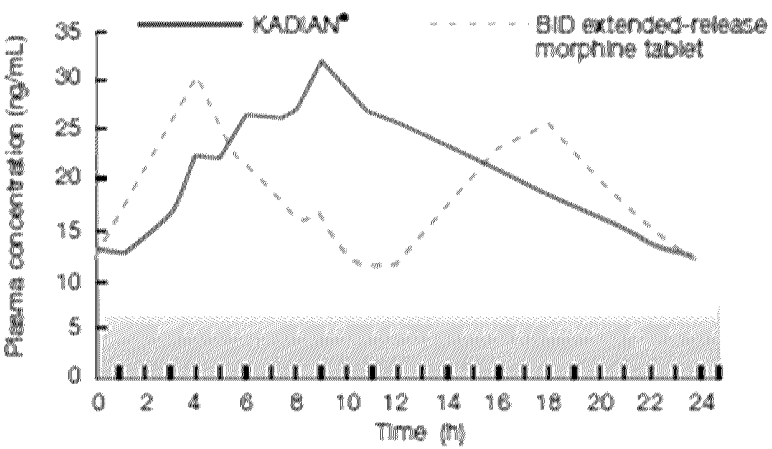
- There is additional information on the two separate pH-dependent coatings
  - PEG coating permits initial release of morphine in gastric space
  - Enteric-coating permits subsequent release in duodenal space
- Tie into absorption?
  - NDA Volume 1.26 Summary of Human PK and Bioavailability suggests that KADIAN's pellet composition is responsible for the slower and more consistent release of morphine

Steady state plasma levels



1. Mean steady state plasma level

Mean steady state plasma morphine concentrations for KADIAN® (twice a day), extended-release morphine tablet (twice a day) and oral morphine solution (every 4 hours); plasma concentrations are normalized to 100 mg every 24 hours, (n=24).

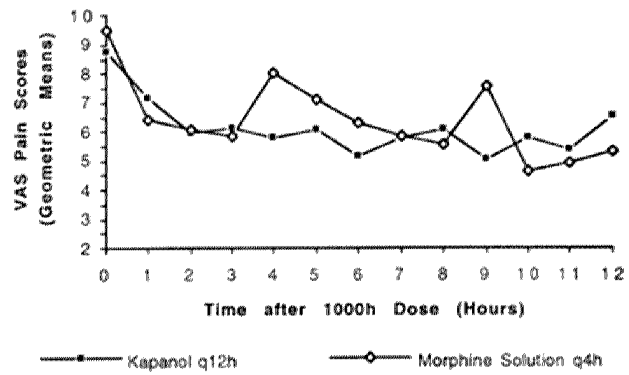


2. Dose-normalized steady state plasma level

Dose normalized mean steady state plasma morphine concentrations for KADIAN® (once a day), and an equivalent dose of a 12-hour, extended-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours, (n=24).

Clinical efficacy – BID dosing

FIGURE 4. Steady-State VAS Pain Scores on Day 7 of Treatment (Study MOBES-8/90)

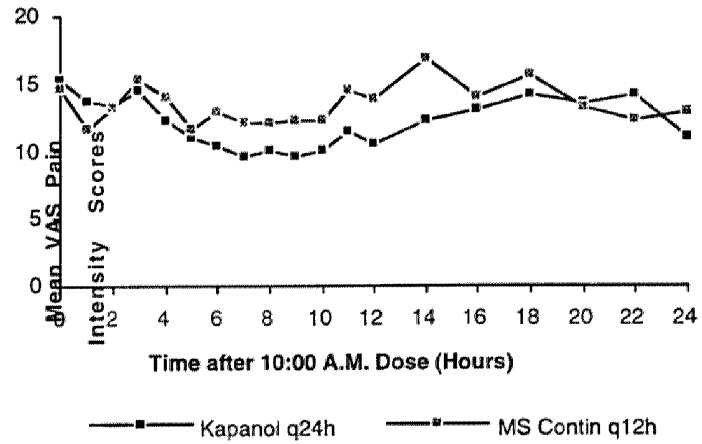


Study MOBES-8/90
Steady-state VAS pain score on Day 7 of treatment; comparison of KADIAN BID to IRM solution q4h

KADIAN steady state plasma levels translate to effective pain management under BID dosing

- VAS pain scores fall steadily in the two hours following administration of KADIAN, then plateau for 9 to 10 hours
- VAS score presented as geometric means

Clinical efficacy – QD dosing



Study MOR 9/92
Comparison of VAS scores for pain intensity for KADIAN q24h and MS-Contin q12h

KADIAN steady state plasma levels translate to effective pain management under QD dosing

- Pain intensity begins to lessen within 3-4 hours and remains low until 16-18 hours post-dose
- VAS scale runs 0 to 100; pain intensity is held to a very low level

Clinical efficacy – pivotal trial 1

Study CDD-14556 (US, n=172)

- This non-inferiority study comparing KADIAN QD and BID to demonstrated:
  - Time to remedication (study med or rescue) were generally longer for KADIAN QD and BID than for MS-Contin
    - 16.0h for KADIAN QD, 9.1h for KADIAN BID vs 8.7h for MS-Contin
  - % morphine dose trended lower for KADIAN QD and BID than for MS-Contin
    - 17.3 for KADIAN QD, 14.9 for KADIAN BID vs 23.1 for MS-Contin
  - VAS and VRS for pain intensity consistently lower for KADIAN than for MS-Contin
  - Patient global assessment
    - KADIAN QD **statistically** greater (89%) than MS-Contin (68%)
    - KADIAN BID (76%) generally higher than MS-Contin
  - Investigator global assessment generally greater with KADIAN (94 and 87% for QD, BID) than MS-Contin (85%)

Clinical efficacy – pivotal trial 2

Study MOR-9/92 (AU, n=29)

- Generally, fewer patients needed rescue when on KADIAN (42%) than MS-Contin (54%)
- Time to remedication (study med or rescue) were generally longer for KADIAN QD than for MS-Contin (16.8h for KADIAN vs 8.7h for MS-Contin)
- % morphine dose trended lower for KADIAN QD and BID than for MS-Contin (4.4 for KADIAN vs 4.9 for MS-Contin)
- VAS pain intensity consistently lower for KADIAN than for MS-Contin over 24h period
- Patient global assessment lower with KADIAN QD (67%) than MS-Contin (85%)
- Investigator global assessment lower with KADIAN (87%) than MS-Contin (91%)

New section - safety

- Safety information actually missing from detail aid
- Safety information briefly mentioned as a bullet in old ISI in dosing guide
- Metabolism section from USPI is not used at all

Safety - AEs

Clinical trial patients with chronic cancer pain (n=227) (AE by Body System as seen in 2% or more of patients)	Percentage %
CENTRAL NERVOUS SYSTEM	**28**
Drowsiness	9
Dizziness	6
Anxiety	5
Confusion	4
Dry Mouth	3
Tremor	2
GASTROINTESTINAL	**26**
Constipation	9
Nausea	7
Diarrhea	3
Anorexia	3
Abdominal pain	3
Vomiting	2
BODY AS A WHOLE	**16**
Pain	3
Disease progression	3
Chest pain	2
Diaphoresis	2
Fever	2
Asthenia	2
Accidental Injury	2
RESPIRATORY	**3**
Dyspnea	3
SKIN & APPENDAGES	**3**
Rash	3
METABOLIC & NUTRITIONAL	**3**
Peripheral edema	3
HEMIC & LYMPHATIC	**4**
Anemia	2
Leukopenia	2

- Add version of AE table from Jul2012 USPI
- Add text:
  - In clinical trials in patients with chronic cancer pain, the most common (≥ 5% of patients) adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (5%).
  - 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.

Safety – Cytochrome p450

- Major pathways of morphine metabolism in the liver include glucuronidation (up to 65% of metabolites), sulfation (up to 30% of metabolites), and demethylaion (less than 5% of metabolites) of morphine is demethylated. (ref. USPI page 9)

- The cytochrome p450 pathway is not involved in hepatic metabolism of the morphine contained within KADIAN. (ref. Smith 2009; Mayo Clinic Proceedings)

Safety – drug-drug interactions

- The following drug-drug interactions are listed in the USPI and the ISI

- Opioids including KADIAN potentially demonstrate the following drug-drug interactions. Patients using these medications concomitantly should be closely monitored:
  - Concomitant use of alcohol with KADIAN® can result in increased plasma levels of morphine and result in a potentially fatal overdose of morphine.
  - Additive effects may be expected when KADIAN® is used concurrently 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 butorphanol) may reduce the analgesic effect of KADIAN® or may precipitate withdrawal symptoms.
  - Opioids may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.
  - Monoamine Oxidase Inhibitors may potentiate the effects of morphine.
  - There is an isolated report of confusion and severe respiratory depression in a hemodialysis patient who was concurrently administered morphine and cimetidine.
  - Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
  - Anticholinergics used concurrently with opioid analgesics may result in urinary retention and/or severe constipation.
  - P-Glycoprotein (PGP) inhibitors may increase the absorption/exposure of morphine by two fold.

Methods of Administration

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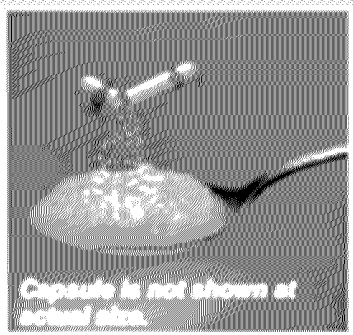
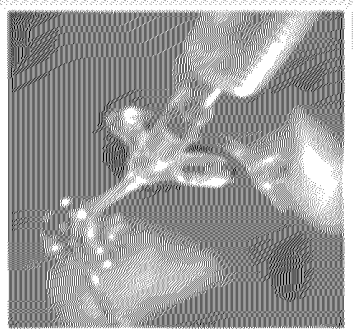
As a capsule	Sprinkle dosing	G-tube dosing
		
Capsule can be swallowed whole.	*Capsule can be opened and the contents sprinkled on apple sauce for patients who have difficulty swallowing.**	*Contents of capsule can be sprinkled in water and administered through a 16 French or larger gastrostomy tube.***

*Apple sauce should be room temperature and used immediately.
**The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

Safety considerations:
KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Cessation of Therapy:
When the patient no longer requires therapy with KADIAN® capsules, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Actavis commitment (new)

- Actavis is committed to supporting appropriate opioid use
  - Actavis is a sponsor for the web site, Painedu.org that provides comprehensive online educational resources for clinicians who are engaged in, or want to learn more about pain assessment, treatment, and a management. We sponsor the site to support educational content for the Kadian Riskmap program.
  - REMS site http://www.er-la-opioidrems.com/IwgUI/rems/home.action

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

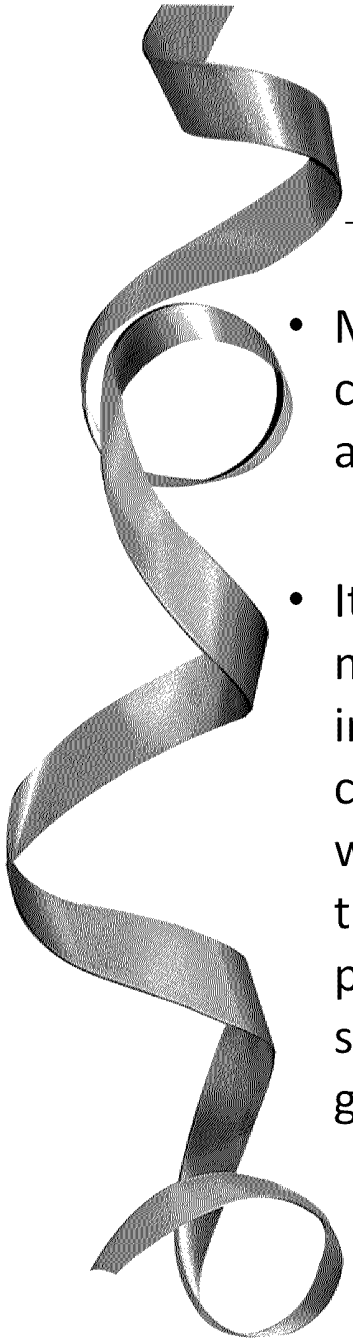
KADIAN®
Detail Pieces

ABM Comments

August 2012

Co-Pay Card & Brochure

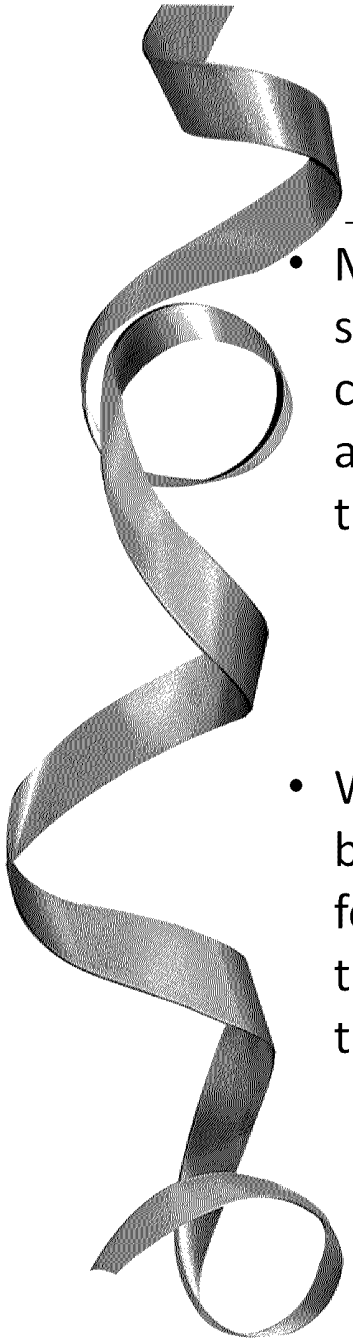
KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg



- Make the co-pay cards a one pager with a strong backing and a card attached by glue to that backing……you will fit more in a pack and we will not need to give as many away packs
  - Issue: ISI does not allow for a one-pager format
- It seems that some of our competition has made co-pay cards more attractive from a cost perspective. Knowing that the cost of insurance/medications have increased for patients (this will only continue to get worse), increasing our amount to $75.00-$100 would be great. This increase may also help us when promoting the new branding strengths. Some docs will continue to give a patient two 20mgs instead of the 40mg bc of cost. We will run into some customers that will not be pleased that the strengths are not generic, so using this marketing tactic could be helpful.
  - Will a higher co-pay card amount truly result in additional Kadian Rxs? Conversely, could we run an analysis to see how much raising the co-pay coverage would cost us?

Co-Pay Card & Brochure

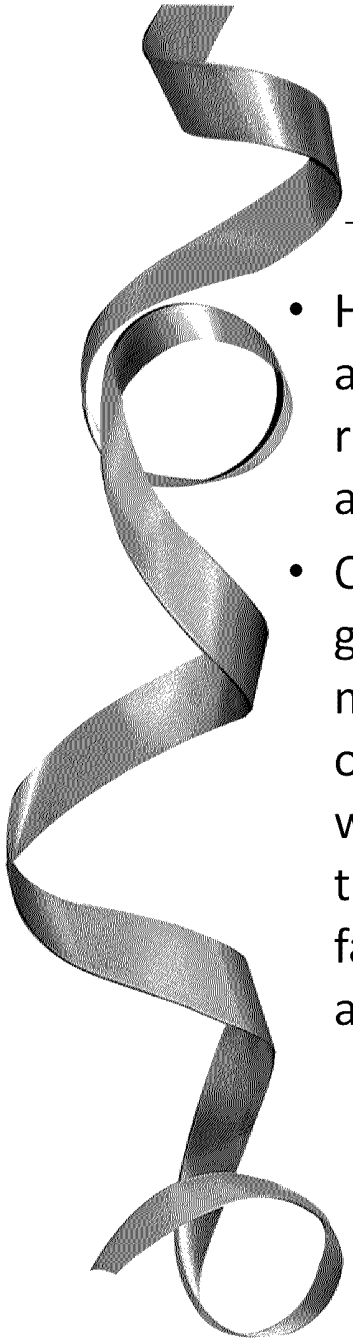
KADIAN® Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg



- My only suggestion would be to go back to the co-pay card that says “$50 off”, as it gave a clear, concise message. With the newer co-pay card that reads “$1200 off (per year)”, offices are confused about the breakdown per month. By the time the patient receives the co-pay card, the $50 off per Rx is lost.
  - This seems to conflict with the general consensus, but perhaps we could include a subhead that clarifies the monthly savings of up to $50/month.
- We need to print on the co-pay cards that they can be used for both the brand and generic Actavis Kadian products. Physicians forget to tell the patients, the patients don’t tell the pharmacist that it works for the generic, or the pharmacist tells the patient the card does not work for the generic.
  - Initially when we wanted to do this, Legal and Regulatory said we would need to include separate ISIs for both the brand and generic, as well as attach both PIs. This was deemed not to be worthwhile at the time but perhaps we could brainstorm/revisit the issue

Dosing Guide

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg



- Have available just a small dosing card with the doses in full color and nothing else and glue a pi to it……Drs. love to have a quick reference of available doses and maybe differentiate what is available for branded vs. generic
- One suggestion I have is that we implement a “pocket guide”. Remember these from way back. Because we have so many dosing strengths with new ones coming out, having them all on one small piece that would show mg and color of each capsule would help prescribers. Prescribers don’t ask why to use Kadian they usually say “Oh I forgot you also had that strength”. And let’s face it they have to get use to the new doses. Maybe having it on a flexible material would help.
  - Same issue: ISI makes a “small dosing card” difficult. Perhaps we could do more to highlight the capsules on the back of the dosing & conversion guides. Not sure that highlighting the generic availability will help sell the new strengths

Dosing Guide

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

- I mainly use the page that shows the different strengths. Customers have asked in the past for that page alone to post on the wall bc they forget the strengths. It may be wise to have a one page handout with the strengths and positive insurance coverage/states with Preferred Medicaid. I believe this would be used more often than most things we have now.
  - Perhaps reprint the preferred Medicaid stickers to add to the new tactics
- I find myself using the dosing guide a lot, especially in stand up situations. I like to use the back page highlighting various dosing strengths and asking the doctor to tell me how they dose. I like the fact that it is a smaller piece and not cumbersome.

Retail Pharmacy

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

- A piece we could give to retail pharmacies would help. Again with all the strengths and the fact that we have a rebate. Retail pharmacies have so many part-time pharmacists they just don't always seem to know what is the most up to date information. When we go in with nothing to leave behind only the person behind the counter at that time gets the updated info from us. I'm sure with these pharmacies so busy they don't usually pass anything along.
- I also think adding a pharmacy sell sheet with NDC numbers for generic and brand would be very helpful.
  - We will create a pharmacy sell sheet for launch

Detail Aid

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

- When using the core vis aid I mostly speak off of pages 6, 7 highlighting Kadian's PK profile and dosing flexibility. It perhaps would be nice if the safety information pages could be moved to the back and these two pages be moved closer to the front. It too may be nice to have on the intro page some type of visual that speaks to the type of patient that could benefit from Kadian
  - ISI needs to remain upfront; however, we could consider moving the PK profile and dosing (especially with the new strength info) up front.
  - We haven't been successful with including patient profiles in the past…could we revisit?

Tactical List

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

- Detail aid
- Dosing guide
- Conversion guide
- Co-Pay card/brochure/easel
- Pharmacy flyer (with NDC numbers) – pharmacy audience
- Pharmacy flyer (with chains carrying new strengths) – physician audience
- PharmAlert?
- Website update
- Cardinal promotional tactic