PURDUE

Purdue Pharma L.P.
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Fax (203) 588 8850
www.purduepharma.com

June 24, 2002

Via Federal Express

SUBMITTED IN DUPLICATE

GENERAL CORRESPONDENCE:
REQUEST FOR COMMENT

Spencer Salis, Pharm. D.
Division of Drug Marketing, Advertising,
and Communications
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-042, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: Competitor's Promotional Advertising

Dear Dr. Salis:

This letter is to request advice on the policy for the Division of Drug Marketing, Advertising, and Communications regarding the use of boxed warnings in promotional labeling. In the promotional labeling for Purdue Pharma LP (PPLP) products having boxed warnings (which were submitted to your Division for comment prior to dissemination), we understood that DDMAC required the boxed warnings to be prominently featured in the text of the promotion. As it relates to prominence, we also understood that this meant exactly as it appears in the package insert, within a prominent boxed border and entitled "WARNING".

Enclosed is a new visual aid, promoting the product Avinza® Capsules, that presents the warning without the box and without the title "WARNING". In addition the piece does not refer to it as a boxed warning. Since this product was just approved by FDA, we would expect that this piece was submitted to DDMAC in draft form prior to dissemination for comment. If so, this warning may have been allowed without the prominence features that were required in PPLP's labeling supplements.

The second enclosure is a direct-to-consumer promotion for the Duragesic® Patch which Janssen pays pharmacists to enclose prescriptions filled for OxyContin® Tablets and other oral opioid products. Again the boxed warning is featured in this space without the border.

In addition the first two paragraphs refer to media reporting of abuse of painkillers. Since the piece is enclosed with prescriptions for oral opioids, this risk concern certainly refers to the patient's prescribed product. The inference plainly intended is that abuse is not associated with Duragesic® Patches, so the patient has a reason to switch medications. This appears to contradict the Drug Abuse and Diversion section of the Duragesic® package insert, and the many reports of abuse of fentanyl patches.

Please advise us whether it is the policy of DDMAC to require the use of the boxed border and the caption of "WARNING" as it appears in the package insert, as part of the prominence of such a warning in promotional labeling.

I will be in touch with you to discuss your response to our question. In the meantime, if you have any questions or require additional information, please contact me at the numbers listed below.

Sincerely,

J. Christopher Prue, R.Ph.
Senior Director, U.S. Regulatory Affairs
Telephone: (203) 588-7558
Facsimile: (203) 588-6229

CP:jmm
enclosure

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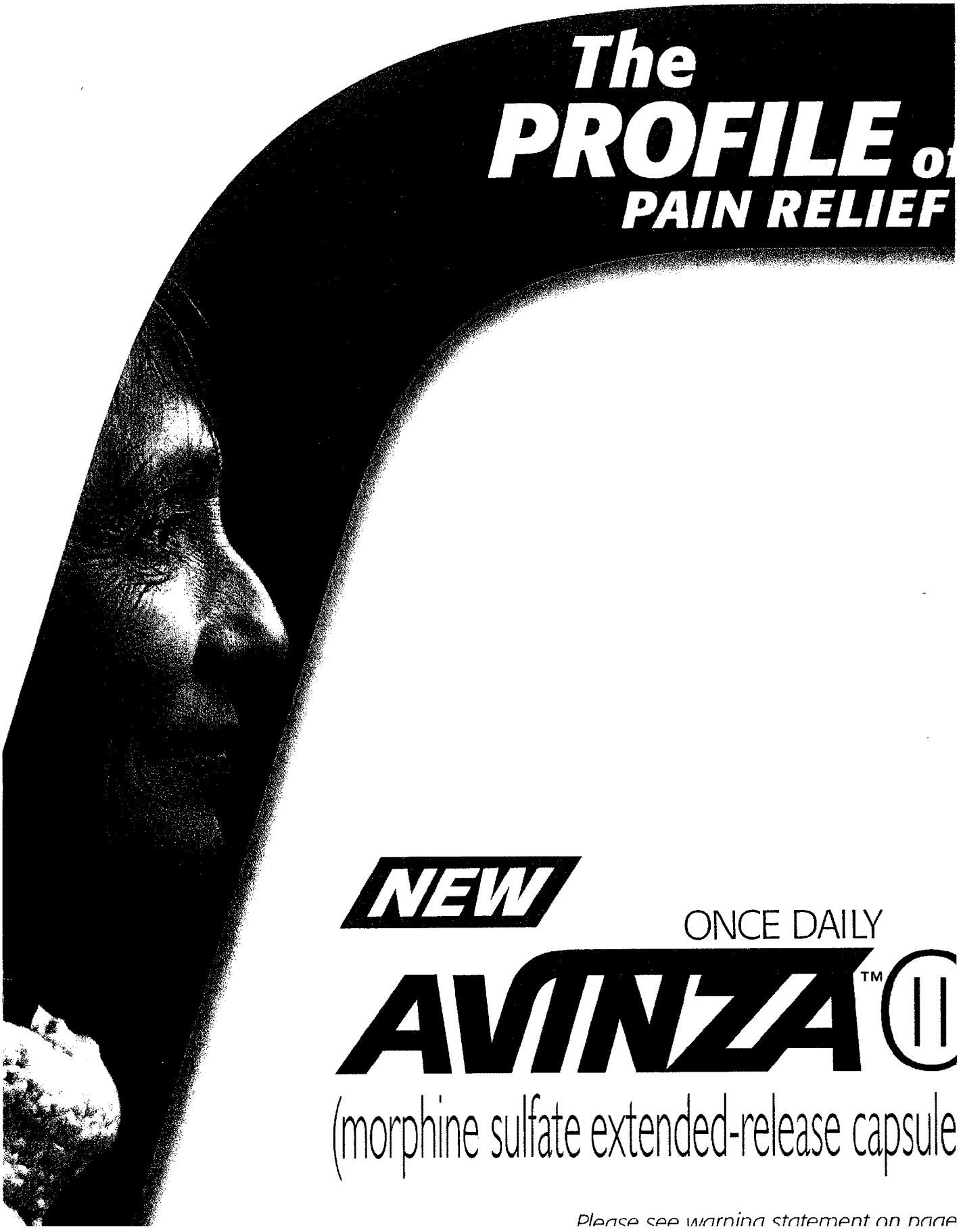
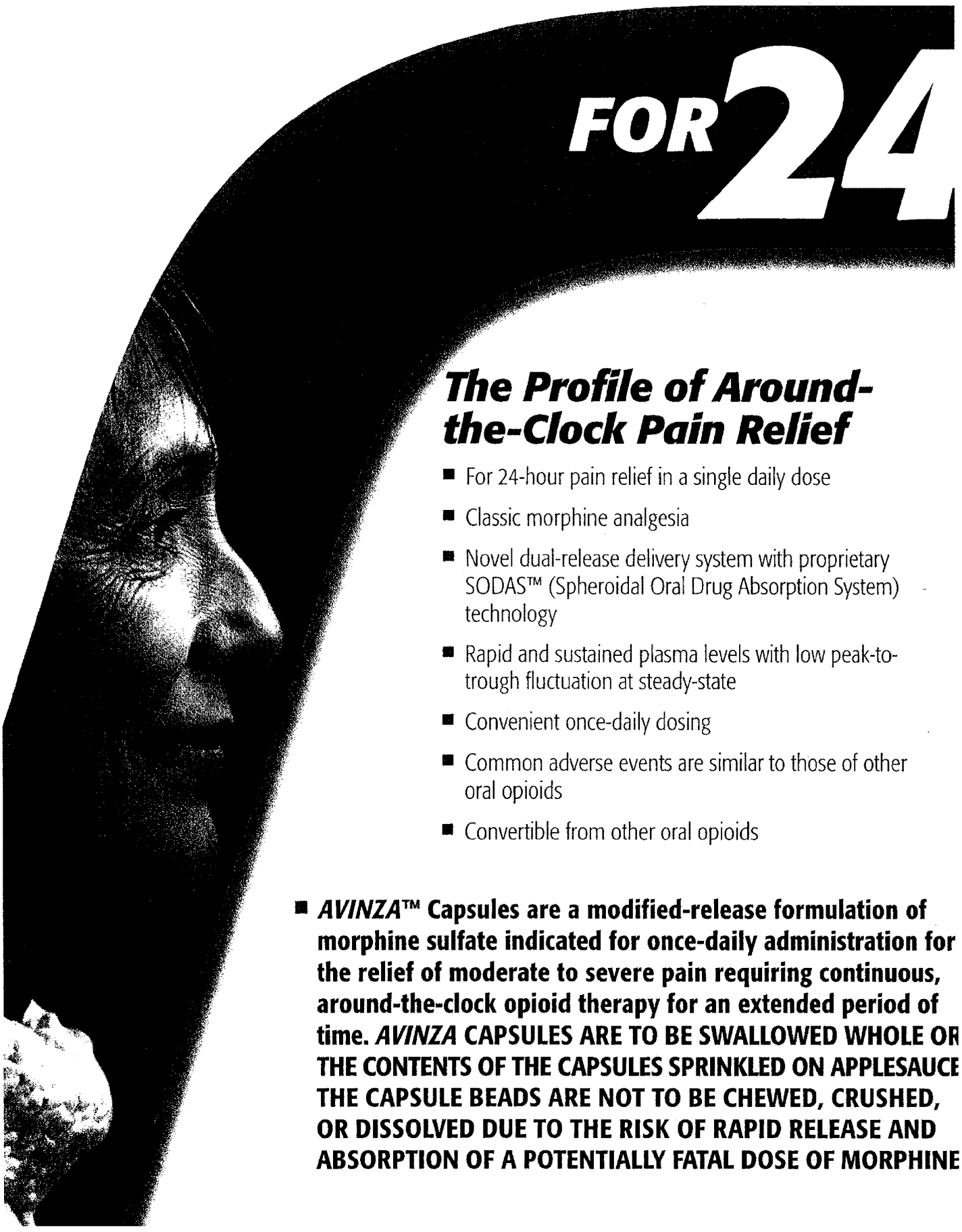




FOR 24

The Profile of Around-the-Clock Pain Relief

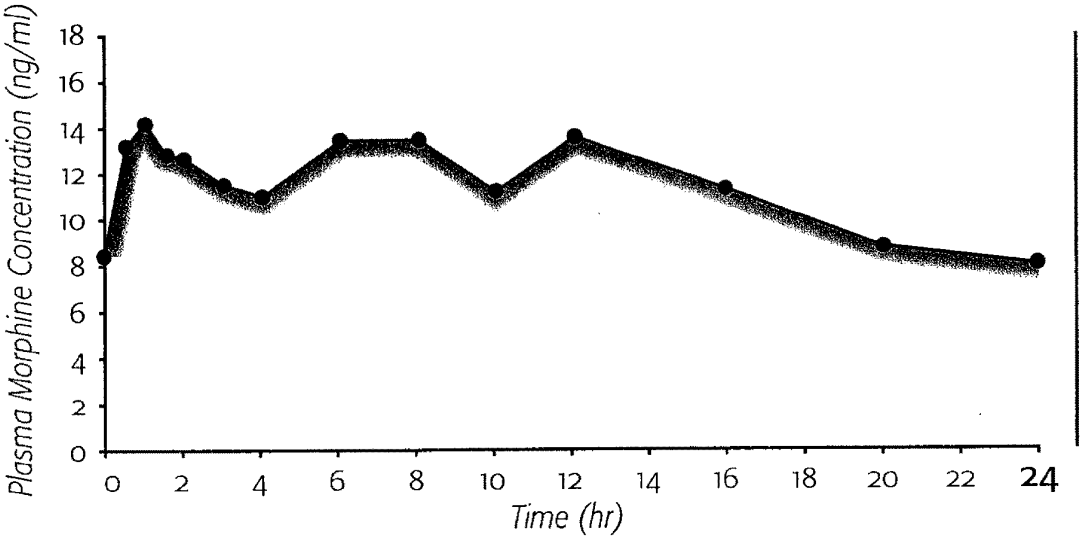
- For 24-hour pain relief in a single daily dose
- Classic morphine analgesia
- Novel dual-release delivery system with proprietary SODAS™ (Spheroidal Oral Drug Absorption System) technology
- Rapid and sustained plasma levels with low peak-to-trough fluctuation at steady-state
- Convenient once-daily dosing
- Common adverse events are similar to those of other oral opioids
- Convertible from other oral opioids

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

-HOUR PAIN RELIEF

in a single daily dos

Once-Daily Pharmacokinetic Profile*



Steady-state plasma concentration following repeated once-daily dosing of 60 mg AVINZ

*Efficacy may not necessarily be inferred from pharmacokinetic profiles.

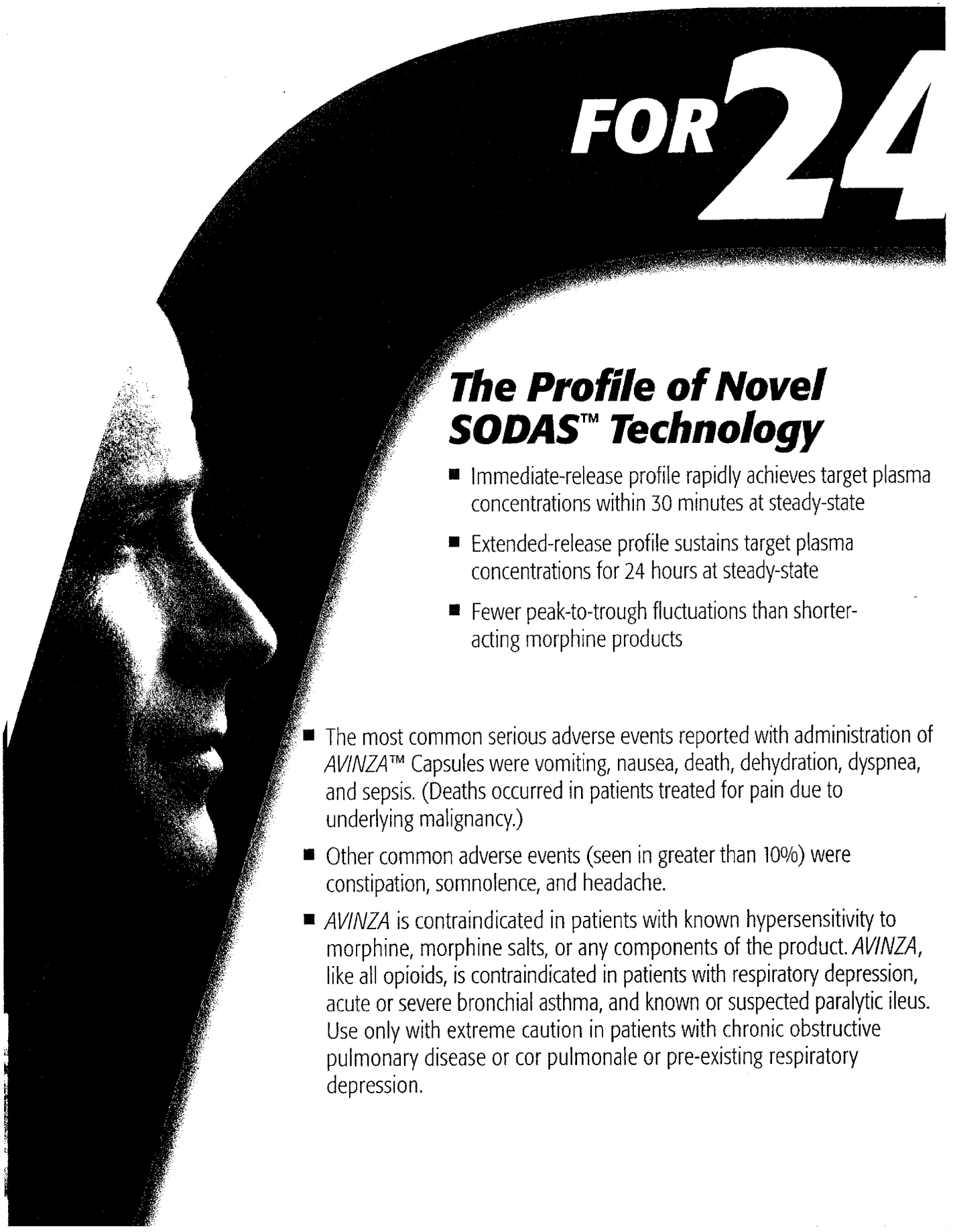
NEW

ONCE DAILY

AVINZA™ (II)

(morphine sulfate extended-release capsule

PDD8013015142



The Profile of Novel SODAS™ Technology

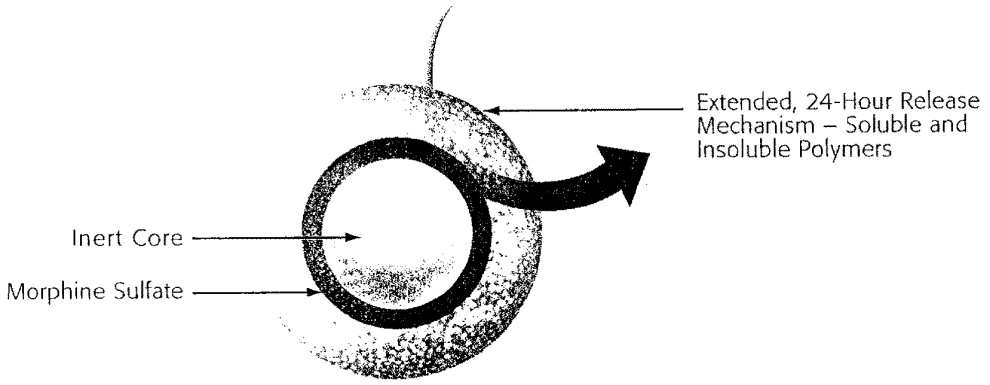
- Immediate-release profile rapidly achieves target plasma concentrations within 30 minutes at steady-state
- Extended-release profile sustains target plasma concentrations for 24 hours at steady-state
- Fewer peak-to-trough fluctuations than shorter-acting morphine products

- The most common serious adverse events reported with administration of *AVINZA*™ Capsules were vomiting, nausea, death, dehydration, dyspnea, and sepsis. (Deaths occurred in patients treated for pain due to underlying malignancy.)
- Other common adverse events (seen in greater than 10%) were constipation, somnolence, and headache.
- *AVINZA* is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. *AVINZA*, like all opioids, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, and known or suspected paralytic ileus. Use only with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale or pre-existing respiratory depression.

-HOUR PAIN RELIEF

in a single daily dos

How SODAS™ Technology Works



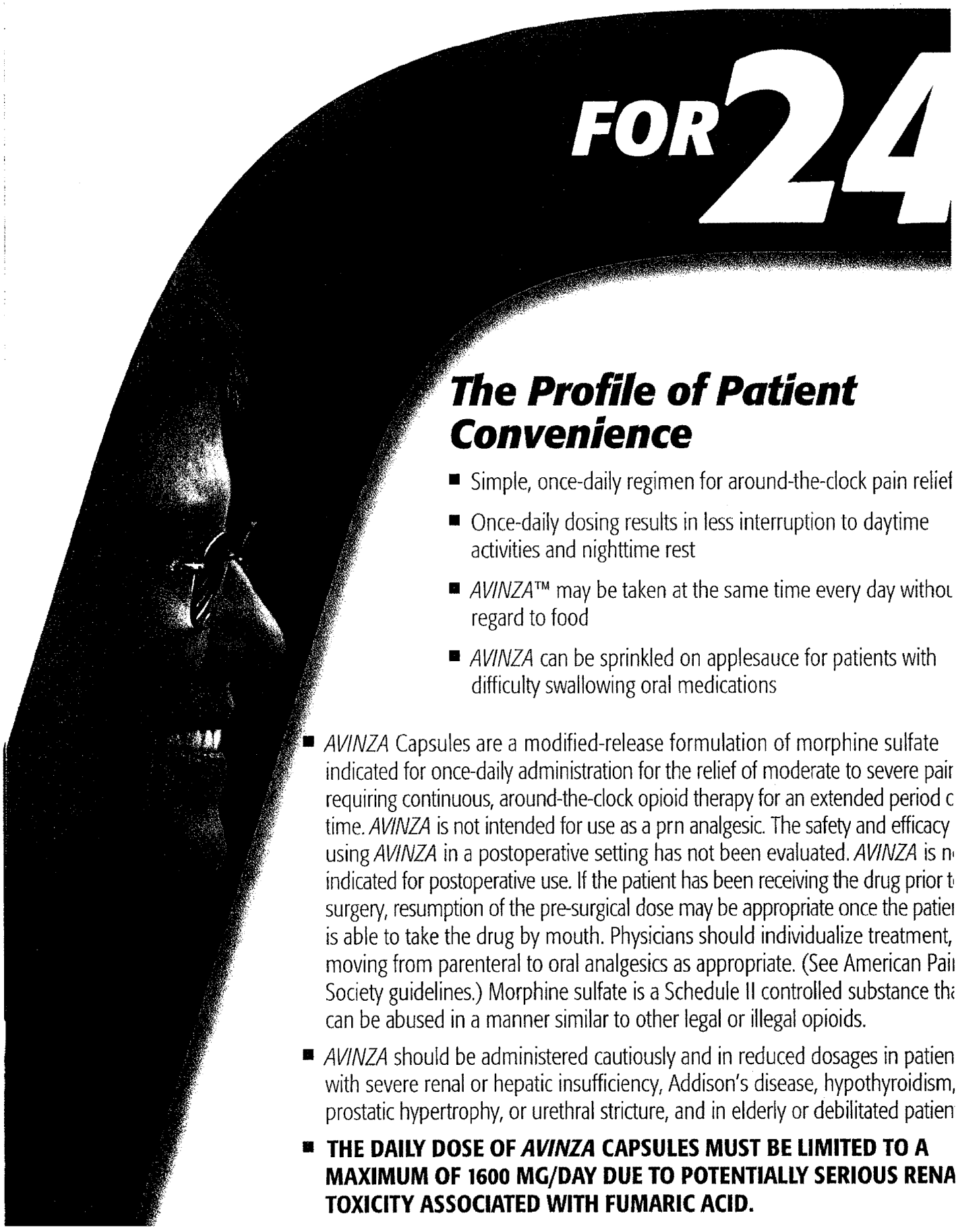
- After administration, the capsule releases the bead contents. GI fluid is drawn into the core of the SODAS™ beads, dissolving the morphine sulfate layer and causing the polymer layer to swell.
- Swelling of the polymers creates pores that allow release of the dissolved morphine in a rate-controlled manner.

NEW

ONCE DAILY

AVINZA™ (II)

(morphine sulfate extended-release capsules)



The Profile of Patient Convenience

- Simple, once-daily regimen for around-the-clock pain relief
- Once-daily dosing results in less interruption to daytime activities and nighttime rest
- *AVINZA*™ may be taken at the same time every day without regard to food
- *AVINZA* can be sprinkled on applesauce for patients with difficulty swallowing oral medications

- *AVINZA* Capsules are a modified-release formulation of morphine sulfate indicated for once-daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. *AVINZA* is not intended for use as a prn analgesic. The safety and efficacy of using *AVINZA* in a postoperative setting has not been evaluated. *AVINZA* is not indicated for postoperative use. If the patient has been receiving the drug prior to surgery, resumption of the pre-surgical dose may be appropriate once the patient is able to take the drug by mouth. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.) Morphine sulfate is a Schedule II controlled substance that can be abused in a manner similar to other legal or illegal opioids.
- *AVINZA* should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients
- **THE DAILY DOSE OF *AVINZA* CAPSULES MUST BE LIMITED TO A MAXIMUM OF 1600 MG/DAY DUE TO POTENTIALLY SERIOUS RENAL TOXICITY ASSOCIATED WITH FUMARIC ACID.**

-HOUR PAIN RELIEF
in a single daily dos

Equianalgesic Table (Based on Total Daily Cumulative Dose)

In converting from other parenteral or oral non-morphine opioids to oral morphine sulfate, 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. In the event that breakthrough pain occurs, *AVINZA* may be supplemented with a small dose (5–15% of the total daily dose of morphine) of a short-acting analgesic.

ORAL MORPHINE	ORAL OXYCODONE	ORAL HYDROMORPHONE	ORAL HYDROCODONE	FENTANYL TRANSDERMAL SYSTEM
30 mg	20 mg	7.5 mg	20 mg	–
60 mg	40 mg	15 mg	40 mg	25 mcg/hr
90 mg	60 mg	22.5 mg	60 mg	25 mcg/hr or 50 mcg/hr
120 mg	80 mg	30 mg	80 mg	25 mcg/hr or 50 mcg/hr
150 mg	100 mg	37.5 mg	100 mg	50 mcg/hr or 75 mcg/hr
180 mg	120 mg	45 mg	120 mg	50 mcg/hr or 75 mcg/hr
210 mg	140 mg	52.5 mg	140 mg	50 mcg/hr or 75 mcg/hr
240 mg	160 mg	60 mg	160 mg	75 mcg/hr
270 mg	180 mg	67.5 mg	180 mg	75 mcg/hr
300 mg	200 mg	75 mg	200 mg	75 mcg/hr or 100 mcg/hr

This table provides you with the current equianalgesic dosing for various opioids and is not intended to replace a prescriber's judgment. No specific product or formulation is referenced in the above table. It is better to underestimate a patient's 24-hour opioid dose and make available rescue medication than to overestimate the 24-hour opioid dose and manage an adverse experience or overdose. Please consult respective package inserts for dosing instructions.

References for the above section include: American Pain Society, Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th edition, 1999, pages 14-15. Derby S, Chin J, Portenoy R. Systemic opioid therapy for chronic cancer pain: Practical guidelines for converting drugs and routes of administration. CNS Drugs 1998;9(2):99-109. Brant JM. Opioid equianalgesic conversion: the right dose. Clin J Oncol Nurs 2001;5(4):163-165. Duragesic® Package Insert.

NEW

ONCE DAILY

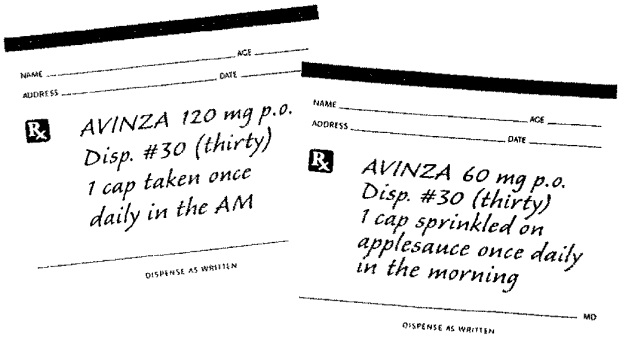
AVINZA™ (II)

(morphine sulfate extended-release capsules)

FOR 24-HOUR PAIN RELIEF
in a single daily dose

The Profile of Around-the-Clock Pain Relief

- For 24-hour pain relief in a single daily dose
- Classic morphine analgesia
- Novel dual-release delivery system with proprietary SODAS™ technology
- Rapid and sustained plasma levels with low peak-to-trough fluctuation at steady-state
- Convenient once-daily dosing
- Common adverse events are similar to those of other opioids
- Convertible from other oral opioids



For convenience and dosage flexibility, AVINZA™ Capsules are supplied in 30 mg, 60 mg, 90 mg, and 120 mg color-coded capsules. The 60 mg, 90 mg, and 120 mg capsules are for use in opioid-tolerant patients only. When the patient no longer require therapy with AVINZA capsules, doses should be tapered graduall to prevent signs and symptoms of withdrawal in the physically dependent patient.

30 mg 60 mg 90 mg 120 mg

Capsules are shown at actual size.

At Ligand® Pharmaceuticals, we are committed to the responsible use of analgesics for pain control and recognize the responsibility inherent in the marketing of opioids to the medical community. That's why we are fully committed to providing communications that include statements of fair balance and appropriate disclosure of the risks and benefits of opioid use in the professional management of chronic moderate to severe pain.

Please see attached full prescribing information including warning statement.

For more information, please contact your Ligand Pharmaceuticals Sales Representative or call Professional Services at 1-800-964-5836.

LIGAND®
PHARMACEUTICALS

Ligand Pharmaceuticals Inc. ■ 10275 Science Center Drive ■ San Diego, CA 92121

www.ligand.com

NEW ONCE DAILY

AVINZA™

(morphine sulfate extended release capsul

18
HA

0391469 0101 1 0000899 2

[redacted]
SOUTH BEND, IN 46628
04/11/75 PH (574)243-5973
NEW

$8.99
04/02/02
BRA

E PROMISED TIME
TUE 12:44PM
04/02/02

HERE

- Drug & Usage Information
- Duplicate Receipts
- Expiration Dates
- Health Tips

Caring For You

Personalized Patient Prescription Information

Walgreens
The Pharmacy America Trusts
www.walgreens.com

Valued Customer

Inside this edition of your Newsletter

- Find Information About Pain Control
- Sponsored by Janssen

Walgreens The Pharmacy America Trusts **Your Personal Prescription Information**

PATIENT [redacted]
MEDICATION OXYCONTIN 10MG TABLETS
QUANTITY 1
DIRECTIONS TAKE AS DIRECTED

NDC 5901
WHITE
Side 1: oc
Side 2: 10

INGREDIENT NAME:
OXYCODONE (ox-i-KOE-done)

COMMON USES:
This medicine is a narcotic analgesic used to treat or prever
treat other conditions as determined by your doctor.

HOW TO USE THIS MEDICINE:
Follow the directions for using this medicine provided by yo
chew before swallowing. STORE THIS MEDICINE at room t
OF THIS MEDICINE and you are using it regularly, take it as
dose, skip the missed dose and go back to your regular dos

CAUTIONS:
IF YOU HAVE HAD A SEVERE ALLERGIC REACTION to cod
as Tylox, Tylenol with Codeine, Vicodin), contact your doct
severe allergic reaction includes a severe rash, hives, breath
about whether you are allergic to this medicine or if a certai
or oxycodone, contact your doctor or pharmacist. DO NOT
recommended by your doctor. Exceeding the recommended
habit-forming. BEFORE YOU HAVE ANY MEDICAL OR DEN
or dentist that you are taking this medicine. AVOID ALCOH
to the effects of alcohol and other depressants. DO NOT DI
COULD BE DANGEROUS until you know how you react to t
or with alcohol may lessen your ability to drive or to perfor
TAKING ANY NEW MEDICINE, either prescription or over-th
WOMEN: IF YOU PLAN ON BECOMING PREGNANT, discus
during pregnancy. THIS MEDICINE IS EXCRETED IN BREAS
while you are using this medicine, check with your doctor c

POSSIBLE SIDE EFFECTS:
SIDE EFFECTS, that may go away during treatment, includ
vomiting, headache, or constipation. If they continue or are
DOCTOR AS SOON AS POSSIBLE if you experience exces
or difficulty breathing. If you notice other effects not listed

For faster service, phone in your refill request 2

KEEP OUT OF REACH OF CHILDREN

Our Focus Is Pharmacy. Our Focus Is You.

Your Walgreens Pharmacist...

Your Partner in Health Care.

You have a right to relief from chronic pain

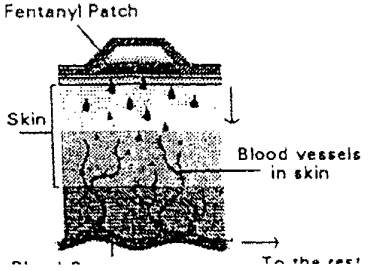
As you may have noticed, there have been many reports in the local and national news media about abuse of prescription painkillers. *Newsweek* and other national magazines have run stories on the problem. Your local paper or TV news may have featured reports on the subject as well.

Because of this increased attention, you may have questions about your chronic pain therapy. Are you using the right medication? Are you taking the right dose? Of course, your doctor considers these issues whenever he or she writes a prescription. You should always follow the instructions your doctor provides.

But also keep in mind that it's relatively rare for patients to become addicted to painkillers when used appropriately. Most abusers of these drugs are not patients, but instead people who obtain the pills without a prescription. Although addiction can be a concern with some painkillers, you have the right to appropriate pain relief.

There is an alternative to pills for treating moderate-to-severe chronic pain. It's called DURAGESIC. Like other long-acting therapies, DURAGESIC can help relieve chronic pain and reduce the number of pills you take for your pain. What makes DURAGESIC unique is that it's a patch, not a pill, and provides relief that lasts up to 3 days! This is different from pills that have to be taken 2, 4, or 6 times a day.

DURAGESIC is a thin patch with an adhesive on the back that you wear on your skin. DURAGESIC delivers a strong pain-relieving medicine called "fentanyl" through the skin and into the bloodstream. The medicine stays in your system, relieving pain, longer than the pills used to treat chronic pain. DURAGESIC has been used for more than 10 years to treat chronic pain.



You've probably come to associate chronic pain with taking lots of pills. You may also be taking pills for other conditions. DURAGESIC is a patch, not a pill. DURAGESIC can reduce your need to interrupt your day 2, 4, or 6 times to take pain pills. And, with appropriate medical use, addiction to DURAGESIC is relatively rare.

You have a right to a life uninterrupted by chronic pain. So if you want the pain relief you deserve without taking a lot of pills, ask your physician about DURAGESIC!

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC IS CONTRAINDICATED:

- In the management of acute or postoperative pain, including use in outpatient surgeries
- In the management of mild or intermittent pain responsive to p.r.n. or non-opioid therapy
- In dosages exceeding 25 mcg/hr at the initiation of opioid therapy

(See CONTRAINDICATIONS section of full Prescribing Information for further information.)

DURAGESIC SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (SEE PRECAUTIONS—PEDIATRIC USE SECTION OF FULL PRESCRIBING INFORMATION FOR FURTHER INFORMATION.)

DURAGESIC is indicated for treatment of chronic pain (such as that of malignancy) that:

- Cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or p.r.n. dosing with short-acting opioids and
- Requires continuous opioid administration

The 50, 75, and 100 mcg/hr dosages should ONLY be used in patients already on and tolerant to opioid therapy.

For more information speak to your doctor or pharmacist.

For more safety information, please see the full Prescribing Information, including the Boxed Warning.

Duragesic®
FENTANYL TRANSDERMAL SYSTEM