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

VANTRELA™ ER (hydrocodone bitartrate) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1943

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **VANTRELA 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 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 VANTRELA ER whole to avoid exposure to a potentially fatal dose of hydrocodone. (5.2)**
- **Accidental ingestion of VANTRELA ER, especially by children, can result in a fatal overdose of hydrocodone. (5.2)**
- **Prolonged use of VANTRELA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required 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)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from VANTRELA ER. (5.4)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.X, 7.X)**

INDICATIONS AND USAGE

VANTRELA ER is an opioid agonist 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 opioid formulations, reserve VANTRELA 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)
- VANTRELA ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- VANTRELA ER 90 mg tablets, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, 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, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Tablets must be swallowed intact and are not to be crushed, dissolved, or chewed due to the risk of overdose or death. (2.1, 5.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 15 mg tablets orally every 12 hours. (2.2)
- To convert to VANTRELA ER from another opioid, always consider starting at the lowest dose or follow the conversion instructions to obtain an estimated dose (2.2)
- Increase dose every 3 to 7 days as needed. (2.5)
- Do not abruptly discontinue VANTRELA ER in a physically-dependent patient. (2.6)
- Mild to Moderate Hepatic Impairment: Initiate therapy with one half of the recommended initial dose and titrate carefully. Use alternative analgesia for patients requiring less than 15 mg. Monitor closely. (2.3, 8.6)
- Moderate to Severe Renal Impairment and End Stage Renal Disease: Initiate therapy with one half of the recommended initial dose and titrate carefully. Use alternative analgesia for patients requiring less than 15 mg. Monitor closely. (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to hydrocodone bitartrate (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease and in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of VANTRELA ER in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use in patients with impaired consciousness or coma. (5.9)
- QTc Prolongation: Consider this observation when making clinical decisions regarding monitoring of patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. Avoid use in patients with congenital long QTc syndrome. In patients who develop QTc prolongation, consider reducing the dose. Do not exceed a dose of 90 mg every 12 hours (180 mg per day). Higher doses have not been studied. (5.14, 12.2)

ADVERSE REACTIONS

Adverse reactions in ≥2% of patients in placebo-controlled trials include nausea, constipation, headache, somnolence, vomiting, dizziness, pruritus, fatigue, dry mouth, diarrhea, insomnia, anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue VANTRELA ER if serotonin syndrome is suspected. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of hydrocodone. Avoid VANTRELA ER in patients receiving MAOIs or within 14 days of stopping an MAOI. (7)
- Mixed Agonists/Antagonists and Partial Agonist Analgesics: Avoid use with VANTRELA ER because they may reduce analgesic effect of VANTRELA ER or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Severe Hepatic Impairment: Use not recommended. (8.6)

- Geriatric Patients: Start at the low end of the dosing range and monitor closely for respiratory depression. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2017

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; CYTOCHROME P450 3A4 INTERACTION and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

VANTRELA 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 VANTRELA ER and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression

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

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of VANTRELA 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 VANTRELA ER with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone 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 hydrocodone plasma concentration. Monitor patients receiving VANTRELA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.4) Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS)

depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of VANTRELA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

VANTRELA™ ER is an opioid agonist 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.

Limitation 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 *[see Warnings and Precautions (5.1)]*, reserve VANTRELA 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.
- VANTRELA ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

VANTRELA ER 90 mg tablets, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. 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, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, 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 and following dosage increases with VANTRELA ER and adjust dosage accordingly *[see Warnings and Precautions (5.2)]*.

Instruct patients to swallow VANTRELA ER tablets whole *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving VANTRELA ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

VANTRELA ER is administered orally every 12 hours. Do not exceed a dose of 90 mg every 12 hours (180 mg per day). Higher doses have not been studied with regard to the effects of hydrocodone on the QT interval.

2.2 Initial Dosing

Use of VANTRELA ER as the First Opioid Analgesic (Opioid-Naïve Patients)

Initiate treatment with VANTRELA ER with the 15 mg tablet orally every 12 hours.

Use of VANTRELA ER in Patients Who Are Not Opioid Tolerant

The starting dosage for patients who are not opioid tolerant is VANTRELA ER 15 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.2)]*.

Conversion from Other Oral Hydrocodone Bitartrate Formulations to VANTRELA ER

Patients receiving other oral hydrocodone bitartrate formulations may be converted to VANTRELA ER by administering one half of the patient's total daily oral hydrocodone bitartrate dose as VANTRELA ER every 12 hours.

Conversion from other Opioids to VANTRELA ER

Discontinue all other around-the-clock opioid drugs when VANTRELA ER therapy is initiated.

There is inter-patient variability in the relative potency of different opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of VANTRELA ER. It is safer to underestimate a patient's 24-hour oral hydrocodone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour hydrocodone dosage and manage an adverse reaction due to an overdose.

In VANTRELA ER clinical trials with an open-label titration period, patients were converted from their prior opioid to VANTRELA ER using Table 1 as a guide for the initial VANTRELA ER dose.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** VANTRELA ER.

- The table **cannot** be used to convert **from** VANTRELA ER to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

To calculate the estimated daily VANTRELA ER dose using Table 1:

- Calculate the approximate total daily oral hydrocodone dose
  - For patients on a single opioid, multiply the current total daily dose of the opioid by the appropriate conversion factor listed in Table 1.
  - For patients on a regimen of more than one opioid, use Table 1 to calculate the total daily oral hydrocodone dose for each opioid and sum the totals.
  - For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products for calculating the approximate total daily oral hydrocodone dose.
- Divide the daily dose in half to obtain the every 12-hour dose of VANTRELA ER.
- Note that the conversion factors in Table 1 include a reduction of the total daily starting dose by 50% for safety.
- Always round the dose down, if necessary, to the appropriate VANTRELA ER strength(s) available.

Table 1: Converting the Current Total Daily Oral Opioid Dose(s) to the 50% Equivalent Daily Oral VANTRELA ER Starting Dose

Prior Oral Opioid	Approximate Oral Conversion Factor[a]
Meperidine	**0.05**
Codeine	**0.075**
Hydrocodone	**0.5**
Morphine	**0.5**
Oxycodone	**0.75**
Oxymorphone	**1.5**
Methadone	**1.5**
Hydromorphone	**2**
Tramadol[b]	**None**

[a] Note that the conversion factor includes the reduction of the total daily starting dose by 50% for safety.
[b] For patients who are on tramadol, the suggested starting dose of VANTRELA ER should be 15 mg every 12 hours.

Example conversion from a single opioid to VANTRELA ER:

- Step 1: Sum the total daily dose of the opioid (in this case, extended-release oxymorphone); 15 mg oxymorphone twice daily = 30 mg total daily dose of oxymorphone.

- Step 2: Calculate the approximate equivalent dose of oral hydrocodone based on the total daily dose of the current opioid using Table 1; 30 mg total daily dose of oxymorphone x 1.5 = 45 mg of oral hydrocodone daily. The daily dose should then be divided in half for administration every 12 hours, which would give 22.5 mg.
- Step 3: Round down to the appropriate VANTRELA ER tablet strengths available, which in this example would be VANTRELA ER 15 mg every 12 hours.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to VANTRELA ER.

Conversion from Methadone to VANTRELA 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 VANTRELA ER

VANTRELA ER treatment may be initiated 18 hours following the removal of the transdermal fentanyl patch. Although there has been no systematic assessment of such conversion and there is limited experience with this conversion, a conservative hydrocodone dose, approximately 15 mg every 12 hours of VANTRELA ER, should be used initially.

2.3 Dosage Modifications in Patients with Mild or Moderate Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. In patients with mild or moderate hepatic impairment, initiate therapy with one half of the recommended initial dose followed by careful dose titration. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg. Monitor closely for adverse events such as respiratory depression. VANTRELA ER is not recommended in patients with severe hepatic impairment *[see Hepatic Impairment (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Dosage Modifications in Patients with Moderate or Severe Renal Impairment or End Stage Renal Disease

Patients with moderate or severe renal impairment or end stage renal disease may have higher plasma concentrations than those with normal renal function. Initiate therapy with one half of the recommended initial dose of VANTRELA ER and titrate carefully. No adjustment in starting dose is required for patients with mild renal impairment. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg. Monitor all patients with renal impairment closely for adverse events such as respiratory depression *[see Renal Impairment (8.7) and Clinical Pharmacology (12.3)]*.

2.5 Titration and Maintenance of Therapy

Individually titrate VANTELA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving VANTELA 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, or 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 opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of VANTRELA 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 VANTRELA ER dosage.

Because steady-state plasma concentrations are achieved within four days, the dose of VANTRELA ER can be increased from the current dose to the next higher dose every 3 to 7 days as needed until adequate pain relief and acceptable adverse reactions have been achieved.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.6 Discontinuation of VANTRELA ER

When a patient no longer requires therapy with VANTRELA ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue VANTRELA ER *[see Warnings and Precautions (5.12), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

VANTRELA ER is available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg extended-release tablets.

- 15 mg: Light red capsule-shaped tablets, debossed with C on one side and 15 on the other.
- 30 mg: Yellow capsule-shaped tablets, debossed with C on one side and 30 on the other.
- 45 mg: White to off-white capsule-shaped tablets, debossed with C on one side and 45 on the other.
- 60 mg: Light blue capsule-shaped tablets, debossed with C on one side and 60 on the other.
- 90 mg: Light green capsule-shaped tablets, debossed with C on one side and 90 on the other.

4 CONTRAINDICATIONS

VANTRELA ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity (e.g., anaphylaxis) to hydrocodone bitartrate or any other ingredients in VANTRELA ER *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

VANTRELA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, VANTRELA ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as VANTRELA 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 hydrocodone present *[see Drug Abuse and Dependence (9)]*.

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

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing VANTRELA ER, and monitor all patients receiving VANTRELA 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 addiction or abuse) 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 opioids such as VANTRELA ER, but use in such patients necessitates intensive counseling about the risks and proper use of VANTRELA ER along with intensive monitoring for signs of addiction, abuse, and misuse. Abuse or misuse of VANTRELA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing VANTRELA 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 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 VANTRELA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression when initiating therapy with and following dosage increases of VANTRELA ER.

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

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of VANTRELA 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of VANTRELA ER with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of hydrocodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of VANTRELA ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in VANTRELA ER-treated patients may increase hydrocodone plasma concentrations and prolong opioid adverse reactions. When using VANTRELA ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in VANTRELA ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of VANTRELA ER until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of VANTRELA ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease hydrocodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using VANTRELA ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid

dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of VANTRELA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when VANTRELA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.6 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease and in Elderly, Cachectic, or Debilitated Patients

The use of VANTRELA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: VANTRELA ER -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of VANTRELA ER *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating VANTRELA ER and when VANTRELA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.5)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.8 Severe Hypotension

VANTRELA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume or concurrent administration of certain CNS depressants (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of VANTRELA ER. In patients with circulatory shock, VANTRELA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of VANTRELA ER in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure as can be caused by certain brain tumors), VANTRELA ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with VANTRELA ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of VANTRELA ER in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

VANTRELA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The hydrocodone in VANTRELA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

The hydrocodone in VANTRELA ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during VANTRELA ER therapy.

5.12 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a course of therapy with a full opioid agonist analgesic, including VANTRELA ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing VANTRELA ER, gradually taper the dosage *[see Dosage and Administration (2.6)]*. Do not abruptly discontinue VANTRELA ER *[see Drug Abuse and Dependence (9.3)]*.

5.13 Risks of Driving and Operating Machinery

VANTRELA ER may impair the mental and 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 VANTRELA ER and know how they will react to the medication.

5.14 Risk of QTc Interval Prolongation

QTc prolongation has been observed with VANTRELA ER *[see Clinical Pharmacology (12.2)]*. Consider this observation when making clinical decisions regarding monitoring of patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. Avoid use of VANTRELA ER in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider changing to an alternate analgesic. Do not exceed a dose of 90 mg every 12 hours (180 mg per day). Higher doses have not been studied.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed 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 Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Withdrawal *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials 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 clinical practice.

The safety of VANTRELA ER was evaluated in 1176 patients who were enrolled in two double-blind clinical trials and in two open-label studies. The adverse drug reactions (reported in ≥2% of patients) by preferred term during the titration period and/or the post-titration treatment period of the two double-blind studies by treatment group are shown on Table 2.

Table 2: Adverse Drug Reactions (Reported in ≥2% of Patients) by Preferred Term and Treatment Group During the Titration Period and/or Double-Blind Post-Titration Treatment Period in Studies 1 and 2

	Titration Period*	**Double-Blind Treatment Period**	
MedDRA 16.0 preferred term	**VANTRELA ER N=1012 n (%)**	**Placebo N=326 n (%)**	**VANTRELA ER N=337 n (%)**
Nausea	168 (17)	23 (7)	39 (12)
Constipation	152 (15)	15 (5)	46 (14)
Headache	85 (8)	16 (5)	21 (6)
Somnolence	81 (8)	3 (<1)	9 (3)
Vomiting	64 (6)	11 (3)	17 (5)
Dizziness	55 (5)	5 (2)	5 (1)
Pruritus	50 (5)	3 (<1)	5 (1)
Fatigue	32 (3)	4 (1)	7 (2)

	Titration Period*	Double-Blind Treatment Period	
MedDRA 16.0 preferred term	**VANTRELA ER N=1012 n (%)**	**Placebo N=326 n (%)**	**VANTRELA ER N=337 n (%)**
Dry mouth	26 (3)	2 (<1)	5 (1)
Diarrhea	22 (2)	10 (3)	12 (4)
Insomnia	18 (2)	9 (3)	4 (1)
Anxiety	7 (<1)	5(2)	13 (4)

Patients are counted only once in each preferred term category.
* Titration Period includes all patients who started the open-label titration for the 2 double-blind studies (Studies 1 and 2), regardless if they entered the Double-Blind Treatment Period or not.

The common (≥1% to <10%) adverse drug reactions reported at least once by patients treated with VANTRELA ER in all four Phase 3 clinical trials (N=1176) and not represented in Table 2 were:

Ear and Labyrinth Disorders: Tinnitus

Gastrointestinal Disorders: Abdominal pain; Abdominal pain upper; Dyspepsia; Gastroesophageal reflux disorder

General Disorders and Administration Site Conditions: Edema peripheral; Pyrexia

Infections and Infestations: Bronchitis; Sinusitis; Upper respiratory tract infection; Urinary tract infection

Injury, Poisoning and Procedural Complications: Contusion; Fall

Musculoskeletal and Connective Tissue Disorders: Arthralgia; Back pain; Muscle spasm; Musculoskeletal pain; Neck pain; Pain in extremity

Nervous System Disorders: Lethargy; Sedation; Tremor

Psychiatric Disorders: Depression

Respiratory, Thoracic, and Mediastinal Disorders: Cough

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

Vascular Disorders: Hot flush

Other important rare (<1%) adverse drug reactions reported at least once by patients treated with VANTRELA ER in all Phase 3 clinical trials were:

Gastrointestinal Disorders: Intestinal obstruction, Pancreatitis

Immune System Disorders: Drug hypersensitivity

Respiratory, Thoracic, and Mediastinal Disorders: Respiratory depression

Skin and Subcutaneous Tissue Disorders: Erythema

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of hydrocodone. 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.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in VANTRELA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with VANTRELA ER.

Table 3: Clinically Significant Drug Interactions with VANTRELA ER

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of VANTRELA ER and CYP3A4 inhibitors can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of VANTRELA ER and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of VANTRELA ER is achieved *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of VANTRELA ER until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the VANTRELA ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of VANTRELA ER and CYP3A4 inducers can

	decrease the plasma concentration of hydrocodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the VANTRELA ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider VANTRELA ER dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacological effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.2)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue VANTRELA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2).*
Intervention:	The use of VANTRELA ER is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	

Clinical Impact:	May reduce the analgesic effect of VANTRELA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Hydrocodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of VANTRELA ER and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when VANTRELA ER is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data on VANTRELA ER use in pregnant women to inform any drug associated risks. In animal toxicology studies, hydrocodone administered to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicities including increased post-implantation loss and non-viable litters at doses approximately 2 fold the human hydrocodone dose of 180 mg/day. In another study, decreases in survival were seen in the offspring of rats administered hydrocodone during gestation and lactation at doses equivalent to the human dose of 180 mg/day. Additionally, in these rats increased post-implantation loss and decreased body weights of the pups from birth through weaning was seen at doses of hydrocodone 3 fold the human hydrocodone dose of 180 mg/day. No teratogenicity was observed in the offspring of rats and rabbits administered oral hydrocodone during the period of organogenesis at doses in both species 5 fold the human dose of 180 mg/day. Advise pregnant women of the potential risks to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse

outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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. 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. VANTRELA ER is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including VANTRELA ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Oral doses of hydrocodone were administered to pregnant rats and rabbits during the period of organogenesis. In rats, embryo-fetal toxicities including increased post-implantation loss and non-viable litters were observed at doses of 33 mg/kg and above (approximately 2 fold the human hydrocodone dose of 180 mg/day based on body surface area comparisons). Maternal toxicity (body weight loss) was present in the study at all doses. In rabbits, no adverse effects on embryo-fetal development were observed at doses up to 48 mg/kg (approximately 5 fold the human hydrocodone dose of 180 mg/day based on body surface area comparisons). No evidence of teratogenicity was observed in either study at doses up to 100 mg/kg in rat and 48 mg/kg in rabbit (approximately 5 fold for both rats and rabbits the human hydrocodone dose of 180 mg/day based on body surface area exposure comparisons).

Hydrocodone was administered orally to female rats during gestation and lactation in a pre- and post-natal development study. Decreases in pup survival at doses of 20 mg/kg and above (equivalent to the human hydrocodone dose of 180 mg/day, based on body surface area comparisons). Increased post-implantation loss and decreased body weights of the F1 generation pups from birth through weaning were seen at 60 mg/kg/day (3 fold the human hydrocodone dose of 180 mg/day, based on body surface area comparisons). Maternally toxic decreases in body weight were also observed at these doses.

8.2 Lactation

Risk Summary

Hydrocodone is present in human milk. Lactation studies have not been conducted with extended-release hydrocodone, including VANTRELA ER, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with VANTRELA ER.

Clinical Considerations

Monitor infants exposed to VANTRELA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

In animal studies, male rats treated with hydrocodone bitartrate at 3.2 times the human daily dose of 180 mg demonstrated decreased epididymides weights and male rats treated with 1 times the human daily dose demonstrated decreased latency to mating. Female rats treated with 1 times the human daily dose of 180 mg demonstrated decreased corpora lutea and at 3.2 times the human daily dose of 180 mg decreased implantation sites *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of VANTRELA ER in patients less than 18 years of age has not been established.

8.5 Geriatric Use

There were no dedicated studies to assess efficacy, safety or PK for the geriatric population. However, when the safety of VANTRELA ER was compared in the phase 3 double-blind studies in patients ≤65 (n=986) and >65 (N=190) years old, there was a higher incidence of adverse events in patients >65 years of age compared with those ≤65 years of age for both the placebo and VANTRELA ER groups. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of VANTRELA ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.6)]*.

Hydrocodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal hepatic function. Therefore, a dosage reduction is recommended in patients with mild and moderate hepatic impairment *[see Dosage and Administration (2.3)]*. VANTRELA ER is not recommended in patients with severe hepatic impairment. Monitor these patients closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No adjustment in starting dose with VANTRELA ER is required for patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease may have higher plasma concentrations than those with normal renal function. Therefore, a dosage reduction is recommended in patients with moderate or severe renal impairment, or end stage renal disease *[see Dosage and Administration (2.4)]*. Monitor all patients closely for adverse events such as respiratory depression, sedation, and hypertension *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VANTRELA ER contains hydrocodone bitartrate, a Schedule II controlled substance.

9.2 Abuse

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

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

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: 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 in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other healthcare provider(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. Healthcare providers 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.

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

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

Risks Specific to Abuse of VANTRELA ER

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

With intravenous abuse the inactive ingredients in VANTRELA ER can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, 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

VANTRELA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that VANTRELA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When VANTRELA ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.

Pharmacokinetics of Manipulated Tablets

The pharmacokinetic profile of manipulated VANTRELA ER tablet contents was characterized following oral and intranasal administration. The studies were conducted in a randomized, cross-over design and are described in the section on Clinical Abuse Potential Studies. In the oral study assessing manipulation by crushing, the most effective crushing method identified in previous in vitro studies was applied to the product(s). For the intranasal study, VANTRELA ER tablets were manipulated to produce a powder suitable for nasal insufflation.

Oral Pharmacokinetic Data

The effect of product manipulation (crushing) on VANTRELA ER pharmacokinetics was measured in an oral clinical abuse potential study. VANTRELA ER tablets were crushed prior to oral administration in healthy, nondependent recreational opioid users. The two comparators in this study were intact VANTRELA ER tablets and an immediate-release hydrocodone powder.

The pharmacokinetic data displayed in Table 4 illustrate the findings from this study. The data demonstrated that crushing VANTRELA ER tablets prior to administration increased the maximum observed plasma concentration (C_{max}) but not the total exposure ($AUC_{0\text{-}inf}$) relative to dosing the intact product. Relative to immediate-release hydrocodone, the C_{max} for all VANTRELA ER treatments was significantly lower and the T_{max} significantly longer, consistent with an extended-release profile.

Table 4: Hydrocodone Pharmacokinetic Parameters, Oral Administration (45 mg)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*ng/mL)
45 mg Vantrela ER intact	28.77 (6.1)	7.1 (6.1 - 12.0)	584 (124.8)
45 mg Vantrela ER finely crushed	40.78 (10.2)	4.0 (1.8 - 7.0)	586 (138.5)
45 mg immediate-release hydrocodone powder	91.46 (16.8)	0.8 (0.3 - 4.1)	625 (137.3)

Values shown for C_{max} and $AUC_{0\text{-}inf}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Data

The pharmacokinetic profile following intranasal administration of manipulated VANTRELA ER tablet contents was characterized in a nasal clinical abuse potential study. VANTRELA ER tablets were finely milled and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. Two comparators in this study were intact VANTRELA ER tablets (oral) and immediate-release hydrocodone powder (intranasal) at an equivalent dose.

The results of the study demonstrated that intranasal administration of manipulated VANTRELA ER tablet contents resulted in higher peak plasma concentration (C_{max}) and shorter time to peak concentration (T_{max}) than taking VANTRELA ER orally and lower C_{max} and longer T_{max} then taking hydrocodone powder intranasally. The pharmacokinetic data from this nasal clinical abuse potential study are displayed in Table 5 to represent these findings.

Table 5: Hydrocodone Pharmacokinetic Parameters, Nasal and Oral Administration

Treatment	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*ng/mL)
45 mg intact Vantrela ER Tablets (oral)	25.05 (7.18)	9.11 (4.10 -12.12)	568 (172)
45 mg Vantrela ER finely milled (nasal)	56.84 (15.1)	2.62 (1.33 - 7.02)	572 (150)
45 mg immediate-release hydrocodone powder (nasal)	71.28 (30.5)	1.38 (0.60 - 7.07)	579 (163)

Values shown for C_{max} and $AUC_{0\text{-}inf}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Abuse Potential Studies

Two randomized, double-blind active- and placebo-controlled studies were conducted in non-dependent opioid abusers to characterize the abuse potential of oral or intranasal administration of VANTRELA ER following physical manipulation. For both studies, 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 Drug Again was measured on a bipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again"), 50 represents a neutral response, and 100 represents the strongest positive response ("definitely would take drug again").

Oral Abuse Potential Study

In a randomized, double-blind, placebo- and active-controlled, 4-period crossover study in non-dependent opioid abusers, 35 of the 49 enrolled subjects completed all treatment conditions: 45 mg VANTRELA ER (intact), 45 mg VANTRELA ER (finely crushed), 45 mg hydrocodone bitartrate powder (immediate release (IR) condition), and placebo.

The oral administration of finely crushed VANTRELA ER was associated with statistically significantly lower mean scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 6.

Table 6: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Oral Administration

Measure	**Statistic**	**Placebo (N=35)**	**Hydrocodone IR 45 mg (N=35)**	**VANTRELA ER 45 mg (finely crushed) (N=35)**	**VANTRELA ER 45 mg (intact) (N = 35)**
Drug Liking	Mean (SE)	53.4 (1.80)	85.0 (2.31)	65.6 (2.46)	54.5 (1.02)

Measure	Statistic	Placebo (N=35)	Hydrocodone IR 45 mg (N=35)	VANTRELA ER 45 mg (finely crushed) (N=35)	VANTRELA ER 45 mg (intact) (N = 35)
	Median (Range)	51.0 (50-100)	88.0 (50-100)	60.0 (50-98)	51.0 (50-70)
Take Drug Again	Mean (SE)	46.3 (2.88)	75.1 (3.04)	55.9 (3.53)	48.5 (2.77)
	Median (Range)	50.0 (0-98)	74.0 (42-100)	56.0 (2-97)	50.0 (1-100)

Intranasal Abuse Potential Study

In a randomized, double-blind, placebo-and active-controlled, 5-period crossover study in non-dependent opioid abusers, 34 of the 45 subjects enrolled completed all treatment conditions: intranasal administration of 45 mg VANTRELA ER (finely milled), intranasal administration of 45 mg hydrocodone bitartrate powder (immediate release condition), oral administration of 45 mg VANTRELA ER (intact), and intranasal administration of placebo.

The intranasal administration of finely milled VANTRELA ER was associated with statistically significantly lower mean and median scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone administered intranasally, as summarized in Table 7.

Table 7: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal Insufflation

Measure	Statistic	Placebo IN (N=34)	Hydrocodone IR 45 mg (N=34)	VANTRELA ER 45 mg Finely Milled (N=34)
Drug Liking	Mean (SE)	58.6 (1.94)	80.2 (2.16)	72.8 (2.35)
	Median (Range)	52.0 (50-90)	79.0 (57-100)	72.5 (50-100)
Take Drug Again	Mean (SE)	56.4 (2.13)	75.5 (2.57)	67.5 (3.45)
	Median (Range)	50.0 (34-90)	76.5 (43-100)	67.0 (30-100)

Summary

The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to make intravenous abuse difficult. The data from the in vitro studies and clinical abuse potential studies indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route and the intranasal route. However, abuse of VANTRELA ER by the intravenous, nasal, and oral routes is still possible.

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

VANTRELA ER contains hydrocodone bitartrate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. VANTRELA 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 dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

VANTRELA ER should not be abruptly discontinued *[see Dosage and Administration (2.6)]*. If VANTRELA ER is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, 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 symptoms *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with VANTRELA 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 *[see Clinical Pharmacology (12.2)]*.

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 and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

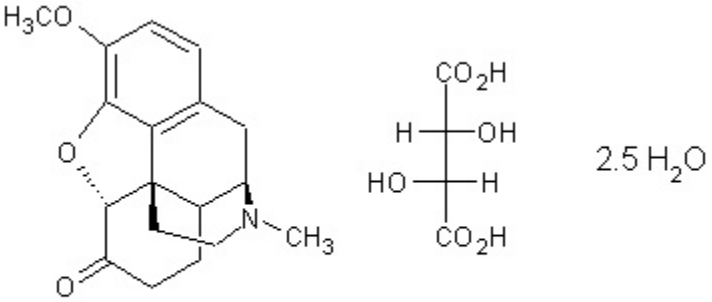
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydrocodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically-significant respiratory or circulatory depression secondary to hydrocodone overdose.

Because the duration of reversal would be expected to be less than the duration of action of hydrocodone in VANTRELA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. VANTRELA ER will continue to release hydrocodone and add to the hydrocodone 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 recommended usual dosage 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 initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

VANTRELA ER (hydrocodone bitartrate) extended-release tablets are an opioid agonist for oral use. The tablets contain hydrocodone bitartrate, an opioid agonist. Hydrocodone bitartrate is a white to slightly yellow-white crystalline powder. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). The structural formula for hydrocodone bitartrate is provided below:



Hydrocodone bitartrate disesquihydrate (hemipentahydrate)

$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5\ H_2O$ Molecular Mass: 494.50 g/mol

VANTRELA ER (hydrocodone bitartrate) extended-release tablets contain 15 mg, 30 mg, 45 mg, 60 mg, or 90 mg of hydrocodone bitartrate.

The 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg tablets contain the following inactive ingredients: lactose monohydrate, ethyl cellulose, hypromellose, glyceryl behenate, and magnesium stearate.

The 15 mg tablets also contain red ferric oxide.

The 30 mg tablets also contain yellow ferric oxide.

The 60 mg tablets also contain FD&C Blue #2 aluminum lake.

The 90 mg tablets also contain yellow ferric oxide and FD&C Blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in two double-blind, placebo-controlled, parallel-group studies of VANTRELA ER. More patients in the group randomized to VANTRELA ER (4/337 pts; 1%) experienced a change from screening in QTcF interval >60 milliseconds than in the group randomized to placebo (1/326 pts; <1%). For clinical implications of the prolonged QTc interval, see Warnings and Precautions (5.14).

Effects on the Central Nervous System

Hydrocodone causes respiratory depression by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Hydrocodone 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 overdose situations *[see Overdosage (10)]*.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

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

Concentration—Efficacy Relationships

The minimum effective plasma concentration of hydrocodone for analgesia varies widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome, and/or potential development of analgesic tolerance*[see Dosage and Administration (2.1, 2.5)]*.

Concentration—Adverse Experience Relationships

There is a relationship between increasing hydrocodone 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 adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.5)]*.

12.3 Pharmacokinetics

As compared to immediate-release hydrocodone combination products, VANTRELA ER at similar daily doses results in similar overall exposure but lower maximum concentrations. Mean half-life following administration of VANTRELA ER (11-12 hours) is longer than that after administration of immediate-release hydrocodone combination products due to the prolonged duration of absorption.

Steady-state concentrations of hydrocodone were confirmed by day 4 of administration of VANTRELA ER every 12 hours. At steady-state, hydrocodone AUC and C_{max} are approximately 3-fold higher than after a single dose. Systemic exposure to hydrocodone following administration of VANTRELA ER increases in a dose-proportional manner over the range of 15 mg through 90 mg.

Table 8: Mean (SD) Single-Dose Pharmacokinetic Parameter Values for VANTRELA ER

Dose Strength (mg)	$AUC_{0\text{-}inf}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)*
15	199 (60)	12.6 (3.5)	7.0 (5.0, 9.0)
30	382 (118)	20.7 (5.5)	8.0 (5.0, 12.0)
45	592 (167)	30.3 (7.5)	8.0 (5.0, 12.1)
60	766 (194)	41.2 (10.1)	8.0 (5.0, 12.0)
90	1189 (341)	62.5 (16.2)	8.0 (5.0, 12.0)

*Median (minimum, maximum)

Absorption

Maximum hydrocodone plasma concentrations (T_{max}) are attained gradually with mean T_{max} of approximately 8 hours following a single dose and 5 hours at steady state.

Food Effect

Administration of a single dose of VANTRELA ER with a high fat meal increases mean peak plasma drug concentrations (C_{max}) by approximately 34% to 45%. At steady-state, C_{max} was approximately 14% higher with a high fat meal. Food has no notable impact on the area under the plasma drug concentration versus time curve (AUC) either following a single dose or at steady-state.

Distribution

Hydrocodone is well distributed beyond the vascular system with an apparent volume of distribution of approximately 1300-1400 L following administration of VANTRELA ER.

Although the extent of protein binding of hydrocodone in human plasma was not determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Elimination

Metabolism

Hydrocodone is known to undergo N-demethylation, O-demethylation, and 6-ketoreduction. N-demethylation occurs via the CYP3A4 pathway to form norhydrocodone. The O-demethylation step occurs via the CYP2D6 pathway to form an active metabolite, hydromorphone. Following administration of VANTRELA ER, hydromorphone plasma concentrations are approximately 1%-2% of those of hydrocodone. Given the involvement of CYP3A4, drugs known to inhibit or induce this enzyme could alter the metabolic profile of hydrocodone *[see Warnings and Precautions (5.12) and Drug Interactions (7.2)]*.

Excretion

Hydrocodone and its metabolites are eliminated primarily in the urine, with a mean apparent plasma half-life after administration of VANTRELA ER of approximately 11-12 hours.

Specific Populations

Sex

Systemic exposure of hydrocodone (C_{max} and AUC) was similar between males (n=325) and females (n=168).

Race

Systemic exposure (as assessed by AUC and C_{max}) was comparable in Caucasian subjects (n=349) and in subjects of other races (n=144).

Hepatic Impairment

In subjects with moderate hepatic impairment (n=8; Child-Pugh classification (CPC) score of 7-9 points), overall systemic exposure to hydrocodone (as assessed by AUC) was approximately 70% higher and C_{max} was approximately 30% higher following a single dose of VANTRELA ER as compared to subjects with normal hepatic function (n=8). Subjects with severe hepatic impairment were not studied.

Renal Impairment

The pharmacokinetics of VANTRELA ER were evaluated in healthy subjects with normal renal function (n=13 subjects with normal renal function [creatinine clearance >80 mL/min]) and compared with patients with mild (n=8; creatinine clearance >50-80 mL/min), moderate (n=9; Creatinine clearance 30-50 mL/min**)**, and severe renal impairment (n=9 Creatinine clearance <30 mL/min**)** or patients with end-stage renal disease (ESRD) undergoing hemodialysis. Patients with mild renal impairment did not show significant difference in C_{max} and AUC of hydrocodone

compared to healthy subjects. Overall systemic exposure to hydrocodone (as assessed by AUC) was up to approximately 70% higher following administration of a single dose of VANTRELA ER to subjects with moderate or severe renal impairment as compared to healthy subjects. Mean peak concentrations were approximately 25% and 50% higher in patients with moderate and severe renal impairment, respectively compared to healthy subjects. Patients with ESRD undergoing hemodialysis after VANTRELA ER administration had similar exposure compared to healthy subjects.

Drug Interaction Studies

No formal drug-drug interaction studies have been performed with VANTRELA ER. Given the involvement of CYP3A4, drugs known to inhibit or induce this enzyme could alter the metabolic profile of hydrocodone *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Hydrocodone was evaluated for carcinogenic potential in rats and mice. In a two-year bioassay in rats, doses up to 30 mg/kg in males and 100 mg/kg in females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.06 times and 0.4 times for males and females, respectively the human hydrocodone dose of 180 mg/day based on AUC exposure comparisons). In a two-year bioassay in mice, doses up to 100 mg/kg in males and females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.6 times and 1.1 times, respectively, the human hydrocodone dose of 180 mg/day based on AUC exposure comparisons.

Mutagenesis

Clastogenicity was observed with hydrocodone in the chromosomal aberration assay in human lymphocytes. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an *in vivo* assay for chromosomal aberrations (mouse bone marrow micronucleus assay).

Impairment of Fertility

In a fertility and general reproductive performance study, rats were administered doses of 0 (vehicle), 7, 20 and 60 mg/kg/day (equivalent to approximately 0.4, 1.1 and 3.2 times an adult human dose of 180 mg/day on a mg/m^2 basis). Male and female rats were dosed prior to cohabitation (28 and 14 days, respectively), during cohabitation and through gestation day 6 (implantation). Females were treated for at least 20 days while males received at least 42 daily doses prior to necropsy. Treated males were mated with untreated females and treated females were mated with untreated males. Overall mating performance was unaffected by treatment with hydrocodone bitartrate, although the weights of male and female reproductive organs were decreased in males and females treated with 20 and 60 mg/kg. Additionally, the latency to mate was increased in the 20 and 60 mg/kg treated males. In the pregnant females, early embryonic development was not affected by treatment with hydrocodone bitartrate at doses up to 60 mg/kg (approximately 3.2 times the adult human daily dose of 180 mg/day on a mg/m^2 basis).

14 CLINICAL STUDIES

The efficacy and safety of VANTRELA ER have been evaluated in a randomized double-blind, placebo-controlled, multi-center clinical trial in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain who required continuous opioid treatment for an extended period of time.

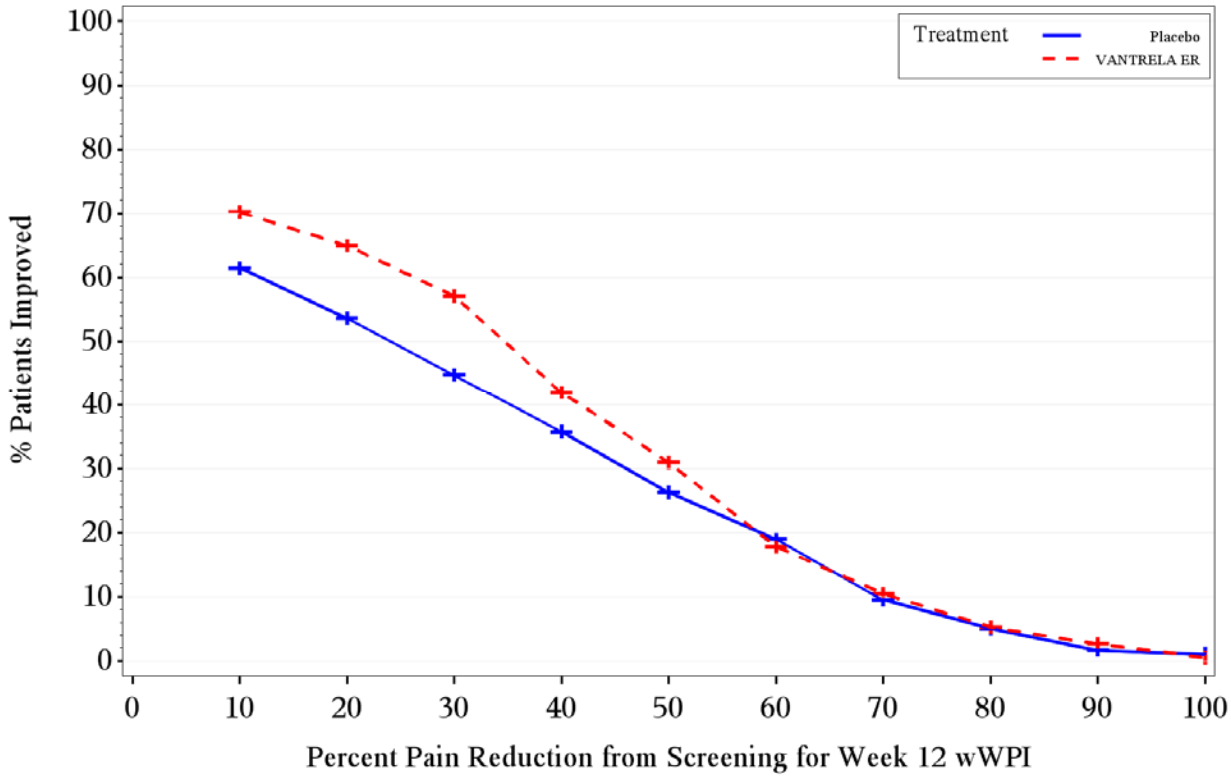
The study consisted of a 6-week open-label titration period followed by a 12-week double-blind treatment period. Opioid-naïve patients initiated VANTRELA ER therapy at the dose 15 mg every 12 hrs. Opioid-experienced patients initiated VANTRELA ER therapy at a dose of hydrocodone that was approximately equivalent to 50% of the dosage of their pre-study opioid medication using a conversion table *[see Dosage and Administration (2.2)]*. Opioid-naïve patients were defined as those taking tramadol or less than 10 mg per day of oxycodone or equivalent during the 14 days before study entry. Opioid-experienced patients were defined as those taking 10 mg or more per day of oxycodone or equivalent but not more than a total of 135 mg/day of oxycodone or equivalent during the 14 days before study entry.

During the open-label titration, the VANTRELA ER dose was titrated by 15 mg increments every 12 hours when titrating from 15 to 30 mg, 30 to 45 mg, and 45 to 60 mg and 30 mg increment when titrating from 60 to 90 mg) every 3 to 7 days until a successful dose was identified, or a maximum dose of 90 mg every 12 hours was reached. A successful dose was defined as having no unacceptable adverse events and achieving an average pain intensity score over the previous 24 hours of 4 or less and a worst pain intensity (WPI) score of 6 or less on an 11-point numerical rating scale (NRS) for either 4 consecutive days or 4 out of 7 consecutive days without exceeding the allowed total daily dosage of rescue medication (immediate-release hydrocodone 5 mg/acetaminophen 325 mg up to 2 doses). Patients who achieved a successful dose of 30 mg to 90 mg were randomly (1:1 ratio) assigned to continue receiving the successful dose of VANTRELA ER or matching placebo during the 12-week double-blind treatment period. A stepwise, double-blind tapering schedule was implemented during the first 2 weeks of the 12-week, double-blind, placebo-controlled period in patients randomly assigned to placebo.

A total of 625 patients (mean age = 51.7 [range 19.0-80.0]; 46% male and 54% female) with moderate to severe chronic low back pain were enrolled in the open-label titration period. Of the 625 patients enrolled, 371 (60%) patients achieved a successful dose and were randomized to remain on VANTRELA ER (191 patients) or to receive placebo (180 patients) during the double-blind treatment period. A total of 277 of the 370 (75%) patients completed the study (VANTRELA ER 147 (77%) patients and placebo 130 (72%) patients). The mean age of these patients was 52 years (range 20 to 80 years). The majority (71%) of these patients was white, and the percentages of men and women were similar (49% men and 51% women). Patients discontinued from the dose-titration period for the following reasons: adverse events (11%); lack of efficacy (5%); consent withdrawn (5%); protocol violation (3%): noncompliance (3%); lost to follow-up (<1%); pregnancy (<1%); not otherwise specified (12%). During the double-blind treatment period 8% of VANTRELA ER patients and 5% of placebo patients discontinued due to adverse events and 3% of VANTRELA ER and 9% of placebo patients discontinued due to lack of efficacy. VANTRELA ER provided greater relief of low back pain than placebo as measured by the weekly average of daily WPI scores (p value<0.001).

The percentage of patients in each group who demonstrated improvement in their average WPI score at week 12, as compared to Screening is shown in Figure 1 The figure is cumulative, so that the patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study treatment were classified as non-responders. The proportion of patients who had up to 30% reduction in their average WPI was higher for the VANTRELA ER treatment group compared with the placebo treatment (57% vs 45%).

Figure 1: Percentage Improvement in Average Worst Intensity (WPI) Score From Screening to Final Visit at Week 12



16 HOW SUPPLIED/STORAGE AND HANDLING

VANTRELA ER (hydrocodone bitartrate) extended-release tablets are capsule-shaped tablets, supplied in 100-count high-density polyethylene bottles with induction-sealed child-resistant (CR) closures and a desiccant. The presentations are as follows:

Strength	Tablet Color	Debossing	NDC Number
15 mg	Light red	"C" on one side and "15"on the other	63459-120-01: 100 count bottles
30 mg	Yellow	"C" on one side and "30" on the other	63459-118-01: 100 count bottles

Strength	Tablet Color	Debossing	NDC Number
45 mg	White to off-white	"C" on one side and "45" on the other	63459-122-01: 100 count bottles
60 mg	Light blue	"C" on one side and "60" on the other	63459-130-01: 100 count bottles
90 mg	Light green	"C" on one side and "90" on the other	63459-136-01: 100 count bottles

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container as defined in the USP, with a child-resistant closure.

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 VANTRELA ER, even when taken as recommended, can result in addiction which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share VANTRELA ER with others and to take steps to protect VANTRELA 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 VANTRELA ER or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Ingestion

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

Interaction with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if VANTRELA ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking VANTRELA ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking VANTRELA ER *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.7)]*.

Important Administration Instructions

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

- Swallow VANTRELA ER tablets whole. Do not crush, chew, or dissolve the tablet or its contents.
- Use VANTRELA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).
- Do not discontinue VANTRELA ER without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.6)]*.

Hypotension

Inform patients that VANTRELA 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) *[see Warnings and Precautions (5.8)]*.

QT interval prolongation

Inform patients that QT prolongation has been observed with VANTRELA ER *[see Clinical Pharmacology (12.2)]*. VANTRELA ER should be avoided in patients with congenital long QT syndrome. Instruct patients with a history of congestive heart failure or bradyarrhythmias, and patients at risk for electrolyte abnormalities, or who are taking other medications known to prolong the QT interval, that periodic monitoring of electrocardiograms and electrolytes may be necessary during therapy with VANTRELA ER *[see Warnings and Precautions (5.14)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in VANTRELA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of VANTRELA 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), Use in Specific Populations (8.1)]*.

Embryofetal Toxicity

Inform female patients of reproductive potential that VANTRELA ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with VANTRELA ER *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that VANTRELA 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 *[see Warnings and Precautions (5.13)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused VANTRELA ER

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

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Medication Guide
VANTRELA ™ ER (van- tre'- lah E-R)
(hydrocodone bitartrate) extended-release tablets, CII

VANTRELA 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 VANTRELA ER:

- **Get emergency help right away if you take too much VANTRELA ER (overdose).** When you first start taking VANTRELA 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.
- Taking VANTRELA ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your VANTRELA ER. They could die from taking it. Store VANTRELA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away VANTRELA ER is against the law.

Do not take VANTRELA ER if you have:

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

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

- head injury, seizures
- problems urinating
- heart rhythm problems (long QT syndrome)
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

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

When taking VANTRELA ER:

- Do not change your dose. Take VANTRELA ER exactly as prescribed by your healthcare provider. Use the lowest dose for the shortest duration needed.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Swallow VANTRELA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject VANTRELA 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 VANTRELA ER without talking to your healthcare provider.**
- After you stop taking VANTRELA ER, flush any unused VANTRELA ER tablets down the toilet.

While taking VANTRELA ER DO NOT:

- Drive or operate heavy machinery, until you know how VANTRELA ER affects you. VANTRELA 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 VANTRELA ER may cause you to overdose and die.

The possible side effects of VANTRELA ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. 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, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of VANTRELA 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**

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