Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Apeneta 150 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains tapentadol maleate hemihydrate equivalent to 150 mg tapentadol.

Excipient with known effect: lactose monohydrate
Each prolonged-release tablet contains 3.3 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet (tablet)

Pale pink, oval, biconvex, film-coated tablets with mark T3 on one side of the tablet.
Tablet dimensions: approx. 16 mm x 8.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Apeneta is indicated for the management of:

- severe chronic pain in adults, which can be adequately managed only with opioid analgesics.
- severe chronic pain in children above 6 years and adolescents, 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.

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

Adults

Initiation of therapy
Initiation of therapy in patients currently not taking opioid analgesics
Patients should start treatment with single doses of 50 mg tapentadol as prolonged-release tablet administered twice daily.

Initiation of therapy in patients currently taking opioid analgesics
When switching from opioids to Apeneta 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 Apeneta for patients currently taking opioids compared to those not having taken opioids before initiating therapy with Apeneta.

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 50 mg tapentadol as prolonged-release tablet twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Total daily doses of tapentadol prolonged-release tablets greater than 500 mg 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 prolonged-release tablets have 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).

Apeneta 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 prolonged-release tablet, and not be administered more frequently than once every 24 hours. At initiation of therapy a daily dose greater than 50 mg tapentadol as prolonged-release tablet is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see sections 4.4 and 5.2).

Tapentadol prolonged-release tablets 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
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 4.4 and 5.2).

Paediatric population
Dose recommendation for children is dependent on age and body weight.

Initiation of therapy
Initiation of therapy in patients currently not taking opioid analgesics
For children and adolescents from 6 years to less than 18 years, the recommended starting dose is 1.5 mg per kg body weight given every 12 hours. Nevertheless, a starting dose of 50 mg should not be exceeded. From the available tablet strengths, either 25 mg or 50 mg should be considered as starting doses.

Initiation of therapy in patients currently taking opioid analgesics
When switching from opioids to Apeneta 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 Apeneta for patients currently taking opioids compared to those not having taken opioids before initiating therapy with Apeneta.

Titration and maintenance
After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician with dose increments of 25 mg for patients less than 40 kg body weight or dose increments of 25 mg or 50 mg for patients >40 kg body weight after a minimum of 2 days since the last dose increase.

The maximum recommended dose is 3.5 mg per kg body weight given every 12 hours. The available tablet strengths should be considered to achieve the optimal dose within the general recommended dose range (1.5 mg/kg to 3.5 mg/kg), as deemed by the prescribing physician. A total dose of 500 mg per day, i.e. 250 mg given every 12 hours should not be exceeded. Individual patients have shown benefit from doses down to 1.0 mg/kg.

Discontinuation of treatment
Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see section 4.4 and 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
Apeneta has not been studied in children and adolescents with renal impairment, therefore the use in this population is not recommended (see sections 4.4 and 5.2).

Hepatic Impairment
Apeneta has not been studied in children and adolescents with hepatic impairment, therefore the use in this population is not recommended (see sections 4.4 and 5.2).

The safety and efficacy of Apeneta in children below 6 years of age has not yet been established. Therefore Apeneta is not recommended for use in this population.

Method of administration
Apeneta is for oral use.

The tablet has to be taken whole, not divided or chewed, to ensure that the prolonged-release mechanism is maintained. Apeneta should be taken with sufficient liquid. Apeneta 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

Apeneta 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

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Physicians should be vigilant for symptoms of withdrawal after repeated administration of tapentadol and avoid abrupt cessation (see section 4.2 and section 4.8).

Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances
Concomitant use of Apeneta 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 Apeneta 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, Apeneta may produce dose-related respiratory depression. Therefore, Apeneta should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and Apeneta 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
Apeneta 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. Apeneta should be used with caution in patients with head injury and brain tumours.

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 Apeneta 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. Apeneta 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. Apeneta should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Mixed opioid agonists/antagonists
Care should be taken when combining Apeneta 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.

Apeneta contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

Pediatric population

The same warnings and precautions for use of Apeneta apply for children, with following additional considerations:

Apeneta has not been studied in children aged below 6 years (see section 4.1 and 4.2) therefore the use in this population is not recommended.

Apeneta has not been systematically evaluated in children and adolescents with obesity, therefore, pediatric patients with obesity should be extensively monitored and the recommended maximum dose should not be exceeded.

Apeneta has not been studied in children and adolescents with renal or hepatic impairment, therefore the use in this population is not recommended (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Centrally-acting medicinal products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs

The concomitant use of Apeneta 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 Apeneta 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).

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Mixed opioid agonists/antagonists

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

Apeneta 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 serotoninergic 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 serotoninergic 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, meclofenamic 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 Apeneta 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).

Apeneta should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Long-term maternal use of opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NOWS). Neonatal opioid withdrawal syndrome can be life-threatening if not recognized and treated. An antidote for the newborn should be readily available.

Labour and Delivery
The effect of tapentadol on labour and delivery in humans is unknown. Apeneta 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.

Breast-feeding
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 in milk (see section 5.3). Therefore, a risk to the suckling child cannot be excluded. Apeneta should not be used during breast-feeding.

Fertility
No human data on the effect of tapentadol on fertility are available. In a fertility and early embryonic development study, no effects on reproductive parameters were observed in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Apeneta 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 prolonged-release tablets 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 prolonged-release tablets and from post-marketing environment. They are listed by class and frequency.

Frequencies are defined as:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥1/1,000 to < 1/100)
- Rare (≥1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

System organ class	Frequency				
	Very common	Common	Uncommon	Rare	Unknown
Immune system disorders			Drug hypensenitivity*		
Metabolism and nutrition disorders		Decreased appetite	Weight decreased		
Psychiatric disorders		Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams, Euphoric mood	Drug dependence, Thinking abnormal	Delirium**
Nervous system disorders	Dizziness, Somnolence, Headache	Disturbance in attention, Tremor, Muscle contractions involuntary	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia	Convulsion, Presyncope, Coordination abnormal	
Eye disorders			Visual disturbance		
Cardiac disorders			Heart rate increased, Heart rate decreased, Palpitations		
Vascular disorders		Flushing	Blood pressure decreased		
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Respiratory depression	
Gastrointestinal disorders	Nausea, Constipation	Vomiting, Diarrhoea, Dyspepsia	Abdominal discomfort	Impaired gastric emptying	
Skin and subcutaneous tissue disorders		Pruritus, Hyperhidrosis, Rash	Urticaria		
Renal and urinary disorders			Urinary hesitation, Pollakiuria		
Reproductive system and breast disorders			Sexual dysfunction		
General disorders and administration site conditions		Asthenia, Fatigue, Feeling of body temperature change, Mucosal	Drug withdrawal syndrome, Feeling abnormal, Irritability	Feeling drunk, Feeling of relaxation	

		dryness, Oedema			
* 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 prolonged-release tablets 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

Paediatric population
Frequency, type and severity of adverse reactions in children and adolescents treated with Apeneta are expected to be the same as in adults treated with Apeneta. No new safety issues have been identified from completed paediatric trial for any of the age subgroups investigated. Limited clinical trial data on withdrawal symptoms in children using PR formulation of tapentadol are available.

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, 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 prolonged-release 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 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 extension of the indication to children > 6 years of age is based on an exposure-matching extrapolation approach supported by popPK model simulations. With the recommended doses in children, similar tapentadol exposure is reach as in adults.

One randomized, active-controlled, open-label non-inferiority study (KF5503/66) has been performed in 69 children aged 6 to less than 18 years old suffering from severe pain that was expected to require opioid treatment for a minimum of 14 days. 45 of these children were randomized to tapentadol PR. Children were treated with weight adjusted doses between 25 mg and 250 mg tapentadol PR twice daily or equivalent doses of the comparator drug during a 14-days treatment period. The safety profile of tapentadol PR in these children was comparable to the comparator drug and similar to the safety profile observed in adults treated with tapentadol PR. The safety profile of tapentadol PR was maintained in 9 children during an open label extension period of up to one year.

Post-marketing data
Two post-marketing studies were performed to address the practical use of tapentadol.

The efficacy of tapentadol prolonged-release 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 prolonged-release 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 prolonged-release 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 prolonged-release tablets 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 prolonged-release tablets.

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

A multiple dose trial with twice daily dosing using 86 mg and 172 mg tapentadol administered as prolonged-release 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 prolonged-release 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 prolonged-release tablets 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%.

Biotransformation
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
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_{max}; 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 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 glucoronidation 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.

Paediatric population

Absorption
Using weight adjusted dosing, mean serum concentrations of tapentadol observed in the paediatric population were in the range of concentrations observed in adult subjects.

Food Effect
A dedicated food effect trial has not been performed in children and adolescents. In the phase II/III trial performed in children and adolescents tapentadol was given irrespective of food intake.
Based on efficacy data obtained during the trial in children and adolescents, the food effect does not appear to be of clinical relevance. Apeneta may be given with or without food.

Distribution
Based on a population pharmacokinetic analysis, the mean (± SD) apparent volume of distribution (V/F) of tapentadol following oral administration of tapentadol PR tablets in paediatrics was 528 L (± 227 L) for children aged 6 years to less than 12 years, and 795 L (± 220 L) for children aged 12 years to less than 18 years.

Biotransformation
In humans aged 5 months or above the metabolism of tapentadol is extensive.

Elimination
Based on a population pharmacokinetic analysis, the mean (± SD) apparent oral clearance (CL/F) of tapentadol following oral administration of tapentadol PR tablets in paediatrics was 135 L/h (± 51 L/h) for children aged 6 years to less than 12 years, and 180 L/h (± 45 L/h) for children aged 12 years to less than 18 years.

Special populations
Renal and Hepatic Impairment
Apeneta has not been studied in children and adolescents with renal and hepatic impairment.

Pharmacokinetic Interactions
Dedicated drug-drug interaction trials have not been performed in children and adolescents.

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.

Juvenile rats were treated from post-natal day 6 to day 90, which covered the period of development corresponding to infancy, childhood and adolescence in humans. During the first 3 days of treatment, a numerically higher incidence of mortality was observed at doses of ≥ 25 mg/kg/day with tapentadol plasma exposure at the lowest observed adverse effect level (LOAEL) comparable to the predicted clinical plasma exposure in children. Tapentadol was well tolerated in pups older than 10 days.

There were no treatment-related clinical signs, effects on body weight, food consumption, pre-weaning or reproductive development, long-bone growth, motor activity, behaviour or learning and memory. Organ weights and macroscopic or microscopic evaluation showed no treatment-related changes. Tapentadol did not influence sexual development, mating or pregnancy parameters in the treated animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium Stearate

Film coating layer:
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Macrogol
Triacetin
Iron oxide, yellow (E172)
Iron oxide, red (E172)

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

Polyethylene (HDPE) container with a child resistant tamper-evident polypropylene (PP) closure: 30, 60 (2 x 30), 100 prolonged-release tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/105/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd October 2021

10 DATE OF REVISION OF THE TEXT

October 2025