# For use in India only

**For the use of a Registered Medical Practitioner only**

**PRESCRIBING INFORMATION**

# Tapal® टेपल

**(Tapentadol Tablet)**

**TAPENTADOL TABLETS 50/75/100 mg** टेपल ५०-७५-१००

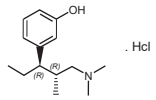
**COMPOSITION:**

**Tapal® 50mg** टेपल ५०
Each film coated tablet contains
Tapentadol hydrochloride IP
Equivalent to Tapentadol 50 mg
Colour: Titanium dioxide IP

**Tapal® 75mg** टेपल ७५
Each film coated tablet contains
Tapentadol hydrochloride IP
Equivalent to Tapentadol 75 mg
Colours: Titanium Dioxide IP, Ferric Oxide Yellow USP NF.

**Tapal® 100mg** टेपल १००
Each film coated tablet contains
Tapentadol hydrochloride IP
Equivalent to Tapentadol 100 mg
Colours: Sunset Yellow FCF & Titanium Dioxide IP

**Chemical Name**:3-[(1R,2R)-3-(dimethylamino)-l-ethyl-2-methylpropyl]phenol monohydrochloride
**Empirical formula:** $C_{14}H_{23}NO{\cdot}HCl$.
**Molecular weight:** 257.80
**Structural formula:**



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**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.
**Renal Impairment**
No dosage adjustment is recommended in patients with mild or moderate renal impairment [see Clinical Pharmacology]
**Hepatic Impairment**
No dosage adjustment is recommended in patients with mild hepatic impairment [see Clinical Pharmacology ].
Tapentadol 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 ].
**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 Recommendations**
Tapentadol 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 in pregnant women. Tapentadol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
**Labor and Delivery**
The effect of tapentadol on labor and delivery in humans is unknown. Tapentadol 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 , neonates whose mothers have been taking Tapentadol 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. Tapentadolshould not be used during breast-feeding.
**Pediatric Use**
The safety and effectiveness of Tapentadol in pediatric patients less than 18 years of age have not been established. Tapentadolis 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, 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]

**INDICATIONS AND USAGE**
**For the relief of moderate to severe acute pain in patients 18years of age or older.**

**CLINICAL PHARMACOLOGY**
**Mechanism of Action**
Tapentadol is a centrally-acting synthetic analgesic. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.
**Pharmacodynamics**
Tapentadol is a centrally-acting synthetic analgesic. It 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. 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.
**Pharmacokinetics**
**Absorption**
Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing.
Dose-proportional increases in the Cmax and AUC values of tapentadol have been observed over the 50 to 150 mg dose range.
A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed a mean accumulation factor of 1.6 for the parent drug and 1.8 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite.
**Food Effect**
The AUC and Cmax increased by 25% and 16%, respectively, when Tapentadol was administered after a high-fat, high-calorie breakfast. Tapentadol may be given with or without food.
**Distribution**
Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.
**Metabolism and Elimination**
In humans, the metabolism of tapentadol is extensive. 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 contributes to the analgesic activity.
Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/-177 ml/min.
**CONTRAINDICATIONS**
**Impaired Pulmonary Function** Like other drugs with mu-opioid agonist activity, Tapentadol is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment. Tapentadol is also contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment
**Paralytic Ileus** Like drugs with mu-opioid agonist activity, Tapentadol is contraindicated in any patient who has or is suspected of having paralytic ileus.
**Monoamine Oxidase Inhibitors** Tapentadolis 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.
**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. [see Clinical Pharmacology].
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 CYP450 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. 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 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, or other CNS depressants (including alcohol) concomitantly with Tapentadol 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 Tapentadol. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.
**Monoamine Oxidase Inhibitors**
Tapentadol 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 )

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

- Respiratory Depression see Contraindications and Warnings and Precautions ]
- CNS Depression see Warnings and Precautions ]
- **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 Tapentadol, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

**WARNINGS AND PRECAUTIONS**
**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.
Tapentadol 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 Tapentadol may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and Tapentadol 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 mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with Tapentadol 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. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.
**Head Injury and Increased Intra cranial Pressure**
Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, Tapentadol 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 had injury due to effects on pupillary response and consciousness. Tapentadol should be used with caution in patients with head injury, intra cranial lesions, or other sources of preexisting increased intra cranial 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.
apentadolan be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing
Tapentadol 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
**Driving and Operating Machinery**
Patients should be cautioned that Tapentadol 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
**Seizures**
Tapentadol as not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. Tapentadol 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**
The development of a potentially life-threatening serotonin syndrome may occur with use of Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) products, including Tapentadol 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 ocur 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).
**Withdrawal**
Withdrawal symptoms may occur if Tapentadols 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 [see Drug Abuse and Dependence ]
**Use in Pancreatic/Biliary Tract Disease**
Like other drugs with mu-opioid agonist activity, Tapentadol may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

**HOW SUPPLIED**
Tapentadol Hydrochloride Tablets available as
White film coated tablets containing Tapentadol 50 mg,
Yellow colored, film coated tablets containing Tapentadol 75mg
Orange colored, film coated tablets containing Tapentadol 100mg

**Shelf life:**
Please see Mfg. Date/ Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

**STORAGE: Store below 30°C, Protect from light and moisture.**
Keep all medicines out of reach of children.

**PACKING INFORMATION:** Pack of 10, 15 Tablets in a Blister.

® Registered Trade Mark

Manufactured by:
**MSN Laboratories Private Limited,**
Formulations Division, Unit-06,
Sy. No. (Parts of), 745,811-813,824 & 825,
Burgul Village, Farooqnagar Mandal,
Ranga Reddy District, Pincode 509202,
Telangana State, India.

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