Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Tapal 50 mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains

Tapentadol Hydrochloride

Equivalent to Tapentadol 50 mg

Excipients with known effect:

Product contains Lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White coloured, round shaped, biconvex, film-coated tablets with break line on one side and Plain surface on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tapentadol is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The dosing regimen should be individualised according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

Patients should start treatment with single doses of 50 mg tapentadol as film-coated tablet administered every 4 to 6 hours. Higher starting doses may be necessary depending on the pain intensity and the patient's previous history of analgesic requirements.

On the first day of dosing, an additional dose may be taken as soon as one hour

after the initial dose, if pain control is not achieved. The dose should then be titrated individually to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescribing physician.

Daily doses greater than 700 mg tapentadol on the first day of treatment and maintenance daily doses greater than 600 mg tapentadol have not been studied and are therefore not recommended.

As soon as stable dosing regimen is achieved and longer treatment is anticipated, the possibility of switching the patient to therapy with the prolonged-release tablets (tapentadol SR) should be considered.

As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.

Discontinuation of treatment

Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see section 4.8). When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Renal Impairment

In patients with mild or moderate renal impairment a dosage adjustment is not required (see section 5.2).

Tapentadol has not been studied in controlled efficacy trials in patients with severe renal impairment, therefore the use in this population is not recommended (see sections 4.4 and 5.2).

Hepatic Impairment

In patients with mild hepatic impairment a dosage adjustment is not required (see section 5.2).

Tapentadol should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at the lowest available dose strength, i.e. 50 mg tapentadol as film-coated tablet, and not be administered more frequently than once every 8 hours. At initiation of therapy a daily dose greater than 150 mg tapentadol as film-coated tablet is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval (see sections 4.4 and 5.2).

Tapentadol has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended (see sections 4.4 and 5.2).

Elderly Patients (persons aged 65 years and over)

In general, a dose adaptation in elderly patients is not required. However, as elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see sections 4.2 and 5.2).

Paediatric Patients

The safety and efficacy of tapentadol in children and adolescents below 18 years of age has not yet been established. Therefore, tapentadol is not recommended for use in this population.

Method of administration

Tapentadol should be taken with sufficient liquid. tapentadol can be taken with or without food.

4.3 CONTRAINDICATIONS

Tapentadol is contraindicated

- in patients with hypersensitivity to tapentadol or to any of the excipients (see section 6.1)
- in situations where active substances with mu-opioid receptor agonist activity are contraindicated,

i.e. patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercapnia

- in any patient who has or is suspected of having paralytic ileus
- in patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic active substances (see section 4.5)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Potential for Abuse and Addiction/ Dependence Syndrome

Tapentadol has a potential for abuse and addiction. This should be considered when prescribing or dispensing tapentadol in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.

All patients treated with active substances that have mu-opioid receptor agonist

activity should be carefully monitored for signs of abuse and addiction.

Respiratory Depression

At high doses or in mu-opioid receptor agonist sensitive patients, tapentadol may produce dose-related respiratory depression. Therefore, tapentadol should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor 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 receptor agonist- induced respiratory depression (see section 4.9).

Head Injury and Increased Intracranial Pressure

Tapentadol should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. tapentadol should be used with caution in patients with head injury and brain tumors.

Seizures

Tapentadol has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical trials. However, like other analgesics with mu-opioid agonist activity 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.

Renal Impairment

Tapentadol has not been studied in controlled efficacy trials in patients with severe renal impairment, therefore the use in this population is not recommended (see section 4.2 and 5.2).

Hepatic Impairment

Subjects with mild and moderate hepatic impairment showed a 2-fold and 4.5-fold increase in systemic exposure, respectively, compared with subjects with normal hepatic function. tapentadol should be used with caution in patients with moderate hepatic impairment (see section 4.2 and 5.2), especially upon initiation of treatment.

Tapentadol has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended (see sections 4.2 and 5.2).

Use in Pancreatic/Biliary Tract Disease

Active substances with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. Tapentadol should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Concomitant treatment with monoamine oxidase inhibitors (MAOI)

Treatment with tapentadol should be avoided 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 synaptic noradrenaline concentrations which may result in adverse cardiovascular events, such as hypertensive crisis (see section 4.5)

Tapentadol film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Treatment with tapentadol should be avoided 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 synaptic noradrenaline concentrations which may result in adverse cardiovascular events, such as hypertensive crisis (see section 4.4)

Medicinal products like benzodiazepines, barbiturates and opioids (analgesics, antitussives or substitution treatments) may enhance the risk of respiratory depression if taken in combination with tapentadol. CNS depressants (e.g. benzodiazepines, antipsychotics, H1-antihistamines, opioids, alcohol) can enhance the sedative effect of tapentadol and impair vigilance. Therefore, when a combined therapy of tapentadol with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered.

In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tapentadol in combination with serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs). Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement.

Treatment depends on the nature and severity of the symptoms.

There is no clinical data on the concomitant use of tapentadol with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine). As with pure mu-opioid agonists, the analgesic effect provided by the mu-opioid component of tapentadol may be theoretically reduced in such circumstances. Therefore, care should be taken when combining tapentadol with these medicinal products.

The major elimination pathway for tapentadol is conjugation with glucuronic acid mediated via uridine diphosphate transferase (UGT) mainly UGT1A6, UGT1A9 and UGT2B7 isoforms. Thus, concomitant administration with strong inhibitors of these isoenzymes may lead to increased systemic exposure of tapentadol. Interaction studies with active substances that potentially

could affect the glucuronidation (paracetamol, acetylsalicylic acid, naproxen and probenecid) did not result in any clinically relevant effect on the serum concentrations of tapentadol (see section 5.2). Interaction studies with substances that can affect absorption of tapentadol (omeprazole and metoclopramide) did not result in any clinically relevant effect on the serum concentrations of tapentadol (see section 5.2).

For patients on tapentadol treatment, caution should be exercised if concomitant drug administration of strong enzyme inducing drugs (e.g. rifampicin, phenobarbital, St John's Wort (hypericum perforatum)) starts or stops, since this may lead to decreased efficacy or risk for adverse effects, respectively.

4.6 PREGNANCY AND LACTATION

Pregnancy

There is very limited amount of data from the use in pregnant women.

Studies in animals have not shown teratogenic effects. However, delayed development and embryotoxicity were observed at doses resulting in exaggerated pharmacology. Effects on the postnatal development were already observed at the maternal NOAEL (see section 5.3).

tapentadol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Labour and Delivery

The effect of tapentadol on labour and delivery in humans is unknown. tapentadol is not recommended for use in women during and immediately before labour and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, new-born infants whose mothers have been taking tapentadol should be monitored for respiratory depression.

Lactation

There is no information on the excretion of tapentadol in human milk. From a study in rat pups suckled by dams dosed with tapentadol it was concluded that tapentadol is excreted via milk (see section 5.3). Therefore, a risk to the suckling child cannot be excluded. tapentadol should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tapentadol may have major influence on the ability to drive and use machines due to the fact that it may adversely affect central nervous system functions (see section 4.8). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilisers (see section 4.4). Patients should be cautioned as to whether driving

or use of machines is permitted.

4.8 UNDESIRABLE EFFECTS

The adverse drug reactions that were experienced by patients in the placebo controlled trials performed with tapentadol were predominantly of mild and moderate severity. The most frequent adverse drug reactions were in the gastrointestinal and central nervous system (nausea, vomiting, somnolence, dizziness and headache).

The table below lists adverse drug reactions that were identified from clinical trials performed with tapentadol. They are listed by class and frequency. Frequencies are defined as very common

(≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

ADVERSE DRUG REACTIONS				
System Organ Class	**Frequency**			
	Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders		Anxiety, Confusional state, Hallucination, Sleep disorder, Abnormal dreams	Depressed mood, Disorientation, Agitation, Nervousness, Restlessness, Euphoric mood	Thinking abnormal
Nervous system disorders	Dizziness, Somnolence, Headache	Tremor	Disturbance in attention, Memory impairment, Presyncope, Sedation, Ataxia, Dysarthria, Hypoaesthesia, Paraesthesia, Muscle contractions involuntary	Convulsion, Depressed level of consciousness, Coordination abnormal
Eye disorders			Visual disturbance	
Cardiac disorders			Heart rate increased	Heart rate decreased

Vascular disorders		Flushing	Blood pressure decreased	
Respiratory, thoracic and mediastinal disorders			Respiratory depression, Oxygen saturation decreased,	

			Dyspnoea,	
Gastrointestinal disorders	Nausea, Vomiting	Constipation, Diarrhoea, , Dyspepsia, Dry mouth	Abdominal discomfort	Impaired gastric emptying
Skin and subcutaneous tissue disorders		Pruritus, Hyperhidrosis, Rash	Urticaria	
Musculoskeletal and connective tissue disorder		Muscle spasms	Sensation of heaviness	
Renal and urinary disorders			Urinary hesitation, Pollakiuria	
General disorders and administration site conditions		Asthenia, Fatigue, Feeling of body temperature change	Drug withdrawal syndrome, Oedema, Feeling abnormal, Feeling drunk, Irritability, Feeling of relaxation	

Clinical trials performed with tapentadol with patient exposure up to 90 days have shown little evidence of withdrawal symptoms upon abrupt discontinuations and these were generally classified as mild, when they occurred. Nevertheless, physicians should be vigilant for symptoms of withdrawal (see section 4.2) and treat patients accordingly should they occur.

The risk of suicidal ideation and suicides committed is known to be higher in patients suffering from chronic pain. In addition, substances with a pronounced influence on the monoaminergic system have been associated with an increased risk of suicidality in patients suffering from depression, especially at the beginning of treatment. For tapentadol data from clinical trials and

post-marketing reports do not provide evidence for an increased risk.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)

https://pv.pharmacyboardkenya.org

4.9 OVERDOSE

Human Experience

Experience with overdose of tapentadol is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In principle, these symptoms include, referring to the clinical setting, in particular miosis, vomiting, cardiovascular collapse, consciousness disorders

up to coma, convulsions and respiratory depression up to respiratory arrest.

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 is suspected.

Pure opioid receptor 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 receptor antagonist. Administration of an opioid receptor antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid receptor antagonists is suboptimal or only brief in nature, an additional dose of antagonist (e.g. naloxone) should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed active substance. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Analgesics; opioids; other opioids

ATC code: N02AX06

Tapentadol is a strong analgesic with μ-agonistic opioid and additional noradrenaline reuptake inhibition properties. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

Tapentadol demonstrated efficacy in preclinical models of nociceptive, neuropathic, visceral and inflammatory pain; Efficacy has been verified in clinical trials with tapentadol film-coated tablets covering nociceptive pain conditions including postoperative orthopaedic and abdominal pain as well as chronic pain due to osteoarthritis of the hip or knee. In general the analgesic effect of

Tapentadol in nociceptive pain trials was similar to that observed with a strong opioid used as comparator.

Effects on the cardiovascular system: In a thorough human QT trial, no effect of multiple therapeutic and supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with tapentadol in all subsets of the paediatric population in moderate to severe acute pain. See section
4.2 for information on paediatric use.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tapentadol is rapidly and completely absorbed after oral administration of tapentadol. 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 administration of film-coated tablets. Dose-proportional increases in

the C_{max} and AUC values of tapentadol have been observed after administration of film-coated tablets over the oral therapeutic dose range.

A multiple (every 6 hour) dose trial with doses ranging from 75 to 175 mg tapentadol administered as film-coated tablets showed an accumulation ratio between 1.4 and 1.7 for the parent active substance and between 1.7 and 2.0 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 C_{max} increased by 25% and 16%, respectively, when film-coated tablets were administered after a high-fat, high-calorie breakfast. The time to maximum plasma concentration was delayed by 1.5 hours under these conditions. Based on efficacy data obtained at early assessment time points during phase II/III trials, the food effect does not appear to be of clinical

relevance tapentadol 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 serum 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 metabolised. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% of the dose is excreted in urine as conjugated forms (55% glucuronide and 15% sulfate of tapentadol). Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of active substance is excreted in urine as unchanged active substance. Tapentadol is additionally metabolised to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are

further metabolised by conjugation. Therefore, active substance 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.

Special populations

Elderly

The mean exposure (AUC) to tapentadol was similar in a trial with elderly subjects (65-78 years of age) compared to young adults (19-43 years of age), 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 are 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 group 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 Interactions

Tapentadol is mainly metabolised by Phase 2 glucuronidation, and only a small amount is metabolised by Phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, which is not easily saturated even in disease, and as therapeutic concentrations of active substances are generally well below the concentrations needed for potential inhibition of glucuronidation, any clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. In a set of drug-drug interaction trials using paracetamol, naproxen, acetylsalicylic acid and probenecid, a possible influence of these active substances on the glucuronidation of tapentadol was investigated. The trials with probe active substances naproxen (500 mg twice daily for 2 days) and probenecid (500 mg twice daily for 2 days) showed increases in AUC of tapentadol by 17% and 57%, respectively. Overall, no clinically relevant effects on the serum concentrations of tapentadol were observed in these trials.

Furthermore, interaction trials of tapentadol with metoclopramide and omeprazole were conducted to investigate a possible influence of these active substances on the absorption of tapentadol. These trials also showed no clinically relevant effects on tapentadol serum concentrations.

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.

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.

5.3 PRECLINICAL SAFETY DATA

Tapentadol was not genotoxic in bacteria in the Ames test. Equivocal findings were observed in an in vitro chromosomal aberration test, but when the test was repeated the results were clearly negative. Tapentadol was not genotoxic in vivo, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose. Long-term animal studies did not identify a potential carcinogenic risk relevant to humans.

Tapentadol had no influence on male or female fertility in rats but there was reduced in utero survival at the high dose. It is not known whether this was mediated via the male or the female. Tapentadol showed no teratogenic effects in rats and rabbits following intravenous and subcutaneous exposure; however, delayed development and embryotoxicity were observed after administration of doses resulting in exaggerated pharmacology.After intravenous dosing in rats reduced in utero survival was seen. In rats tapentadol caused increased mortality of the F1 pups that were directly exposed via milk between days 1 and 4 post partum already at dosages that did not provoke maternal toxicities. There were no effects on neurobehavioral parameters.

Excretion into breast milk was investigated in rat pups suckled by dams dosed with tapentadol. Pups were dose-dependently exposed to tapentadol and tapentadol O-glucuronide. It is concluded that tapentadol is excreted via milk.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: Microcrystalline cellulose PH 101, Lactose monohydrate, Croscarmellose sodium, PovidoneK29/32, Colloidal silicon dioxide & Magnesium stearate

Tablet coat:

Poly vinyl alcohol, Titanium dioxide, Talc, Macrogol/PEG, Lecithin.

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30^0C. Protect form Light and Moisture. Keep out of reach to children.

6.5 NATURE AND CONTENTS OF CONTAINER

Ten tablets of Tapentadol are Packed in PVC/PVDC foil on one side and printed aluminium foil on other side in the form of blister pack. Such 1 blister is further packed in preprinted carton along with pack insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. Marketing authorisation holder

MSN LABORATORIES PRIVATE LIMITED
MSN House, Plot No.: C-24, Industrial
Estate, Sanath Nagar, Hyderabad –
500 018 Telangana, India.

8. Marketing Authorization Number

H2022/CTD8811/17841

9. Date of first authorization/renewal of the authorization

11/01/2022

10. Date of revision of the text

24/08/2026