HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TARGINIQ™ ER safely and effectively. See full prescribing information for TARGINIQ ER.

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII
Initial U.S. Approval: 2014

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION
See full prescribing information for complete boxed warning.

- **TARGINIQ™ ER exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow TARGINIQ ER tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2)**
- **Accidental ingestion of TARGINIQ ER, especially in children, can result in a fatal overdose of oxycodone. (5.2)**
- **Prolonged use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from TARGINIQ ER. (5.13)**

----------INDICATIONS AND USAGE----------
TARGINIQ ER is a combination product consisting of oxycodone, an opioid agonist, and naloxone, an opioid antagonist, indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve TARGINIQ ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- TARGINIQ ER is not indicated as an as-needed (prn) analgesic. (1)
- Total daily dose should not exceed 80 mg/40 mg (40 mg/20 mg q12h) because higher doses may be associated with symptoms of opioid withdrawal. (1)

----------DOSAGE AND ADMINISTRATION----------
- For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg/5 mg tablets orally every 12 hours. (2.1)
- Do not abruptly discontinue TARGINIQ ER in a physically dependent patient. (2.5)
- Tablets must be swallowed intact and are not to be cut, broken, chewed, crushed, or dissolved (risk of potentially fatal dose). (2.6, 5.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Extended-release tablets: 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg (3)

----------CONTRAINDICATIONS----------
- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus and GI obstruction (4)
- Known hypersensitivity to oxycodone or naloxone (4)
- Moderate to severe hepatic impairment (4)

----------WARNINGS AND PRECAUTIONS----------
- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effects: Monitor during dose initiation and titration. (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of TARGINIQ ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)
- Symptoms consistent with opioid withdrawal occurred in some patients in the clinical trials. Monitor patients for symptoms of withdrawal during treatment with TARGINIQ ER. (5.11)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.13)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 5%) are nausea and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTION, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with TARGINIQ ER because they may reduce analgesic effect of TARGINIQ ER or precipitate withdrawal symptoms. (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm; may precipitate fetal withdrawal. (8.1)
- Nursing mothers: Discontinue nursing or discontinue drug depending on importance of drug to mother. (8.2)
- Geriatrics: Evaluate elderly patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. (8.5)
- Hepatic impairment: Reduce the starting dose of TARGINIQ ER to 1/3 to 1/2 the usual starting dose in patients with mild hepatic impairment. (8.6)
- Renal impairment: Reduce the initial dose to1/2 the usual dose when administering TARGINIQ ER to patients with renal impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

TARGINIQ™ ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing TARGINIQ ER and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TARGINIQ ER. Monitor for respiratory depression, especially during initiation of TARGINIQ ER or following a dose increase. Instruct patients to swallow TARGINIQ ER tablets whole; crushing, chewing, or dissolving TARGINIQ ER tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of TARGINIQ ER, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of TARGINIQ ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition,

discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving TARGINIQ ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.13) and Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

TARGINIQ ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve TARGINIQ ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- TARGINIQ ER is not indicated as an as-needed (prn) analgesic.
- The maximum total daily dose of TARGINIQ ER should not exceed 80 mg/40 mg (40 mg/20 mg q12h) because higher doses may be associated with symptoms of opioid withdrawal or decreased analgesia *[see Warnings and Precautions 5.11]*.

2 DOSAGE AND ADMINISTRATION

TARGINIQ ER is administered every 12 hours.

2.1 Initial Dosing

TARGINIQ ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

A single dose of TARGINIQ ER greater than 40 mg/20 mg or a total daily dose greater than 80 mg/40 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with TARGINIQ ER *[see Warnings and Precautions (5.2)]*.

Crushing, chewing, or dissolving TARGINIQ ER tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Use of TARGINIQ ER as the First Opioid Analgesic
Initiate treatment with TARGINIQ ER with one 10 mg/5 mg tablet orally every 12 hours.

Use of TARGINIQ ER in Patients who are not Opioid Tolerant
The starting dose for patients who are not opioid tolerant is TARGINIQ ER 10 mg/5 mg orally every 12 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Other Oral Oxycodone Formulations to TARGINIQ ER
Patients receiving other oral oxycodone formulations may be converted to TARGINIQ ER by administering one-half of the patient's total daily oral oxycodone dose as TARGINIQ ER every 12 hours.

Conversion from Other Opioids to TARGINIQ ER
Discontinue all other around-the-clock opioid drugs when TARGINIQ ER therapy is initiated.

When converting patients to TARGINIQ ER, it is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone requirements, which could result in adverse reactions.

In a TARGINIQ ER clinical trial with an open-label titration period, patients were converted from their prior opioid to TARGINIQ ER using both Table 1 and Table 2 below.

Consider the following when using the information in Table 1 and Table 2:

- These are not tables of equianalgesic doses. The conversion factors in Table 1 are only for the conversion from one of the listed oral opioid analgesics to the Equivalent Daily Oral Morphine Dose.
- The conversion factors in Table 2 are only for conversion from the calculated Equivalent Daily Oral Morphine Dose to TARGINIQ ER.
- The tables cannot be used to convert from TARGINIQ ER to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in a fatal overdose.

Convert patients from their previous opioid to TARGINIQ ER as follows:

1. Using Table 1, calculate the Equivalent Daily Oral Morphine Dose by multiplying the current total daily dose of each opioid by the appropriate Conversion Factor.

2. Using Table 2, determine the starting dose of TARGINIQ ER by reading across from the appropriate Equivalent Daily Dose of Oral Morphine range, rounding down, if necessary.

Table 1. Converting the Current Total Daily Oral Opioid Dose(s) to the Equivalent Daily Oral Morphine Dose

Current Oral Opioid	Conversion Factor
Morphine	1
Codeine	0.3
Hydrocodone	1.8
Hydromorphone	8
Methadone†	3
Oxycodone	2
Oxymorphone	4
Tramadol*	-
Tapentadol	0.3
† See note on conversion of methadone to TARGINIQ ER below * patients on tramadol should be initiated on the lowest available TARGINQ ER dose, 10 mg/5 mg every 12 hours	

Table 2. Initial TARGINIQ ER Dose

Equivalent Daily Oral Morphine Dose	Recommended TARGINIQ ER Starting Dose
20 to <70 mg	10 mg/5 mg every 12 hours (ie. 20 mg oxycodone daily)
70 to <110 mg	20 mg/10 mg every 12 hours (ie. 40 mg oxycodone daily)
110 to <150 mg	30 mg/15 mg every 12 hours (ie. 60 mg oxycodone daily)
150 to 160 mg	40 mg/20 mg every 12 hours (ie. 80 mg oxycodone daily)

Example conversion from a single opioid to TARGINIQ ER:
Step 1: A patient receiving oxymorphone at a total daily dose of 10 mg would equate to an Equivalent Daily Oral Morphine Dose of 40 mg (10 mg x 4; Table 1).

Step 2: Based on Table 2, the starting dose is TARGINIQ ER 10 mg/5 mg every 12 hours.

- For patients on a regimen of more than one opioid, use Table 1 to calculate the Equivalent Daily Oral Morphine dose for each opioid and sum the totals, then use Table 2 to obtain the starting dose of TARGINIQ ER.
- Round down, if necessary, to the appropriate TARGINIQ ER tablet strengths available.
- Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to TARGINIQ ER.

- Titrate appropriately to a stable and tolerated dose.

Conversion from Methadone to TARGINIQ ER
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to TARGINIQ ER
Eighteen hours following the removal of the transdermal fentanyl patch, TARGINIQ ER treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative dose, approximately 10 mg/5 mg every 12 hours of TARGINIQ ER, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to TARGINIQ ER, as there is limited documented experience with this conversion.

Conversion from Transdermal Buprenorphine to TARGINIQ ER
For patients receiving transdermal buprenorphine ($\leq$ 20 mcg/hr), the recommended starting dose is TARGINIQ ER 10 mg/5 mg every 12 hours. Follow the patient closely during conversion from transdermal buprenorphine to TARGINIQ ER, as there is limited experience with this conversion.

2.2 Titration and Maintenance of Therapy

Individually titrate TARGINIQ ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving TARGINIQ ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of TARGINIQ ER or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the TARGINIQ ER dose.

As a guideline, the dose of TARGINIQ ER can be up-titrated from the current dose by increasing the dose 10 mg/5 mg q12h every 1 to 2 days as needed based on efficacy, safety, and tolerability. The total daily dose of TARGINIQ ER should not exceed 80 mg/40 mg (40 mg/20 mg q12h).

The highest total daily dose of TARGINIQ ER studied in the main clinical program is 80 mg/40 mg (40 mg/20 mg twice daily). Total daily doses above 80 mg/40 mg have not been studied sufficiently to ensure patient safety and may be associated with symptoms of opioid withdrawal or decreased analgesia.

If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.

2.3 Patients with Hepatic Impairment

TARGINIQ ER is contraindicated in patients with moderate and severe hepatic impairment. When administering TARGINIQ ER to patients with mild hepatic impairment, reduce the dose to 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

2.4 Patients with Renal Impairment

When administering TARGINIQ ER to patients with renal impairment, reduce the initial dose to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

2.5 Discontinuation of TARGINIQ ER

When the patient no longer requires opioid therapy, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue TARGINIQ ER.

Table 3 presents a suggested taper schedule that was used in a clinical trial to discontinue patients from TARGINIQ ER:

Table 3. Suggested Taper Schedule

Patient's Dose of TARGINIQ ER		**Taper Dose (mg/mg)**									
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
10 mg/5 mg q12h	AM	10/5	10/5	-	-	-	-	-	-	-	-
	PM	-	-	-	-	-	-	-	-	-	-
20 mg/10 mg q12h	AM	20/10	20/10	10/5	10/5	10/5	10/5	-	-	-	-
	PM	10/5	10/5	10/5	10/5	-	-	-	-	-	-
30 mg/15 mg q12h*	AM	20/10	20/10	20/10	20/10	10/5	10/5	10/5	10/5	-	-
	PM	20/10	20/10	10/5	10/5	10/5	10/5	-	-	-	-
40 mg/20 mg q12h	AM	30/15	30/15	20/10	20/10	20/10	20/10	10/5	10/5	10/5	10/5
	PM	30/15	30/15	20/10	20/10	10/5	10/5	10/5	10/5	-	-

* 30 mg/15 mg dose was achieved by administering a 20 mg/10 mg + a 10 mg/5 mg tablet

2.6 Administration of TARGINIQ ER

Instruct patients to swallow TARGINIQ ER tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg/5 mg film-coated extended-release tablets (capsule shaped, white film-coated tablets debossed with "ONX" on one side and "10" on the other)
- 20 mg/10 mg film-coated extended-release tablets (capsule shaped, pink film-coated tablets debossed with "ONX" on one side and "20" on the other)
- 40 mg/20 mg film-coated extended-release tablets (capsule shaped, yellow film-coated tablets debossed with "ONX" on one side and "40" on the other)

4 CONTRAINDICATIONS

TARGINIQ ER 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 gastrointestinal obstruction
- Hypersensitivity (e.g., anaphylaxis) to oxycodone or naloxone
- Moderate to severe hepatic impairment

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TARGINIQ ER contains oxycodone, a Schedule II controlled substance. As an opioid, TARGINIQ ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as TARGINIQ ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TARGINIQ ER. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse or misuse, prior to prescribing TARGINIQ ER, and monitor all patients receiving TARGINIQ ER for the development of these behaviors or conditions. Risks are 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). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations

such as TARGINIQ ER, but use in such patients necessitates intensive counseling about the risks and proper use of TARGINIQ ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of TARGINIQ ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)]*.

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 TARGINIQ ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. 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)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TARGINIQ ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with TARGINIQ ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of TARGINIQ ER are essential *[see Dosage and Administration (2)]*. Overestimating the TARGINIQ ER dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of TARGINIQ ER, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TARGINIQ ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Hypotension and profound sedation, coma, or respiratory depression may result if TARGINIQ ER is used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of TARGINIQ ER 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. Additionally, evaluate the patient's use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin TARGINIQ ER therapy is made, start with 1/3 to 1/2 the usual dose of TARGINIQ ER, monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating TARGINIQ ER and when TARGINIQ ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with TARGINIQ ER, as in these patients, even usual therapeutic doses of TARGINIQ ER may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Hypotensive Effects

TARGINIQ ER 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) *[see Drug Interactions (7.1)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of TARGINIQ ER. In patients with circulatory shock, TARGINIQ ER may cause

vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TARGINIQ ER in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking TARGINIQ ER who may be susceptible to the intracranial effects of CO_2 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 TARGINIQ ER. TARGINIQ ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of TARGINIQ ER in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

TARGINIQ ER is contraindicated in patients with GI obstruction, including paralytic ileus. The oxycodone in TARGINIQ ER may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

5.10 Use in Patients with Convulsive or Seizure Disorders

The oxycodone in TARGINIQ ER may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during TARGINIQ ER therapy.

5.11 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including TARGINIQ ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing TARGINIQ ER, gradually taper the dose *[see Dosage and Administration (2.5)]*. Do not abruptly discontinue TARGINIQ ER.

Symptoms of opioid withdrawal occurred in some patients in clinical trials *[see Adverse Reactions (6.1)]*. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Monitor patients for symptoms of opioid withdrawal. In opioid tolerant patients, if symptoms of opioid withdrawal occur following conversion to TARGINIQ ER or following dose escalation, consider lowering the dose to determine whether symptoms are reduced.

Parenteral use of naloxone has been associated with abrupt and complete reversal of opioid effects leading to withdrawal symptoms (e.g., abdominal cramping, muscle aches, sweating, anxiety, nausea, vomiting, diarrhea). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with parenteral naloxone used postoperatively.

5.12 Driving and Operating Machinery

TARGINIQ ER 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 TARGINIQ ER and know how they will react to the medication.

5.13 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of TARGINIQ ER, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid effects.

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.

If co-administration is necessary, caution is advised when initiating TARGINIQ ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

5.14 Laboratory Monitoring

Not every urine drug test for “opioids” or “opiates” detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified “cut-off” value as “negative”. Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive Effects *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2,396 patients were treated in controlled and open-label clinical studies with TARGINIQ ER. Seven hundred and ninety-four of these patients (33%) were treated for approximately six months and 621 (26%) were treated for approximately one year.

TARGINIQ ER may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

Commonly Observed Treatment-Emergent Adverse Reactions in a Clinical Study with TARGINIQ ER in Opioid-Experienced Patients with Uncontrolled Moderate to Severe Chronic Low Back Pain

The safety data described in Table 4 below are based on a 12-week, randomized, double-blind, placebo-controlled clinical trial in opioid-experienced patients with moderate to severe chronic low back pain. This trial included 1,095 TARGINIQ ER-treated patients in an open-label titration period, and 298 TARGINIQ ER and 302 placebo-treated patients in a double-blind treatment period. The mean age was 52 years old; 55% were female, and 45% were male; 74% were Caucasian, 22% were Black, and 11% were Hispanic.

The most common treatment-emergent adverse reactions (reported by ≥ 5% of TARGINIQ ER subjects) during the open-label or double-blind periods were nausea and vomiting.

The most common reason for discontinuation during the open-label period due to treatment-emergent adverse reactions (reported by ≥ 1% of subjects) was nausea (2%).

The most common reason for discontinuation during the double-blind period due to treatment-emergent adverse reactions (reported by ≥ 1% of subjects with TARGINIQ ER or placebo) was drug withdrawal syndrome (<1% vs. 1%), respectively.

The incidence of treatment-emergent adverse reactions reported by ≥ 2% of subjects in a clinical trial comparing TARGINIQ ER with placebo is shown in Table 4 below:

Table 4. Incidence of Treatment-Emergent Adverse Reactions Reported in ≥ 2% of Subjects Taking TARGINIQ ER: Safety Population (Open-Label Titration Period) and Randomized Safety Population (Double-Blind Period)

	Open-Label Period	Double-Blind Period	
MedDRA System Organ Class Preferred Term	TARGINIQ ER (N=1095) (%)	Placebo (N=302) (%)	TARGINIQ ER (N=298) (%)
Nausea	7	5	8
Headache	4	3	3
Constipation	3	1	3
Abdominal pain	3	2	3
Vomiting	2	2	5
Pruritus	2	1	2
Anxiety	1	0	3
*Drug withdrawal syndrome	1	2	3
Insomnia	1	1	2
Back pain	0	1	3

*Percentages in the table are based on adverse reaction reports of Drug Withdrawal Syndrome in the key efficacy and safety study. In addition to the adverse reaction reports, an independent Adjudication Committee identified additional subjects with possible drug withdrawal syndrome, resulting in a total (adverse reactions plus adjudicated cases) of 2% of subjects in the Open-Label Period, and in the Double-Blind Period 4% of subjects treated with TARGINIQ ER and 2% treated with placebo.

In a clinical trial, the following adverse reactions were reported in patients treated with TARGINIQ ER with an incidence between ≥ 1% and <2%:

Eye disorders: lacrimation increased
General disorders and administration site conditions: fatigue
Infections and infestations: influenza
Injury, poisoning, and procedural complications: fall
Musculoskeletal and connective tissue disorders: arthralgia
Nervous system disorders: dizziness, sinus headache, somnolence
Psychiatric disorders: drug abuse
Skin and subcutaneous tissue disorders: pruritus, rash, cold sweat
Vascular disorders: hot flush, hypertension

6.2 Postmarketing Experience

The following most frequently reported adverse reactions have been identified during post-approval use of oxycodone/naloxone extended-release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: abdominal pain, constipation, diarrhea, nausea, and vomiting

General Disorders and Administration Site Conditions: drug withdrawal syndrome, fatigue, pain, malaise, and drug ineffective

Injury, Poisoning, and Procedural Complications: inadequate analgesia

Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps): malignant neoplasm progression

Nervous System Disorders: dizziness, headache, tremor, and somnolence

Psychiatric Disorders: restlessness, confusional state, and anxiety

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea

Skin and Subcutaneous Tissue Disorders: hyperhidrosis and pruritus

7 DRUG INTERACTIONS

7.1 CNS Depressants

The concomitant use of TARGINIQ ER and other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma, or death. Monitor patients receiving CNS depressants and TARGINIQ ER for signs of respiratory depression, sedation, and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

7.2 Muscle Relaxants

Oxycodone may enhance the neuromuscular blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and TARGINIQ ER for signs of respiratory depression that may be greater than otherwise expected.

7.3 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4 and 2D6
Because the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with TARGINIQ ER is necessary, monitor patients for respiratory

depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4
CYP450 3A4 inducers may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration with TARGINIQ ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression *[see Clinical Pharmacology (12.3)]*.

7.4 Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of oxycodone or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving TARGINIQ ER.

7.5 Diuretics

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

7.6 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when TARGINIQ ER is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies with TARGINIQ ER in pregnant women. The naloxone component of TARGINIQ ER may precipitate opioid withdrawal in a fetus due to the immaturity of the fetal blood brain barrier. Animal reproduction studies were not conducted

with the combination of oxycodone and naloxone, the components of TARGINIQ ER. However, animal data are available from studies conducted with the individual components. Embryo-fetal toxicity was not observed following oral administration of oxycodone to rats and rabbits during the period of organogenesis at doses equal to or 30 times, respectively, the maximum recommended daily dose (MRDD) of 80 mg oxycodone/day on a body surface area basis. Decreased pup weight was observed in rats with oral administration of oxycodone throughout pregnancy at doses 0.8 times the MRDD dose of 80 mg oxycodone/day. Embryo-fetal toxicity was not observed following oral administration of naloxone (800 mg/kg or 400 mg/kg) to pregnant rats and rabbits, respectively, during organogenesis at doses 192 times the MRDD of 40 mg naloxone/day, on a body surface area basis. TARGINIQ ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss.

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. TARGINIQ ER is not recommended for use in women during or immediately prior to labor. Neonates, whose mothers received opioid analgesics during labor, must be observed closely for signs of respiratory depression. An opioid antagonist, such as naloxone, must be available for reversal of narcotic-opioid induced respiratory depression in the neonate.

Data

Animal Data

There are no studies examining the reproductive and developmental effects of the combination of oxycodone and naloxone; however, there are data with the individual agents.

Oxycodone

Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 1 and 30 times the maximum total daily dose of 80 mg oxycodone/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term developmental or reproductive effects in the pups.

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive

performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.8-times the maximum total daily dose of 80 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

Naloxone

Orally administered naloxone was not teratogenic in the rat or rabbit at the maximum dosages tested (800 mg/kg/day or 400 mg/kg/day, respectively) which were equivalent to approximately 192-times the intake of naloxone at the maximum recommended dose of 40 mg naloxone/day on a mg/m^2 basis.

In a peri-/post-natal development study with naloxone in rats, the highest dosage of 800 mg/kg/day (192-times the intake of naloxone at the maximum total daily dose of 40 mg naloxone/day, on a mg/m^2 basis) produced mortality and significant toxicity in maternal rats, which was associated with increased pup deaths in the immediate postpartum period. Mild toxic signs were also observed in maternal rats that received 200 mg/kg/day (approximately 48-times the intake of naloxone at the maximum daily dose of 40 mg naloxone on a body surface area basis); however, there were no adverse effects on the pups.

8.3 Nursing Mothers

The oxycodone component of TARGINIQ ER is likely present in breast milk because oxycodone when given as a single agent is present in breast milk. It is unknown whether naloxone is present in breast milk. Instruct patients not to undertake nursing while receiving TARGINIQ ER. Do not initiate therapy with TARGINIQ ER in a nursing woman because of the possibility of sedation or respiratory depression in an infant.

Withdrawal signs can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. Furthermore, naloxone may precipitate opioid withdrawal in a breast-fed infant.

8.4 Pediatric Use

Safety and effectiveness of TARGINIQ ER in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

A prospective study conducted in two age groups (younger: 19-44 years old vs. elderly: 65-77 years old) to assess age effects on the PK of TARGINIQ ER (10 mg/5 mg) demonstrated slightly higher steady-state oxycodone AUC (18% increase), and higher steady-state naloxone AUC (82% increase) for elderly subjects compared with younger subjects. Evaluate elderly patients at

frequent intervals and consider TARGINIQ ER dose adjustments until stable drug effects are achieved.

8.6 Hepatic Impairment

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone. When administering TARGINIQ ER to patients with mild hepatic impairment, reduce the initial dose to 1/3 to 1/2 the usual dose and monitor patients closely for signs of central nervous system or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naloxone. TARGINIQ ER is contraindicated in patients with moderate and severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment. Naloxone concentrations were affected to a higher degree than oxycodone. When administering TARGINIQ ER to patients with renal impairment, reduce the initial dose to one half of the usual dose and monitor patients closely for signs of central nervous system or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naloxone. As patients with severe renal impairment may be at greater risk for opioid withdrawal-related adverse events, consideration should be given to alternative products without naloxone *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TARGINIQ ER contains oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. TARGINIQ ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is

not limited to, the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

TARGINIQ ER, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

Risks Specific to Abuse of TARGINIQ ER

TARGINIQ ER is for oral use only. Abuse of TARGINIQ ER poses a risk of overdose and death. The risk is increased with concurrent use of TARGINIQ ER with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved TARGINIQ ER enhances drug release and increases the risk of overdose and death.

If TARGINIQ ER tablets are crushed and administered via intranasal or intravenous routes, the resulting systemic naloxone concentrations are much higher and can induce a severe withdrawal syndrome in opioid-dependent individuals. Cases have been reported to the international drug safety database that involved attempts to manipulate the product for injection or insufflation, which resulted in withdrawal symptoms. In the majority of these cases, emergency attention was required.

With parenteral abuse, the inactive ingredients in TARGINIQ ER can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and

valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the controlled-release formulation of TARGINIQ ER and separating the oxycodone component from naloxone, a potent opioid antagonist. Laboratory test data demonstrate that TARGINIQ ER can be crushed and dissolved in solution. However, complete separation or complete inactivation of naloxone from oxycodone was not achieved despite using various techniques and conditions.

Clinical Abuse Potential Studies
In the clinical abuse potential studies described below, drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again"). Response to subjective feeling of getting "high" was measured on a unipolar scale of 0 to 100, where 0 represents "definitely not" and 100 represents "definitely so".

Study in Non-Dependent, Opioid Abusers (Intranasal (IN) Administration)
In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 23 non-dependent, opioid abusers with moderate experience with opioids received IN administered TARGINIQ ER 40 mg/20 mg (finely crushed tablets), oxycodone HCl 40 mg powder (active control), and placebo treatments.

IN administration of finely crushed TARGINIQ ER was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to powdered oxycodone HCl, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 5.

Table 5. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal (IN) Administration of TARGINIQ ER, Oxycodone, and Placebo in Non-Dependent, Opioid Abusers (N=23)

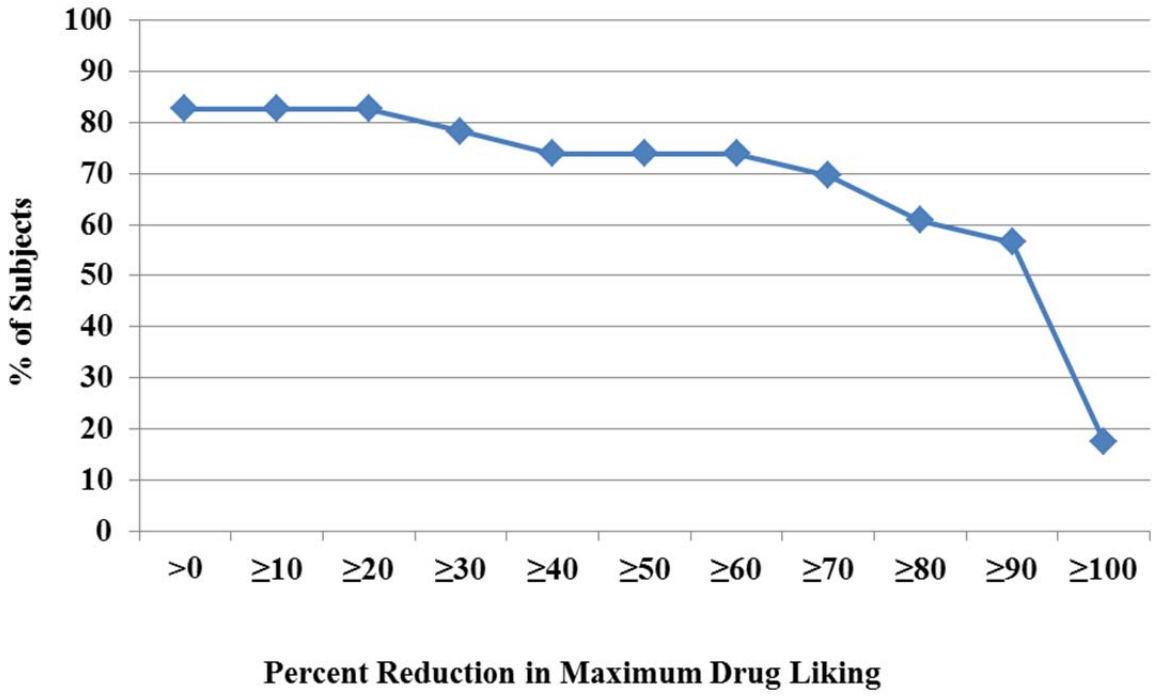
VAS		TARGINIQ ER 40 mg/20 mg (finely crushed)	Oxycodone HCl 40 mg (powdered)	Placebo (lactose powder)
Drug Liking*	Mean (SE)	59.1 (2.8)	94.8 (2.2)	53.2 (2.1)
	Median (Range)	51 (50-100)	100 (61-100)	51 (50-100)
Take Drug Again**	Mean (SE)	42.6 (6.4)	93.6 (2.3)	30.7 (6.1)
	Median (Range)	50.0 (0-100)	100 (62-100)	50 (0-100)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.

**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so.

Figure 1 demonstrates a comparison of maximum drug liking for finely crushed TARGINIQ ER compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in maximum drug liking for TARGINIQ ER vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Among non-dependent, opioid drug abusers, 78% (n = 18) of subjects had a reduction of at least 30% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl, and approximately 74% (n = 17) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl.

Figure 1. Percent Reduction in Maximum Drug Liking for Finely Crushed TARGINIQ ER 40 mg/20 mg vs. Powdered Oxycodone HCl 40 mg Following Intranasal Administration in Non-Dependent Opioid Abusers



Study in Non-Dependent, Opioid Abusers (Intravenous (IV) Administration)
In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 22 non-dependent, opioid abusers with moderate experience with opioids received intravenously administered 0.07 mg/kg oxycodone HCl and 0.035 mg/kg naloxone HCl solution (simulated version of TARGINIQ ER), oxycodone HCl (0.07 mg/kg solution; active control) and placebo (saline) treatments.

The intravenous administration of simulated TARGINIQ ER solution was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to oxycodone

solution, and was associated with similar mean and median scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 6.

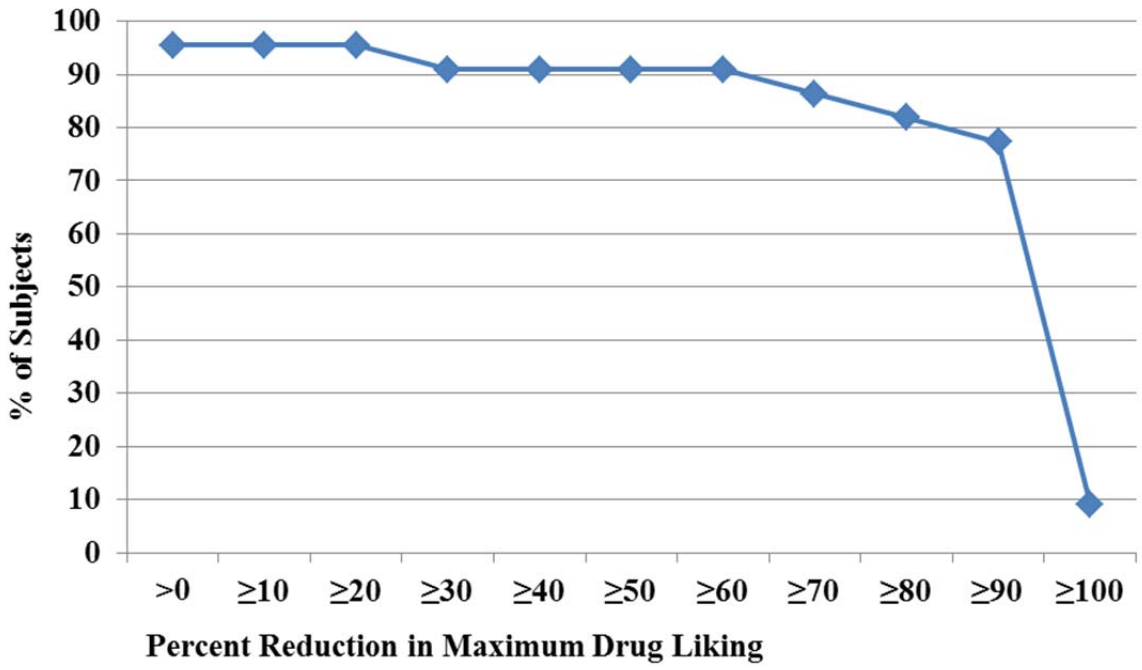
Table 6. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again Following IV Administration of Oxycodone HCl + Naloxone HCl (Simulated TARGINIQ ER Solution), Oxycodone HCl, and Placebo in Non-Dependent, Opioid Abusers (N=22)

VAS		Oxycodone HCl/ Naloxone HCl 0.07/0.35 mg/kg	Oxycodone HCl 0.07 mg/kg	Placebo saline (0.9% NaCl)
Drug Liking*	Mean (SE)	56.5 (2.8)	96.4 (2.3)	48.7 (2.3)
	Median (Range)	51 (50-100)	100 (50-100)	51.0 (0-53)
Take Drug Again**	Mean (SE)	37.0 (6.2)	82.0 (6.0)	34.5 (5.1))
	Median (Range)	50.0 (0-100)	99.0 (0-100)	50.0 (0-55)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so; Values obtained at 8 hours post dose.

Figure 2 demonstrates a comparison of maximum drug liking for simulated TARGINIQ ER solution compared to oxycodone HCl solution in subjects who received both treatments. Among non-dependent, opioid drug abusers, approximately 91% (n = 20) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone solution.

Figure 2. Percent Reduction in Maximum Drug Liking for Oxycodone 0.07 mg/kg + Naloxone 0.035 mg/kg (Simulated TARGINIQ ER) vs. Oxycodone HCl 0.07 mg/kg Following Intravenous Administration in Non-Dependent, Opioid Abusers



Study in Opioid-Dependent Subjects
In a randomized, double-blind, placebo- and positive-controlled, 4-period crossover pharmacodynamic study, 29 opioid-dependent, methadone-maintained subjects received orally administered TARGINIQ ER 60 mg/30 mg chewed and intact tablets, oxycodone HCl solution 60 mg (active control) and placebo (chewed and intact tablets and solution) treatments.

The oral administration of TARGINIQ ER, either chewed or intact, was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower scores for take drug again ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 7.

Table 7. Summary of High, Maximum Drug Liking (E_{max}), and Take Drug Again Following Oral Administration of TARGINIQ ER (Intact and Chewed), Oxycodone HCl solution, and Placebo in Opioid-Dependent Subjects (N=29)

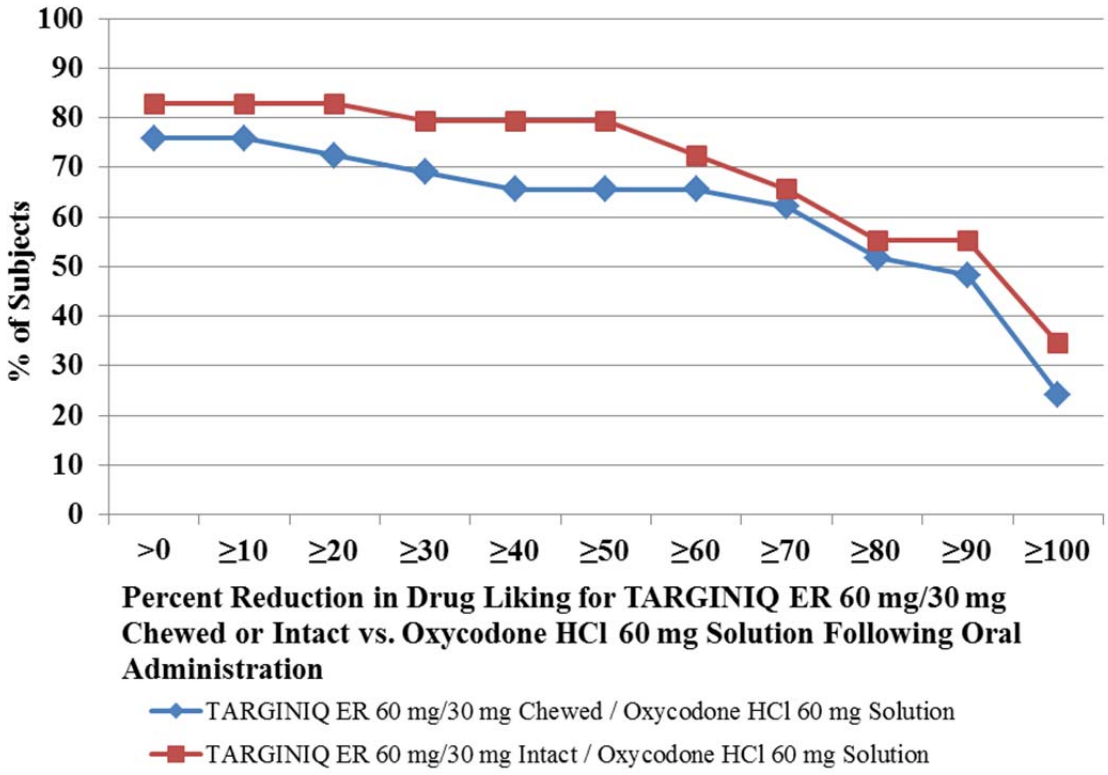
VAS		TARGINIQ ER 60 mg/30 mg intact	TARGINIQ ER 60 mg/30 mg chewed	Oxycodone HCl solution 60 mg	Placebo chewed and intact tablet, solution
Drug Liking*	Mean (SE)	54.7 (2.0)	54.6 (3.2)	77.9 (3.8)	54.4 (2.1)
	Median (Range)	51.0 (50-99)	51.0 (0-100)	78.0 (50-100)	51.0 (50-100)
Take Drug Again**	Mean (SE)	38.5 (5.7)	32.6 (5.9)	61.4 (5.9)	41.5 (5.0)
	Median (Range)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)
Getting High***	Mean (SE)	20.6 (5.1)	27.7 (6.5)	77.9 (5.0)	20.6 (5.0)

	Median (Range)	1.0 (0-73)	1.0 (0-100)	86.0 (0-100)	1.0 (0-82)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so; Values obtained at 12 hours post dose.
***Getting High Question Text: "I am feeling high"; scale: 0 = definitely not, 100 = definitely so.

Figure 3 demonstrates a comparison of maximum drug liking (E_{max}) for TARGINIQ ER either chewed or intact compared to oxycodone solution in subjects who received both treatments. Among opioid-dependent subjects, 69.0% (n = 20) had a reduction of at least 30%, and 65.5% (n = 19) of subjects had a reduction of at least 50% in maximum drug liking with chewed TARGINIQ ER tablets compared to oxycodone solution; 79.3% (n = 23) of subjects had a reduction at least 50% in maximum drug liking with intact TARGINIQ ER tablets compared to oxycodone solution.

Figure 3. Percent Reduction in Maximum Drug Liking for TARGINIQ ER 60 mg/30 mg Chewed or Intact vs. Oxycodone HCl 60 mg Solution Following Oral Administration in Opioid-Dependent Subjects



Summary

Based on the *in vitro* study results, it is expected that abuse of oxycodone from physically and chemically manipulated TARGINIQ ER tablets will be deterred by the inability to separate the two active components.

The data from the clinical abuse potential studies indicate that TARGINIQ ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration. However, abuse of TARGINIQ ER by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of TARGINIQ ER on the abuse liability of the drug in the community. Accordingly, this section may be updated in the future as appropriate.

TARGINIQ ER contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. TARGINIQ ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

TARGINIQ ER should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If TARGINIQ ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with TARGINIQ ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete

airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Although TARGINIQ ER contains naloxone, in overdose situations, administration of naloxone should be repeated as clinically necessary. Higher than normal doses and repeated administration may be necessary. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on TARGINIQ ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

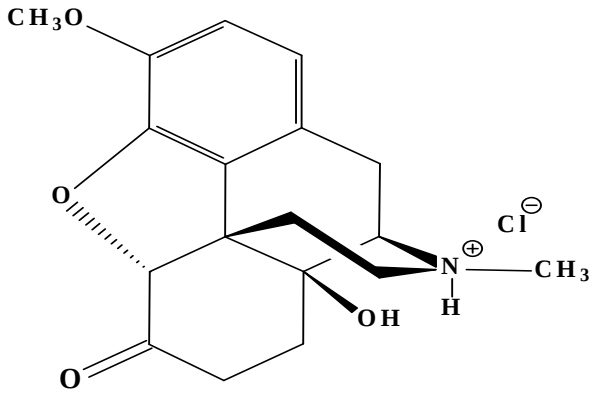
Because the duration of reversal would be expected to be less than the duration of action of oxycodone in TARGINIQ ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. TARGINIQ ER will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely supervised environment.

11 DESCRIPTION

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) is a combination product containing an opioid agonist, oxycodone, and an opioid antagonist, naloxone. TARGINIQ ER is supplied as 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tablets for oral administration. The tablet strengths, a 2:1 ratio in each, describe the amount of oxycodone and naloxone per tablet as the hydrochloride salts, respectively. The structural formula for oxycodone hydrochloride is as follows:

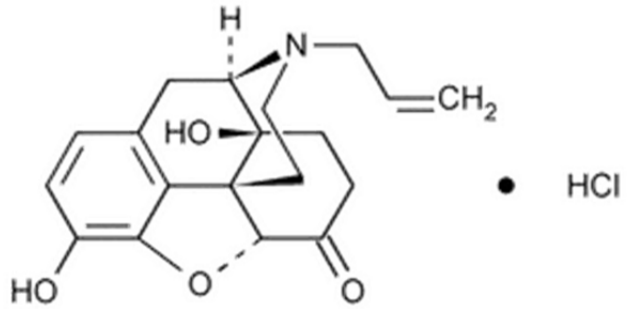


$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The structural formula for naloxone hydrochloride is as follows:



$C_{19}H_{21}NO_4 \bullet HCl$ MW 363.84

The chemical name is (-)-17-Allyl-4,5α -epoxy-3,14-dihydroxy-morphinan-6-one hydrochloride.

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

The 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg extended-release tablets contain the following inactive ingredients: lactose monohydrate, stearyl alcohol, ethyl cellulose, povidone, talc, magnesium stearate, polyvinyl alcohol partially hydrolyzed, titanium dioxide, and Macrogol. The 20 mg/10 mg extended-release tablets also contain: Iron oxide red. The 40 mg/20 mg extended-release tablets also contain: Iron oxide yellow.

The film-coated extended-release tablets are color coded to distinguish different strengths as follows:
The 10 mg/5 mg extended-release tablets are white.
The 20 mg/10 mg extended-release tablets are pink.
The 40 mg/20 mg extended-release tablets are yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone
Oxycodone hydrochloride is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Naloxone
Naloxone is an antagonist acting on mu, kappa, and delta opioid receptors in the brain, spinal cord, and peripheral organs (e.g, intestine, heart, kidney, and lungs). Naloxone antagonizes opioid effects by competing for the mu, kappa, and delta opioid receptor sites with the greatest affinity for the mu receptor. Naloxone produces opioid withdrawal signs and symptoms in individuals physically dependent on opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in CO_2 tension and to electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose *[see Overdosage (10)]*.

Naloxone prevents or reverses the effects of opioids, including respiratory depression and sedation, when administered intravenously *[see Overdosage (10)]*. When naloxone is administered orally, at the same doses as in TARGINIQ ER, these effects would not be expected due to low circulating plasma concentrations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Although naloxone prevents or reverses the hypotensive effects of opioids when administered intravenously, these effects would not be expected with orally administered naloxone, due to low circulating plasma concentrations.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

Studies with oxycodone in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective “drug effect”, and analgesia.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration –Adverse Reaction Relationships

In studies with oxycodone, there is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

The dose of TARGINIQ ER must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients *[see Dosage and Administration (2.1)]*.

12.3 Pharmacokinetics

The analgesic activity of TARGINIQ ER is primarily due to the parent drug oxycodone. TARGINIQ ER is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing, or dissolving TARGINIQ ER impairs the extended-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Absorption

Oxycodone
Oxycodone from TARGINIQ ER tablets was rapidly absorbed with the median T_{max} 3 to 4 hours following a single oral administration over a range of doses from 10 mg/5 mg to 80 mg/40 mg. About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. Dose proportionality for oxycodone has been established for the 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg TARGINIQ ER tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 8 and Table 9, below) following single or multiple oral dose with q12h administration. Steady-state plasma concentrations are reached in approximately 2 days for oxycodone and naloxone and for their metabolites.

Naloxone
Absolute bioavailability of naloxone from TARGINIQ ER tablets was very low (≤ 2%) following oral administration. However in an abuse potential study conducted in nondependent drug users, naloxone bioavailability was much higher (approximately 31%) following intranasal administration of crushed TARGINIQ ER 40 mg/20 mg tablets, due to circumvention of GI and hepatic first-pass naloxone metabolism. Mean AUC and C_{max} values of naloxone were 29.9 ng•hr/mL and 20.2 ng/mL following intranasal administration of crushed TARGINIQ ER 40 mg/20 mg tablets, while mean AUC and C_{max} values were 0.833 ng• hr/mL and 0.0845 ng/mL under normal use condition *[see Drug Abuse and Dependence (9.2)]*.

Table 8. Pharmacokinetic Parameters for Oxycodone (Mean [SD])

Regimen	TARGINIQ ER Dose (mg/mg)	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hour) ††	Trough Conc. (ng/mL)

Single Dose	10/5	130 [25.6]	12.1 [2.67]	3 [1, 6]	NA
	20/10	247 [62.7]	22.2 [4.19]	3 [1, 6]	NA
	40/20	506 [128]	40.9 [9.52]	3.5 [1, 6]	NA
Multiple Dose	10/5 q12h	129 [33.4]	15.0 [3.25]	1.75 [1, 5]	5.69 [1.78]
	40/20 q12h	507 [100]	57.0 [10.0]	2 [0.5, 5]	24.7 [5.68]

† for single-dose, AUC = $AUC_{0\text{-}inf}$; for multiple-dose, AUC = AUC_{tau}
†† median (range)
Data obtained from healthy subjects receiving naltrexone.

Table 9. Pharmacokinetic Parameters for Naloxone (Mean [SD])

Regimen	TARGINIQ ER Dose (mg/mg)	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hour) ††	Trough Conc. (ng/mL)
Single Dose	10/5	0.136 [0.141]	0.0306 [0.0236]	5 [1, 12]	NA
	20/10	0.657 [0.585]	0.0839 [0.0812]	1.5 [0.5, 12]	NA
	40/20	0.833 [0.526]	0.0845 [0.0834]	2 [1, 16]	NA
Multiple Dose	10/5 q12h	0.416 [0.367]	0.0725 [0.0885]	3.75 [0.5, 8]	0.0154 [0.00882]
	40/20 q12h	1.55 [1.02]	0.217 [0.173]	5 [0.5, 12]	0.0711 [0.0410]

† for single-dose, AUC = $AUC_{0\text{-}t}$; for multiple-dose, AUC = AUC_{tau}
†† median (range)
Data obtained from healthy subjects receiving naltrexone.

Food Effects

Administration of TARGINIQ ER with a standardized high-fat meal did not meaningfully affect the extent of absorption of oxycodone, naloxone, or naloxone-3β-glucuronide. In the clinical trial program, TARGINIQ ER was administered to chronic pain patients without regard to meals. Therefore, TARGINIQ ER can be administered with or without food.

Distribution

Plasma protein binding for oxycodone measured in healthy subjects was <24%. Following IV administration, the mean volume of distribution for oxycodone (0.07 mg/kg) was 245 L. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone is found in breast milk *[see Use in Specific Populations (8.3)]*. Oxycodone crossed the blood-brain barrier in preclinical species.

Plasma protein binding for naloxone measured in healthy subjects, was <60%. Following IV administration, the mean volume of distribution for naloxone (0.035 mg/kg) was 378 L. It is not known whether naloxone passes into breast milk. Naloxone crossed the blood-brain barrier in preclinical species.

Metabolism

Oxycodone metabolism is primarily mediated by CYP3A4/5 and CYP2D6. Oxycodone is mainly metabolized to Phase 1 metabolites including noroxycodone, oxymorphone and noroxymorphone. Oxycodone metabolites are present in plasma at lower concentrations than the parent drug. Noroxycodone and noroxymorphone are the major metabolites in the blood circulation. The mean molar ratio of metabolite to parent (oxycodone), as evaluated by AUC across proposed therapeutic doses of TARGINIQ ER, was 0.928 for noroxycodone, 0.379 for noroxymorphone, and 0.0251 for oxymorphone, respectively.

Naloxone metabolism is primarily mediated by UGT1A8 and UGT2B7. Naloxone is mainly metabolized to 6β-naloxol, naloxone-3β-glucuronide and 6β-naloxol-3β-glucuronide. The mean molar ratio of metabolite to parent (naloxone), as evaluated by AUC across proposed therapeutic doses TARGINIQ ER was 31.5 for 6β-naloxol, 1459 for naloxone-3β-glucuronide, and 1301 for 6β-naloxol-3β-glucuronide, respectively. Naloxone metabolites were present in plasma at higher concentrations than the parent drug, especially for naloxone-3β-glucuronide and 6β-naloxol-3β-glucuronide due to the extremely low plasma naloxone concentrations following oral administration of TARGINIQ ER.

Excretion

Oxycodone is rapidly eliminated from the body with a mean $t_{1/2}$ of approximately 3.9-5.3 hours after a single oral dose administration of TARGINIQ ER in healthy subjects. Oxycodone and its metabolites are excreted in both urine and feces. Following an IV dose (0.07 mg/kg), the mean total plasma clearance was 47.8 L/hour in healthy subjects. Following TARGINIQ ER 10/5 mg administration, the mean renal clearance was approximately 3.66-4.37 L/hour. Following an oral dose of oxycodone immediate-release (15 mg), the mean total urine recovery (48 hour cumulative recovery) of oxycodone and its metabolites from 16 healthy subjects was 72%. These findings suggest that metabolism is the major route of elimination.

Naloxone is eliminated from the body with mean $t_{1/2}$ ranging from 4.1 to 17.2 hours after a single oral dose administration of TARGINIQ ER in healthy subjects. The mean total plasma clearance was 217 L/hour following an IV dose (0.035 mg/kg), and the mean renal clearance was 7.85-31.9 L/hour following an oral dose of TARGINIQ ER 10 mg/5 mg. These findings suggest that the metabolism is the major route of elimination.

Special Populations

Elderly (≥ 65 years)

A prospective study conducted in 2 age groups (younger: 19-44 years old vs. elderly: 65-77 years old) to assess age effects on the PK of TARGINIQ ER (10 mg/5 mg) demonstrated slightly higher steady state oxycodone AUC (18% increase), and higher steady state naloxone AUC (82% increase) for elderly subjects compared with younger subjects. *[see Use in Specific Populations (8.5)]*

Gender

Pharmacokinetic properties of TARGINIQ ER were not affected by gender.

Renal Impairment

Oxycodone
Following oral TARGINIQ ER administration, mean oxycodone AUC was 111, 171, 186 and 253 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in oxycodone AUC was approximately 53%, 66% and 124% for subjects with mild, moderate and severe renal impairment, respectively, as compared with that for healthy subjects. Mean oxycodone C_{max} was 10.6, 11.7, 14.4 and 17.8 ng/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in oxycodone C_{max} was approximately 10%, 35%, and 67% for subjects with mild, moderate, and severe renal impairment, respectively, as compared with that for healthy subjects. *[see Use in Specific Populations (8.7)]*

Naloxone
Following oral TARGINIQ ER administration, mean naloxone AUC_{0-t} was 0.115, 1.02, 0.459 and 1.12 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. Mean naloxone C_{max} was 0.0345, 0.0435, 0.0347 and 0.0678 ng/mL for healthy subjects, and subjects with mild, moderate, and severe renal impairment, respectively. The mean increase in naloxone C_{max} was approximately 976%, 758%, and 1575% for subjects with mild, moderate, and severe renal impairment, respectively, as compared with that for healthy subjects *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment

Oxycodone
Oxycodone pharmacokinetics from TARGINIQ ER was significantly altered by hepatic impairment, especially in subjects with moderate or severe hepatic impairment as compared with healthy subjects. Mean oxycodone AUC was 99.1, 143, 319 and 314 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in oxycodone AUC was approximately 43%, 219%, and 210% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects. Mean oxycodone C_{max} was 9.00, 10.8, 18.1 and 17.2 ng/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in oxycodone C_{max} was approximately 20%, 101%, and 91% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects.

Naloxone
Naloxone pharmacokinetics from TARGINIQ ER was significantly altered by hepatic impairment, especially in subjects with moderate or severe hepatic impairment. Mean naloxone AUC_{0-t} was 0.238, 0.908, 14.1 and 13.7 ng•hr/mL for healthy subjects, and subjects with mild, moderate, and severe hepatic impairment, respectively. The mean increase in naloxone AUC was approximately 311%, 11418%, and 10566% for subjects with mild, moderate, and severe hepatic impairment subjects, respectively, as compared with that for healthy subjects. Mean naloxone C_{max} was 0.0278, 0.0537, 1.47 and 1.46 ng/mL for healthy subjects, and subjects with mild,

moderate, and severe hepatic impairment, respectively. The mean increase in naloxone C_{max} was approximately 93%, 5192%, and 5152% for subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with that for healthy subjects *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*.

Drug-Drug Interactions

Oxycodone
At therapeutic concentrations, TARGINIQ ER is not expected to affect concomitantly administered medicines metabolized by CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4. There were no pharmacokinetic drug interactions between oxycodone and naloxone.

CYP3A4 Inhibitors
CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of an oxycodone controlled release tablet (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7.3)]*.

CYP3A4 Inducers
A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7.3)]*.

CYP2D6 Inhibitors
Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with TARGINIQ ER *[see Drug Interactions (7.3)]*.

Naloxone
UGT1A8 and 2B7 are responsible for the metabolism of naloxone. Metabolic drug interactions with naloxone are unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies have not been conducted with oxycodone alone or the oxycodone and naloxone combination.

Naloxone was tested in two carcinogenicity studies in rats and transgenic mice. Naloxone was not carcinogenic in a 2-year rat bioassay at doses as high as 100 mg/kg/day (24-times the maximum recommended daily dose of 40 mg naloxone/day on a mg/m^2 basis).

Naloxone did not produce evidence of carcinogenic potential in the Tg.rasH2 mouse model.

Mutagenesis
Oxycodone was genotoxic in the mouse lymphoma assay. Clastogenicity was observed with oxycodone in the presence of metabolic activation in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 mcg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation; however, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium* and *E. coli* test with and without metabolic activation at concentrations up to 5000 µg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at concentrations up to 1500 µg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 µg/mL).

Naloxone was genotoxic in the mouse lymphoma assay. Naloxone produced a non-dose-related increase in chromosomal aberrations in the presence of metabolic activation that was statistically significant at concentrations of 375 and 1500 mcg/mL but not at 750 or 3000 mcg/mL. In contrast, naloxone was not mutagenic in the *S. typhimurium*/*E. coli* bacterial mutagenicity test with or without metabolic activation nor was it genotoxic in *in vivo* mouse bone marrow micronucleus test at a dose of 500 mg/kg.

Impairment of Fertility
Fertility studies to evaluate the combination of oxycodone and naloxone have not been conducted. In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride doses up to 8 mg/kg (equivalent to the maximum recommended daily dose of 80 mg/day on a mg/m^2 basis). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats.

Oral administration of naloxone to male and female rats at dosages as high as 800 mg/kg/day had no effect on fertility or general reproductive performance (approximately 192-times the maximum recommended daily dose of 40 mg naloxone/day, on a mg/m^2 basis).

14 CLINICAL STUDIES

The efficacy of TARGINIQ ER was evaluated in one 12-week, randomized, double-blind, placebo-controlled clinical trial in opioid-experienced patients with uncontrolled moderate to severe chronic low back pain.

12-Week Study in Opioid-Experienced Patients with Uncontrolled Chronic Low Back Pain

A total of 1095 patients (mean age = 52 years [range 20-88]; 45% male and 55% female) with uncontrolled moderate to severe chronic low back pain entered an open-label, dose-titration period for up to four weeks. Patients initiated TARGINIQ ER therapy at an oxycodone dose approximately equivalent to their current therapy *[see Dosage and Administration (2.1)]*). The dose of TARGINIQ ER could be up-titrated to a maximum of 40/20 mg twice daily by the investigator every 1-2 days as needed based on efficacy, safety, and tolerability considerations or down-titrated at any time for safety and/or tolerability reasons. During open-label titration, subjects were allowed supplemental pain medication (immediate-release oxycodone HCl 5 mg capsules) for low back pain every 4 hours as needed up to 8 capsules per day.

Fifty-five percent (55%) of patients who entered the open-label titration period achieved adequate analgesia and tolerability on TARGINIQ ER and were then randomized to their final titrated dose of TARGINIQ ER or matching placebo for 12 weeks of double-blind treatment. Nine percent (9%) of patients discontinued from the open-label titration period due to an adverse event; 10% discontinued due to lack of a therapeutic effect, and 11% discontinued for other reasons. Sixteen (16%) percent did not qualify for randomization. During double-blind treatment, subjects were allowed one capsule of supplemental pain medication (immediate-release oxycodone HCl 5 mg capsules) for low back pain as needed, up to 2 capsules per day.

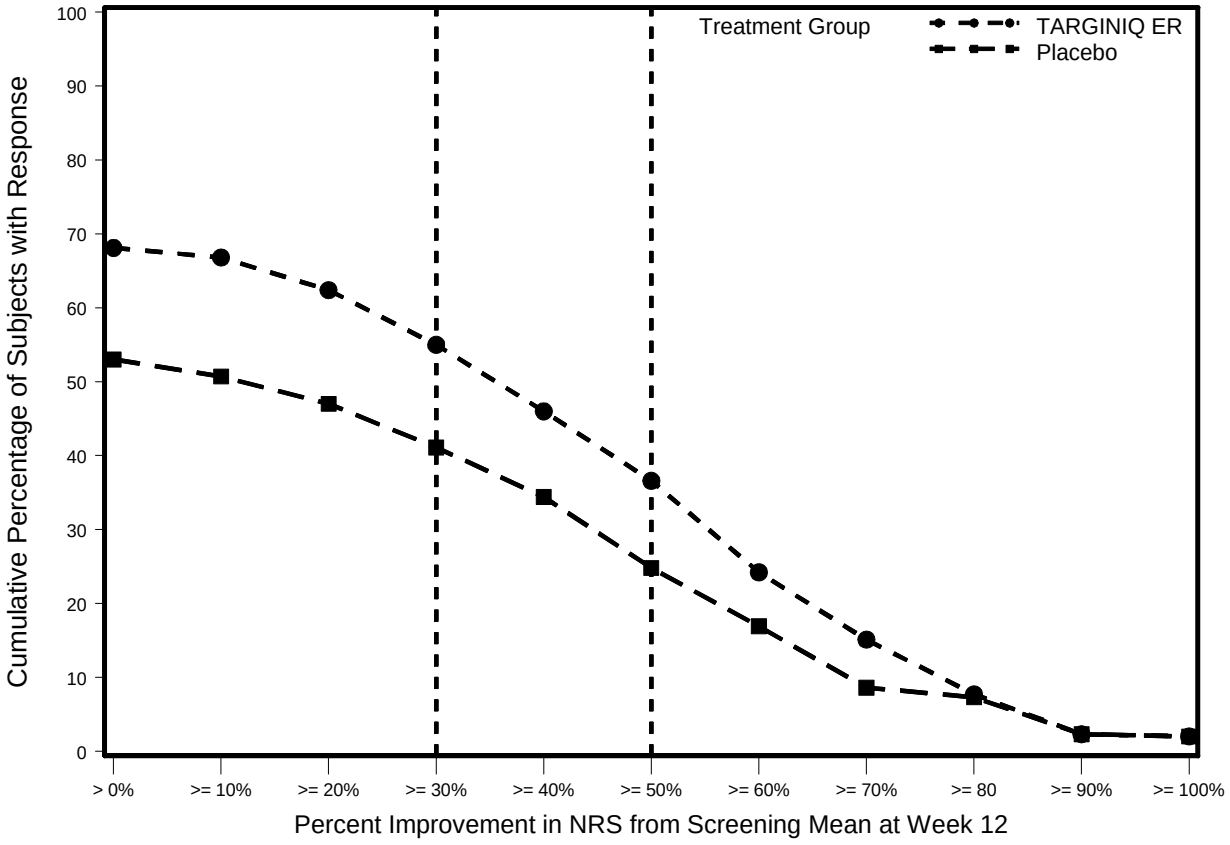
Of the 298 patients randomized to TARGINIQ ER, 73% of the patients completed the 12-week double-blind treatment on study drug. Of the 302 patients randomized to placebo, 60% of the patients completed the study. Fewer patients randomized to TARGINIQ ER discontinued due to lack of efficacy compared to placebo, 10% versus 24%. Discontinuation due to adverse events was the same for both TARGINIQ ER (8%) and placebo (8%).

Of the patients who were randomized, pain scores were similar at screening and end of the open-label titration for TARGINIQ ER and placebo subjects. The mean average pain over the last 24 hours (SE) scores were 7.0 (0.06) and 7.1 (0.06) at screening and 3.1 (0.06) and 3.1 (0.06) at pre-randomization (beginning of double-blind phase) for the TARGINIQ ER and placebo groups, respectively.

The mean score of average pain over the last 24 hours at the end of the study (Week 12/Early Termination) was statistically significantly lower in patients treated with TARGINIQ ER (SE), 3.9 (0.1), compared to patients treated with placebo (SE), 4.3 (0.1).

A plot of distribution of responders based on pain intensity at week 12 is shown in Figure 4 below. The figure is cumulative, such that patients whose change from baseline, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. A higher proportion of patients treated with TARGINIQ ER (55%) had at least a 30% reduction in pain score from screening to week 12 compared to placebo patients (41%). Also, a higher proportion of patients treated with TARGINIQ ER (37%) had at least a 50% reduction in pain score from screening to week 12 compared to placebo patients (25%).

Figure 4. Plot of Distribution of Responders Based on Pain Intensity at Week 12



NRS – Numeric Rating Scale

16 HOW SUPPLIED/STORAGE AND HANDLING

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) 10 mg/5 mg are capsule shaped, white film-coated tablets debossed with "ONX" on one side and "10" on the other and are supplied as child-resistant closure, opaque HDPE bottles of 100 **(NDC 59011-520-01).**

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) 20 mg/10 mg are capsule shaped, pink film-coated tablets debossed with "ONX" on one side and "20" on the other and are supplied as child-resistant closure, opaque HDPE bottles of 100 **(NDC 59011-521-01)**.

TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) 40 mg/20 mg are capsule shaped, yellow film-coated tablets debossed with "ONX" on one side and "40" on the other and are supplied as child-resistant closure, opaque HDPE bottles of 100 **(NDC 59011-522-01)**.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container, with a child-resistant closing.

CAUTION

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of TARGINIQ ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share TARGINIQ ER with others and to take steps to protect TARGINIQ ER from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression including information that the risk is greatest when starting TARGINIQ ER or when the dose is increased and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store TARGINIQ ER securely and to dispose of unused TARGINIQ ER by flushing the tablets down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if TARGINIQ ER is used with other CNS depressants, and not to use such drugs unless supervised by a healthcare provider.

Important Administration Instructions

Instruct patients how to properly take TARGINIQ ER, including the following:

- TARGINIQ ER is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved TARGINIQ ER tablets can result in a fatal overdose or other serious side effects (e.g., withdrawal symptoms).
- Do not discontinue TARGINIQ ER without first discussing the need for a tapering regimen with the prescriber.

Hypotension

Inform patients that TARGINIQ ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that TARGINIQ ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in TARGINIQ ER. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that TARGINIQ ER can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Opioid Withdrawal Symptoms
Advise patients that TARGINIQ ER may be associated with symptoms possibly related to opioid withdrawal, including sweating, tremors, anxiety, chills, diarrhea, abdominal pain, irritability, and yawning, and to contact their prescriber if these symptoms occur.

Disposal of Unused TARGINIQ ER

Advise patients to flush the unused tablets down the toilet when TARGINIQ ER is no longer needed.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers: 6,277,384; 6,696,066; 7,674,799; 7,674,800; 7,683,072 and 8,673,355.

Medication Guide
TARGINIQ™ ER (tar-gih-NEEK E-R)
(oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), CII

TARGINIQ ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about TARGINIQ ER:

- **Get emergency help right away if you take too much TARGINIQ ER (overdose).** When you first start taking TARGINIQ ER, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Never give anyone else your TARGINIQ ER. They could die from taking it. Store TARGINIQ ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away TARGINIQ ER is against the law.

Do not take TARGINIQ ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TARGINIQ ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid or heart problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- problems urinating
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of TARGINIQ ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** TARGINIQ ER passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TARGINIQ ER with certain other medicines can cause serious side effects that could lead to death.

When taking TARGINIQ ER:

- Do not change your dose. Take TARGINIQ ER exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow TARGINIQ ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject TARGINIQ ER because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TARGINIQ ER without talking to your healthcare provider.**
- After you stop taking TARGINIQ ER, flush any unused tablets down the toilet.

While taking TARGINIQ ER DO NOT:

- Drive or operate heavy machinery, until you know how TARGINIQ ER affects you. TARGINIQ ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with TARGINIQ ER may cause you to overdose and die.

The possible side effects of TARGINIQ ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, anxiety, and sweating. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, lightheadedness when changing positions, or you are feeling faint.

Call your healthcare provider if you get symptoms that may be related to opioid withdrawal including tremors, chills, diarrhea, irritability, and yawning.

These are not all the possible side effects of TARGINIQ ER. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, www.purduepharma.com or call 1-888-726-7535

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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