資料３－② タペンタドール（tapentadol）

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRADENAME™ safely and effectively. See full prescribing information for TRADENAME™.

TRADENAME™ (tapentadol) immediate release oral tablets
Initial U.S. Approval : 2008

----------INDICATIONS AND USAGE----------

TRADENAME™ is an opioid analgesic indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. (1)

----------DOSAGE AND ADMINISTRATION----------

- As with many centrally-acting analgesic medications, the dosing regimen of TRADENAME™ should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to monitor the patient. (2)
- Initiate TRADENAME™ with or without food at a dose of 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 50 mg, 75 mg, 100 mg (3)

----------CONTRAINDICATIONS----------

- Impaired pulmonary function (significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment) (4.1)
- Paralytic ileus (4.2)
- Concomitant use with monoamine oxidase inhibitors (MAOI) or use within 14 days (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.1)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.2)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, other intracranial lesions. (5.3)
- Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.4)
- Impaired mental/physical abilities. Caution must be used with potentially hazardous activities. (5.5)
- Seizures: Use with caution in patients with a history of seizures. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic administration. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse events were nausea, dizziness, vomiting and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Use TRADENAME™ with caution in patients currently using specified centrally-acting drugs or alcohol. (7.3)
- Do not use TRADENAME™ in patients currently using or within 14 days of using a monoamine oxidase inhibitor (MAOI). (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Labor and delivery: should not use during and immediately prior to labor and delivery. Monitor neonates, whose mothers have been taking TRADENAME™, for respiratory depression. (8.2)
- Nursing mothers: should not breast-feed. (8.3)
- Pediatric use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
- Renal or hepatic impairment: not recommended in patients with severe renal or hepatic impairment. Use with caution in patients with moderate hepatic impairment. (8.6, 8.7)
- Elderly: care should be taken when selecting an initial dose. (2.3)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 11/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

[*Sections or subsections omitted from the full prescribing information are not listed]

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRADENAME™ is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

2 DOSAGE AND ADMINISTRATION

As with many centrally-acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to monitor the patient.

The dose is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity.

On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.

Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are not recommended.

TRADENAME™ may be given with or without food *[see Clinical Pharmacology (12.3)]*.

2.1 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*.

TRADENAME™ has not been studied in patients with severe renal impairment. The use in this population is not recommended.

2.2 Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

TRADENAME™ should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg with the interval between doses no less than every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval *[see Clinical Pharmacology (12.3)]*.

TRADENAME™ has not been studied in patients with severe hepatic impairment and use in this population is not recommended *[see Warnings and Precautions (5.10)]*.

2.3 Elderly Patients

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.

3 DOSAGE FORMS AND STRENGTHS

TRADENAME™ Tablets are round, biconvex and film-coated and are available in the following strengths, colors, and debossings: 50 mg of tapentadol (yellow with "O-M" on one side and "50" on the other side), 75 mg of tapentadol (yellow-orange with "O-M" on one side and "75" on the other side), and 100 mg of tapentadol (orange with "O-M" on one side and "100" on the other side).

4 CONTRAINDICATIONS

4.1 Impaired Pulmonary Function

Like other drugs with mu-opioid agonist activity, TRADENAME™ is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment. TRADENAME™ is also contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment *[see Warnings and Precautions (5.1)]*.

4.2 Paralytic Ileus

Like drugs with mu-opioid agonist activity, TRADENAME™ is contraindicated in any patient who has or is suspected of having paralytic ileus.

4.3 Monoamine Oxidase Inhibitors

TRADENAME™ is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Drug Interactions (7.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.

TRADENAME™ should be administered with caution to patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma. In such patients, even usual therapeutic doses of TRADENAME™ may increase airway resistance and decrease respiratory

drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and TRADENAME™ should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression *[see Overdosage (10.2)]*.

5.2 CNS Depression

Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with TRADENAME™ may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with TRADENAME™. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

5.3 Head Injury and Increased Intracranial Pressure

Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, TRADENAME™ should not be used in patients who may be susceptible to the effects of raised cerebrospinal fluid pressure such as those with evidence of head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. TRADENAME™ should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.

5.4 Misuse and Abuse

Tapentadol is a mu-opioid agonist. Such drugs are sought by drug abusers and people with addiction disorders.

TRADENAME™ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing TRADENAME™ in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction, since use of mu-opioid agonist analgesic products carry the risk of addiction even under appropriate medical use *[see Drug Abuse and Dependence (9.2)]*.

TRADENAME™ may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9)]*.

5.5 Driving and Operating Machinery

Patients should be cautioned that TRADENAME™ may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any

change of dosage as well as in combination with alcohol or tranquilizers *[see Drug Interactions (7.3)]*.

5.6 Interactions with Alcohol and Drugs of Abuse

Due to its mu-opioid agonist activity, TRADENAME™ may be expected to have additive effects when used in conjunction with alcohol, opioids, or illicit drugs that cause central nervous system depression, respiratory depression, hypotension, and profound sedation, coma or death *[see Drug Interactions (7.3)]*.

5.7 Seizures

TRADENAME™ has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. TRADENAME™ should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

5.8 Serotonin Syndrome Risk

The development of a potentially life-threatening serotonin syndrome may occur with use of Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) products, including TRADENAME™, particularly with concomitant use of serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans, and with drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose. Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

5.9 Withdrawal

Withdrawal symptoms may occur if TRADENAME™ is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering TRADENAME™ *[see Drug Abuse and Dependence (9.3)]*.

5.10 Hepatic Impairment

A study of TRADENAME™ in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. TRADENAME™ should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

TRADENAME™ has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended.

5.11 Use in Pancreatic/Biliary Tract Disease

Like other drugs with mu-opioid agonist activity, TRADENAME™ may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

6 ADVERSE REACTIONS

The following treatment-emergent adverse events are discussed in more detail in other sections of the labeling:

- Respiratory Depression *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*
- CNS Depression *[see Warnings and Precautions (5.2)]*

Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Based on data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled and one Phase 3 active-controlled safety study) the most common adverse events (reported by ≥10% in any TRADENAME™ dose group) were: nausea, dizziness, vomiting and somnolence.

The most common reasons for discontinuation due to adverse events in the studies described above (reported by ≥1% in any TRADENAME™ dose group) were dizziness (2.6% vs. 0.5%), nausea (2.3% vs. 0.6%), vomiting (1.4% vs. 0.2%), somnolence (1.3% vs. 0.2%) and headache (0.9% vs. 0.2%) for TRADENAME™- and placebo-treated patients, respectively.

Seventy-six percent of TRADENAME™-treated patients from the nine studies experienced adverse events.

TRADENAME™ was studied in multiple-dose, active- or placebo-controlled studies, or noncontrolled studies (n = 2178), in single-dose studies (n = 870), in open-label study extension (n = 483) and in Phase 1 studies (n = 597). Of these, 2034 patients were treated with doses of 50 mg to 100 mg of TRADENAME™ dosed every 4 to 6 hours.

The data described below reflect exposure to TRADENAME™ in 3161 patients, including 449 exposed for 45 days. TRADENAME™ was studied primarily in placebo- and active-controlled studies (n = 2266, and n = 2944, respectively). The population was 18 to 85 years old (mean age 46 years), 68% were female, 75% white and 67% were postoperative. Most patients received TRADENAME™ doses of 50 mg, 75 mg, or 100 mg every 4 to 6 hours.

6.1 Commonly-Observed Treatment-Emergent Adverse Events in Double-Blind Controlled Clinical Trials

Table 1 lists the adverse events reported in ≥1% or more of TRADENAME™-treated patients with acute moderate to severe pain in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study).

Table 1 Treatment-Emergent Adverse Events* Reported by ≥1% of TRADENAME™-Treated Patients In Seven Phase 2/3 Placebo- and/or Oxycodone-Controlled, One Noncontrolled, and One Phase 3 Oxycodone-Controlled Safety, Multiple-Dose Clinical Studies

System/Organ Class MedDRA Preferred Term	TRADENAME™ 21 mg – 120 mg (n=2178) %	Placebo (n=619) %
Gastrointestinal disorders		
Nausea	30	13
Vomiting	18	4
Constipation	8	3
Dry mouth	4	<1
Dyspepsia	2	<1
General disorders and administration site conditions		
Fatigue	3	<1
Feeling hot	1	<1
Infections and infestations		
Nasopharyngitis	1	<1
Upper respiratory tract infection	1	<1
Urinary tract infection	1	<1
Metabolism and nutrition disorders		
Decreased appetite	2	0
Musculoskeletal and connective tissue disorders		
Arthralgia	1	<1
Nervous system disorders		
Dizziness	24	8
Somnolence	15	3
Tremor	1	<1
Lethargy	1	<1
Psychiatric disorders		
Insomnia	2	<1
Confusional state	1	0
Abnormal dreams	1	<1
Anxiety	1	<1
Skin and subcutaneous tissue disorders		
Pruritus	5	1
Hyperhidrosis	3	<1
Pruritus generalized	3	<1
Rash	1	<1
Vascular disorders		
Hot flush	1	<1

* A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

6.2 Other Adverse Reactions Observed During the Premarketing Evaluation of TRADENAME™

The following adverse drug reactions occurred in <1% of TRADENAME™-treated patients in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven were placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study):

Cardiac disorders: heart rate increased, heart rate decreased

Eye disorders: visual disturbance

Gastrointestinal disorders: abdominal discomfort, impaired gastric emptying

General disorders and administration site conditions: irritability, edema, drug withdrawal syndrome, feeling drunk

Immune system disorders: hypersensitivity

Investigations: gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: involuntary muscle contractions, sensation of heaviness

Nervous system disorders: hypoesthesia, paresthesia, disturbance in attention, sedation, dysarthria, depressed level of consciousness, memory impairment, ataxia, presyncope, syncope, coordination abnormal, seizure

Psychiatric disorders: euphoric mood, disorientation, restlessness, agitation, nervousness, thinking abnormal

Renal and urinary disorders: urinary hesitation, pollakiuria

Respiratory, thoracic and mediastinal disorders: oxygen saturation decreased, cough, dyspnea, respiratory depression

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: blood pressure decreased

In the pooled safety data, the overall incidence of adverse reactions increased with increased dose of TRADENAME™, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

7 DRUG INTERACTIONS

TRADENAME™ is mainly metabolized by glucuronidation. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid *[see Clinical Pharmacology (12.3)]*.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively *[see Clinical Pharmacology (12.3)]*.

7.1 Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that TRADENAME™ does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. To a lesser extent, tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Since only a minor amount of TRADENAME™ is metabolized via the oxidative pathway clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.3 Centrally-Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with TRADENAME™ may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with TRADENAME™. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions (5.2) and (5.6)]*.

7.4 Monoamine Oxidase Inhibitors

TRADENAME™ is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Contraindications (4.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1 times the plasma exposure at the maximum recommended human dose (MRHD) of 700 mg/day based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e. reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.2, 0.6, and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥ 10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed through postnatal Day 4.

There are no adequate and well controlled studies of TRADENAME™ in pregnant women. TRADENAME™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. TRADENAME™ is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of TRADENAME™, neonates whose mothers have been taking TRADENAME™ should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

8.3 Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. TRADENAME™ should not be used during breast-feeding.

8.4 Pediatric Use

The safety and effectiveness of TRADENAME™ in pediatric patients less than 18 years of age have not been established. TRADENAME™ is not recommended in this population.

8.5 Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of TRADENAME™, 19% were 65 and over, while 5% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The rate of constipation was higher in subjects greater than or equal to 65 years than those less than 65 years (12% vs. 7%).

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

In patients with severe renal impairment, the safety and effectiveness of TRADENAME™ has not been established. TRADENAME™ is not recommended in this population *[see Dosage and Administration (2.1)]*.

8.7 Hepatic Impairment

Administration of TRADENAME™ resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. TRADENAME™ should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2)]*.

TRADENAME™ has not been studied in patients with severe hepatic impairment, therefore, use of TRADENAME™ is not recommended in this population *[see Warnings and Precautions (5.10)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TRADENAME™ contains tapentadol, a mu-opioid agonist. TRADENAME™ has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

9.2 Abuse

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Concerns about abuse and addiction should not prevent the proper management of pain. However, 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.

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of mu-opioid agonists can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of TRADENAME™ poses a risk of overdose and death. This risk is increased with concurrent abuse of TRADENAME™ with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 drugs with mu-opioid agonist properties.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.1)]*. Use of TRADENAME™ in this population has not been characterized. As TRADENAME™ has mu-opioid agonist activity, infants whose mothers have taken TRADENAME™, should be carefully monitored.