

## **Tapentadol 50mg tablets**

### **1. Name of the medicinal product**

Tapentadol 50mg tablets Taj Pharma

### **2. Qualitative and quantitative composition**

Each tablet contains 50mg Tapentadol (as hydrochloride).  
For the full list of excipients, see section 6.1.

### **3. Pharmaceutical form**

Tablet

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

Tapentadol is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

#### **4.2 Posology and method of administration**

##### Posology

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.

Tapentadol should be taken twice daily, approximately every 12 hours.

##### *Initiation of therapy*

Initiation of therapy in patients currently not taking opioid analgesics

Patients should start treatment with single doses of 50mg Tapentadol as tablet administered twice daily.

##### *Initiation of therapy in patients currently taking opioid analgesics*

When switching from opioids to Tapentadol and choosing the initial dose, the nature of the previous medicinal product, administration and the mean daily dose should be taken into account. This may require higher initial doses of Tapentadol for patients currently taking opioids compared to those not having taken opioids before initiating therapy with Tapentadol.

##### *Titration and maintenance*

After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimises undesirable effects under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50mg Tapentadol as tablet twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Total daily doses of Tapentadol greater than 500mg Tapentadol have not yet been studied and are therefore not recommended.

##### *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 is 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. 50mg Tapentadol as tablet, and not be administered more frequently than once every 24 hours. At initiation of therapy a daily dose greater than 50mg Tapentadol as tablet is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability (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 has to be taken whole, not divided or chewed, to ensure that the mechanism is maintained. Tapentadol should be taken with sufficient liquid. Tapentadol can be taken with or without food.

The shell (matrix) of the Tapentadol tablet may not be digested completely and therefore it can be eliminated and seen in the patient's stool. However, this finding has no clinical relevance, since the active substance of the tablet will have already been absorbed.

### **4.3 Contraindications**

TAPENTADOL is contraindicated

- in patients with hypersensitivity to Tapentadol or to any of the excipients listed in 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.

##### *Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances*

Concomitant use of Tapentadol and sedating medicinal products such as benzodiazepines or related substances may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tapentadol concomitantly with sedating medicinal products, the reduction of dose of one or both agents should be considered and the duration of the concomitant treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

##### *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 is not recommended in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures. In addition, tapentadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold (see section 4.5).

##### *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.

#### *Mixed opioid agonists/antagonists*

Care should be taken when combining Tapentadol with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine). In patients maintained on buprenorphine for the treatment of opioid dependence, alternative treatment options (like e.g. temporary buprenorphine discontinuation) should be considered, if administration of full mu-agonists (like Tapentadol) becomes necessary in acute pain

situations. On combined use with buprenorphine, higher dose requirements for full mu-receptor agonists have been reported and close monitoring of adverse events such as respiratory depression is required in such circumstances.

Tapentadol 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**

##### *Sedative medicines such as benzodiazepines or related drugs*

The concomitant use of Tapentadol with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. 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 and the duration of the concomitant use should be limited (see section 4.4).

##### *Mixed opioid agonists/antagonists*

Care should be taken when combining Tapentadol with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine) (see also section 4.4).

Tapentadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other medicinal products that lower the seizure threshold to cause convulsions.

There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of Tapentadol in combination with serotonergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and inducible ocular clonus.

Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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 (e.g. ketoconazole, fluconazole, meclufenamic acid) may lead to increased systemic exposure 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

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.

#### **4.6 Fertility, 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 (mu-opioid-related CNS effects related to dosing above the therapeutic range). 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, because it may adversely affect central nervous system functions (see section 4.8). This has to be expected especially at the beginning of treatment, when any change of dosage occur as well as in connection with the use of 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, dizziness, constipation, headache and somnolence).

The table below lists adverse drug reactions that were identified from clinical trials performed with Tapentadol and from post-marketing environment. They are listed by class and frequency. Frequencies are defined as very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

<b>ADVERSE DRUG REACTIONS</b>					
<b>System Organ Class</b>	<b>Frequency</b>				
	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Unknown</b>
<b>Immune system disorders</b>			Drug hypersensitivity*		
<b>Metabolism and nutrition disorders</b>		Decreased appetite	Weight decreased		
<b>Psychiatric disorders</b>		Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams,	Drug dependence, Thinking abnormal	Delirium**

			Euphoric mood		
<b>Nervous system disorders</b>	Dizziness, Somnolence, Headache	Disturbance in attention, Tremor, Muscle contractions involuntarily	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia	Convulsion, Presyncope, Coordination abnormal	
<b>Eye disorders</b>			Visual disturbance		
<b>Cardiac disorders</b>			Heart rate increased, Heart rate decreased, Palpitations		
<b>Vascular disorders</b>		Flushing	Blood pressure decreased		
<b>Respiratory, thoracic</b>		Dyspnoea		Respiratory	

<b>and mediastinal disorders</b>				depression	
<b>Gastrointestinal disorders</b>	Nausea, Constipation	Vomiting, Diarrhoea, Dyspepsia	Abdominal discomfort	Impaired gastric emptying	
<b>Skin and subcutaneous tissue disorders</b>		Pruritus, Hyperhidrosis, Rash	Urticaria		
<b>Renal and urinary disorders</b>			Urinary hesitation, Pollakiuria		
<b>Reproductive system and breast disorders</b>			Sexual dysfunction		
<b>General disorders and administration site conditions</b>		Asthenia, Fatigue, Feeling of body temperature change, Mucosal dryness, Oedema	Drug withdrawal syndrome, Feeling abnormal, Irritability	Feeling drunk, Feeling of relaxation	

\* Post-marketing rare events of angioedema, anaphylaxis and anaphylactic shock have been reported.

\*\* Post marketing cases of delirium were observed in patients with



*additional risk factors such as cancer and advanced age.*

Clinical trials performed with Tapentadol with patient exposure up to 1 year 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

### **4.9 Overdose**

#### *Symptoms*

Human 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*

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



Tapentadol is a strong analgesic with  $\mu$ -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 tablets in non-malignant nociceptive and neuropathic chronic pain conditions as well as chronic tumour-related pain. The trials in pain due to osteoarthritis and chronic low back pain showed similar analgesic efficacy of Tapentadol to a strong opioid used as a comparator. In the trial in painful diabetic peripheral neuropathy Tapentadol separated from placebo which was used as comparator.

Effects on the cardiovascular system: In a thorough human QT trial, no effect of multiple therapeutic and suprathreshold 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 severe chronic pain (see section 4.2 for information on paediatric use).

#### *Post-marketing data*

Two post-marketing studies were performed to address the practical use of Tapentadol.

The efficacy of Tapentadol tablets has been verified in a multicenter, randomized, double blind parallel-group trial with patients suffering from low back pain with a neuropathic component (KF5503/58). Reductions in average pain intensity were similar in the Tapentadol treatment group and the comparator treatment group i.e. receiving a combination of Tapentadol tablets and pregabalin immediate release tablets.

In an open-label, multicenter, randomized trial with patients having severe chronic low back pain with a neuropathic component (KF5503/60), Tapentadol tablets were associated with significant reductions in average pain intensity.

## **5.2 Pharmacokinetic properties**

### *Absorption*

Mean absolute bioavailability after single-dose administration (fasting) of Tapentadol is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of Tapentadol are observed at between 3 and 6 hours after administration of tablets.

Dose proportional increases for AUC have been observed after administration of the tablets over the therapeutic dose range.

A multiple dose trial with twice daily dosing using 86mg and 172mg Tapentadol administered as tablets showed an accumulation ratio of about 1.5 for the parent active substance which is primarily determined by the dosing interval and apparent half-life of Tapentadol. Steady state serum concentrations of Tapentadol are reached on the second day of the treatment regimen.

### *Food Effect*

The AUC and  $C_{max}$  increased by 8% and 18%, respectively, when tablets were administered after a high-fat, high-calorie breakfast. This was judged to be without clinical relevance as it falls into the normal inter-subject variability of Tapentadol PK parameters. TAPENTADOL may be given with or without food.

#### *Distribution*

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

#### *Metabolism*

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 glucuronidation.

None of the metabolites contributes to the analgesic activity.

#### *Elimination*

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The total clearance after intravenous administration is 1530 +/- 177 ml/min. Terminal half-life is on average 5-6 hours after oral administration.

#### *Special populations*

##### *Elderly patients*

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  $C_{max}$  observed in the elderly subject group compared to young adult subjects.

##### *Renal Impairment*

AUC and  $C_{max}$  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 C<sub>max</sub>; and 1.2 and 1.4, respectively, for t<sub>1/2</sub>. The rate of formation of Tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

#### *Pharmacokinetic Interactions*

Tapentadol is mainly metabolised by glucuronidation, and only a small amount is metabolised by 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 glucuronidation 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 (500mg twice daily for 2 days) and probenecid (500mg 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 (mu-opioid related CNS effects related to dosing above the therapeutic range). 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 postpartum 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 was concluded that Tapentadol is excreted in milk.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Tablet core (all doses):

Hypromellose Microcrystalline cellulose Colloidal anhydrous silica  
Magnesium stearate

Tablet coat:

Hypromellose Lactose monohydrate Talc Macrogol Propylene glycol

Titanium dioxide Yellow iron oxide Red iron oxide

Black iron oxide

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

PVC/PVDC-aluminium/paper/PET blisters

Packs with 7, 10, 14, 20, 24, 28, 30, 40, 50, 54, 56, 60, 90, 100 tablets.

PVC/PVDC aluminium/paper/PET perforated unit-dose blisters

Packs with 10, 14, 20, 28, 30, 50, 56, 60, 90, 100 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

No special requirements.

## **7. Manufactured By:**

**Taj Pharmaceuticals Ltd.**

at: Plot. No. 220, Mahagujarat

Industrial Estate, At & Post-Moraiya,

Tal-Sanand, Dist- Ahmedabad Gujarat (India)