Tapentadol ER Tablets 50/100 mg

Label Claim:
TAPAL- ER-50
Tapentadol ER Tablets 50 mg
Each film coated extended release tablet contains
Tapentadol Hydrochloride IP equivalent to
Tapentadol----------50 mg
Colours: Titanium Dioxide IP

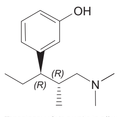
TAPAL- ER-100
Tapentadol ER Tablets 100 mg
Each film coated extended release tablet contains
Tapentadol Hydrochloride IP equivalent to
Tapentadol----------100 mg
Colours : Yellow Iron Oxide & Titanium Dioxide IP

Chemical Name:3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride.

Molecular weight : 257.80 g/mol

Molecular formula : $C_{14}H_{23}NO{\cdot}HCl$.

Structural Formula:



Tapentadol HCl is a white to off-white crystalline powder. The n-octanol:water partition coefficient log P value is 2.87. The pKa values are 9.34 and 10.45.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI), and analgesia in animal models is derived from both of these properties.

Pharmacodynamics

Tapentadol is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2–3 times less potent in producing analgesia in animal models. Tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid antagonists (e.g., naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

Effects on the cardiovascular system: There was no effect of therapeutic and supratherapeutic doses of tapentadol on the QT interval. In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects were administered five consecutive immediate-release formulation doses of tapentadol 100 mg every 6 hours, tapentadol 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, the immediate-release formulation tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Pharmacokinetics

Absorption

The mean absolute bioavailability after single-dose administration (fasting) of Tapentadol ER is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of Tapentadol ER. Dose proportional increases for AUC have been observed after administration of Tapentadol ER over the therapeutic dose range.
Steady-state exposure of tapentadol is attained after the third dose (i.e., 24 hours after first twice daily multiple dose administration). Following dosing with 250 mg every 12 hours, minimal accumulation was observed.

Food Effect

The AUC and Cmax increased by 6% and 17%, respectively, when Tapentadol ER tablet was administered after a high-fat, high-calorie breakfast. Tapentadol ER may be given with or without food.

Distribution

Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.

Metabolism and Elimination

In humans, about 97% of the parent compound is metabolized. Tapentadol is mainly metabolized via Phase 2 pathways, and only a small amount is metabolized by Phase 1 oxidative pathways. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% O-glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.
None of the metabolites contribute to the analgesic activity.
Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 5 hours after oral administration. The total clearance of tapentadol is 1603 +/-227 mL/min.

Special Populations

Elderly

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean Cmax observed in the elderly subject group compared to young adult subjects.

Renal Impairment

AUC and Cmax of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function groups were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for Cmax; and 1.2 and 1.4, respectively, for t1/2. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Drug Interactions

Tapentadol is mainly metabolized by Phase 2 glucuronidation, a high capacity/low affinity system; therefore, clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. Naproxen and probenecid increased the AUC of tapentadol by 17% and 57%, respectively. These changes are not considered clinically relevant and no change in dose is required.
No changes in the pharmacokinetic parameters of tapentadol were observed when acetaminophen and acetylsalicylic acid were given concomitantly.
In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.
The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.
Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

In Vivo Tapentadol ER Formulation-Alcohol Interaction

Tapentadol ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma or death may result .
An in vivo study examined the effect of alcohol (240 mL of 40%) on the bioavailability of a single dose of 100 mg and 250 mg of Tapentadol ER tablet in healthy, fasted volunteers. After co-administration of a 100 mg Tapentadol ER tablet and alcohol, the mean Cmax value increased by 48% compared to control with a range of 0.99-fold to 4.38-fold. The mean tapentadol AUClast and AUCinf were increased by 17%; the Tmax and t½ were unchanged. After co-administration of a 250 mg Tapentadol ER tablet and alcohol, the mean Cmax value increased by 28% compared to control with a range of 0.90-fold to 2.67-fold. The mean tapentadol AUClast and AUCinf were increased by 16%; the Tmax and t½ were unchanged.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Tapentadol was administered to rats (diet) and mice (oral gavage) for two years.
In mice, tapentadol HCl was administered by oral gavage at dosages of 50, 100 and 200 mg/kg/day for 2 years (up to 0.34 times in the male mice and 0.25 times in the female mice the plasma exposure at the maximum recommended human dose [MRHD] for Tapentadol ER on an area under the time-curve [AUC] basis). No increase in tumor incidence was observed at any dose level.
In rats, tapentadol HCl was administered in diet at dosages of 10, 50, 125 and 250 mg/kg/day for two years (up to 0.20 times in the male rats and 0.75 times in the female rats the MRHD on an AUC basis). No increase in tumor incidence was observed at any dose level.

Mutagenesis

Tapentadol did not induce gene mutations in bacteria, but was clastogenic with metabolic activation in a chromosomal aberration test in V79 cells. The test was repeated and was negative in the presence and absence of metabolic activation. The one positive result for tapentadol was not confirmed in vivo in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose.

Impairment of Fertility

Tapentadol HCl was administered intravenously to male or female rats at dosages of 3, 6, or 12 mg/kg/day (representing exposures of up to approximately 0.56 times in the male rats and 0.50 times in the female rats the exposure at the MRHD on an AUC basis, based on extrapolation from toxicokinetic parameters in a separate 4-week intravenous study in rats). Tapentadol did not alter fertility at any dose level. Maternal toxicity and adverse effects on embryonic development, including decreased number of implantations, decreased numbers of live conceptuses, and increased pre- and post-implantation losses occurred at dosages ≥ 6 mg/kg/day.

Animal Toxicology and/or Pharmacology

In toxicological studies with tapentadol, the most common systemic effects of tapentadol were related to the mu-opioid receptor agonist and norepinephrine reuptake inhibition pharmacodynamic properties of the compound. Transient, dose-dependent and predominantly CNS-related findings were observed, including impaired respiratory function and convulsions, the latter occurring in the dog at plasma levels (Cmax), which are in the range associated with the maximum recommended human dose .

INDICATIONS AND USAGE

Tapentadol ER is an extended-release formulation of tapentadol indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
Tapentadol ER is NOT intended for use as an as-needed analgesic.
Tapentadol ER is not indicated for the management of acute or postoperative pain.

DOSAGE AND ADMINISTRATION

Selection of patients for treatment with Tapentadol ER is governed by the same principles that apply to the use of similar opioid analgesics. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization and Federation of State Medical Boards Model Guidelines.
Tapentadol ER tablets must be swallowed whole and must not be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, dissolved, or crushed Tapentadol ER Tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.
Tapentadol ER tablets must be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Initiating Therapy with Tapentadol ER

It is critical to initiate the dosing regimen for each patient individually giving attention to:

- risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;
- the age, general condition and medical status of the patient;
- the patient's opioid exposure and opioid tolerance (if any);
- the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
- the balance between pain management and adverse reactions.

Discontinue all other tapentadol and acetaminophen products when beginning and while taking Tapentadol ER .Although the maximum approved total daily dose of Tapentadol immediate-release formulation is 600 mg per day, the maximum total daily dose of Tapentadol ER is 500 mg.
Do not exceed a total daily dose of Tapentadol ER of 500 mg.
Once therapy with Tapentadol ER is initiated, assess pain intensity and adverse reactions frequently.
Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every three days.
During periods of changing analgesic requirements, including initial titration, maintain frequent contact between the healthcare provider and the patient.

Patients Currently Not Taking Opioid Analgesics

The starting dose of Tapentadol ER in patients currently not taking opioid analgesics is 50 mg twice a day (approximately every 12 hours). Individually titrate the dose within the therapeutic range of 100 mg to 250 mg twice daily.

Patients Currently Taking Opioid Analgesics

There are no adequate data on the direct conversion from other opioids to Tapentadol ER.
The initial dose of Tapentadol ER in patients previously taking other opioids is 50 mg titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily.
In the dose selection of Tapentadol ER in patients currently taking opioids, give attention to the following:

- There is a substantial patient variation in the relative potency of different opioid drugs and formulations;
- It is extremely important to monitor all patients closely 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 tends to accumulate in the plasma.
- The recommended doses are only a starting point, and close observation and titration are indicated until a satisfactory dose is obtained on the new therapy.

Conversion from Tapentadol to Tapentadol ER

Patients can be converted from Tapentadol to Tapentadol ER using the equivalent total daily dose of Tapentadol and dividing it into two equal doses of Tapentadol ER separated by approximately 12-hour intervals. As an example, a patient receiving 50 mg of Tapentadol four times per day (200 mg/day) may be converted to 100 mg Tapentadol ER twice a day.

Cessation of Therapy

Periodically reassess the continued need for Tapentadol ER during chronic therapy. When discontinuing Tapentadol ER, potential withdrawal symptoms may be reduced by tapering the dose of Tapentadol ER.

Renal Impairment

Tapentadol ER has not been studied in patients with severe renal impairment; therefore, the use of Tapentadol ER in this population is not recommended. No dosage adjustment is recommended in patients with mild or moderate renal impairment .

Hepatic Impairment

Tapentadol ER has not been studied in patients with severe hepatic impairment. The use of Tapentadol ER in this population is not recommended.
Use Tapentadol ER with caution in patients with moderate hepatic impairment. Initiate treatment in these patients using 50 mg Tapentadol ER and administer no more frequently than once every 24 hours. The maximum recommended dose for patients with moderate hepatic impairment is 100 mg of Tapentadol ER once daily .
No dosage adjustment is recommended in patients with mild hepatic impairment .

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.

DOSAGE FORMS AND STRENGTHS

Tablets : 50 mg, 100 mg, 150 mg 200 mg and 250 mg

CONTRAINDICATIONS

Tapentadol ER is contraindicated in patients with significant respiratory depression, or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment .
Tapentadol ER is contraindicated in any patient who has or is suspected of having a paralytic ileus.
Tapentadol ER 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.
Tapentadol ER is contraindicated in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product. Angioedema has been reported in association with use of tapentadol.

WARNINGS AND PRECAUTIONS

Information Essential for Safe Administration

Tapentadol ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, crushed or dissolved Tapentadol ER tablets leads to the rapid release and absorption of a potentially fatal dose of tapentadol.
Tapentadol ER tablets must be kept in a secure place out of the reach of children. Accidental consumption of Tapentadol ER, especially in children, can result in a fatal overdose of tapentadol.

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.
Use Tapentadol ER with caution in 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 Tapentadol ER may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and Tapentadol ER 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 .

CNS Depression

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, centrally acting muscle relaxants, or other CNS depressants (including alcohol) concomitantly with Tapentadol ER 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 Tapentadol ER. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

Head Injury and Increased Intracranial Pressure

Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, Tapentadol ER 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. Tapentadol ER should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.

Misuse and Abuse

Tapentadol is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.
Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.
Tapentadol ER can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Tapentadol ER 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 .
Drug abusers may attempt to abuse Tapentadol ER by crushing, chewing, snorting or injecting the product. These practices may result in the uncontrolled delivery of Tapentadol ER and pose a significant risk to the abuser that could result in overdose and death .

Hypotension

Tapentadol ER may cause severe hypotension. Patients at higher risk of hypotension include those with hypovolemia or those taking concurrent products that compromise vasomotor tone (e.g., phenothiazines, general anesthetics).

Driving and Operating Machinery

Patients should be cautioned that Tapentadol ER 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.

Interactions with Alcohol and Drugs of Abuse

Tapentadol ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma or death may result.

Seizures

Tapentadol ER has not been evaluated in patients with a predisposition to a seizure disorder, and such patients were excluded from clinical studies .As with other opioids, Tapentadol ER 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.

Serotonin Syndrome Risk

Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (e.g. mirtazapine, trazodone, and tramadol), and 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) and can be fatal.

Withdrawal

Withdrawal symptoms may occur if Tapentadol ER 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 Tapentadol ER .

Hepatic Impairment

A study with the immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Tapentadol should be used with caution in patients with moderate hepatic impairment .
Tapentadol ER has not been studied in patients with severe hepatic impairment and use in this population is not recommended.

Use in Pancreatic/Biliary Tract Disease

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

Other Special Risk Groups

Tapentadol ER should be used with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease); delirium tremens; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; and, toxic psychosis.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Respiratory Depression
- CNS Depression
- Hypotension
- Seizures
- Serotonin Syndrome

DRUG INTERACTIONS

Tapentadol 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 .
The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively .

Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that tapentadol does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

Drugs That Inhibit or Induce Cytochrome P450 Enzymes

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

Centrally Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, centrally acting muscle relaxants, or other CNS depressants (including alcohol) concomitantly with Tapentadol ER may experience additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with Tapentadol ER. If such combined therapy is contemplated, a dose reduction of one or both agents should be considered.
The co-administration of alcohol with Tapentadol ER may result in increased serum levels and a potentially fatal overdose of tapentadol. Do not use Tapentadol ER with alcohol .

Monoamine Oxidase Inhibitors

Tapentadol ER 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 .

Serotonergic Drugs

There have been post-marketing reports of serotonin syndrome with the concomitant use of tapentadol and serotonergic drugs (e.g., SSRIs and SNRIs). Caution is advised when Tapentadol ER is co-administered with other drugs that may affect serotonergic neurotransmitter systems such as SSRIs, SNRIs, MAOIs, and triptans. If concomitant treatment of Tapentadol ER with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Mixed Agonist/Antagonist Opioid Analgesics

The concomitant use of Tapentadol ER with mixed agonist/antagonists (e.g., butorphanol, nalbuphine, and pentazocine) and partial agonists (e.g., buprenorphine) could lead to a reduction of the analgesic effect by competitive blocking of opioid receptors, and/or withdrawal. Therefore, this combination is not recommended.

Anticholinergics

The use of Tapentadol ER with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Dosage Recommendations

Tapentadol ER should be used for severe acute pain only for a period not exceeding 5 days.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.
There are no adequate and well-controlled studies of Tapentadol ER in pregnant women. Tapentadol ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
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 (systemic exposure up to 1.36 times the plasma exposure at the maximum recommended human dose (MRHD) of 500 mg/day for Tapentadol ER 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 0.3, 0.8, and 2.5 times the plasma exposure at the MRHD based on an AUC comparison, respectively] 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 2.28 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 to postnatal Day 4.

Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. Tapentadol ER is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of Tapentadol ER, neonates whose mothers have been taking Tapentadol ER 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.

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. Tapentadol ER should not be used during breast-feeding.

Pediatric Use

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

Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of Tapentadol ER, 28% (1023/3613) were 65 years and over, while 7% (245/3613) were 75 years and over. No overall differences in effectiveness or tolerability were observed between these patients and younger 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 .

Neonatal Withdrawal Syndrome

Chronic maternal use of opiates or opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn.

Renal Impairment

The safety and effectiveness of Tapentadol ER has not been established in patients with severe renal impairment. Tapentadol ER is not recommended in this population.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels of tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function . Tapentadol ER should be used with caution in patients with moderate hepatic impairment .
Tapentadol ER has not been studied in patients with severe hepatic impairment, therefore, use of Tapentadol ER is not recommended in this population .

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Tapentadol ER contains tapentadol, a mu-opioid agonist and is a Schedule II controlled substance. Tapentadol ER has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

Abuse

Drug addiction 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.
The risks of misuse and abuse should be considered when prescribing or dispensing Tapentadol ER. 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 Tapentadol ER poses a risk of overdose and death. This risk is increased with concurrent abuse of Tapentadol ER with alcohol and other substances. Tapentadol ER tablets are intended for oral use only and must not be administered by any other route. If abused by parenteral routes, the tablet excipients may cause serious or even fatal complications. 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. Use of Tapentadol ER in this population has not been characterized. As Tapentadol ER has mu-opioid agonist activity, infants whose mothers have taken Tapentadol ER should be carefully monitored.

Dependence

Tolerance to opioids is the need for increasing doses of opioids to maintain a constant effect such as analgesia (in the absence of disease progression or other external factors). The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance occur frequently during chronic opioid therapy.
The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and dilated pupils. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.
Tolerance and/or a withdrawal syndrome are more likely to occur the longer a patient is on continuous opioid therapy. In clinical trials, patients who stopped taking Tapentadol ER abruptly experienced mild (12%) or moderate (2%) withdrawal. Withdrawal symptoms included: nausea, diarrhea, insomnia, sweating, anxiety, arthralgia, and chills. Withdrawal symptoms may be reduced by tapering Tapentadol ER.

OVERDOSAGE

Human Experience

Experience with Tapentadol ER overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid agonist activity are to be expected upon intoxication with tapentadol. In principle, the clinical manifestations of opioid overdose include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest, and death.

Management of Overdose

Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of Tapentadol ER is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of cardiac and/or pulmonary failure as needed. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
Take the extended-release characteristics of Tapentadol ER into account when treating the overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects
Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to the initial administration of opioid antagonists is suboptimal or only brief in nature, repeated doses or an alternative antagonist should be administered as directed by the label of the antagonist.
Only administer opioid antagonists in the presence of clinically significant respiratory or circulatory depression secondary to tapentadol overdose. In patients who are physically dependent on any opioid agonist including Tapentadol ER, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered.

STORAGE

Store below 30°C.
Protect from light and moisture.
Keep out of reach of children.

PACKING INFORMATION:

Pack of 10, 15 Tablets in a Blister.

Manufactured by:
MSN Laboratories Private Limited,
Mekaguda, Telangana-509 228,
INDIA.

® Registered Trade Mark

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