Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Palexia 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 116.48 mg tapentadol hydrochloride equivalent to 100 mg tapentadol.
Excipient(s) with known effect:
PALEXIA100 mg contains 49.5mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pale pink round shaped film-coated tablets of 9 mm diameter, marked with Grünenthal logo on one side and “H8” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Palexia 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

Treatment goals and discontinuation
Before initiating treatment with PALEXIA, a treatment strategy including treatment goals and treatment duration, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with PALEXIA, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

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.
Total 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.

Duration of treatment
The film-coated tablets are intended for acute pain situations. If longer term treatment is anticipated or becomes necessary and effective pain relief in the absence of intolerable adverse events was achieved with PALEXIA, the possibility of switching the patient to therapy with PALEXIA prolonged-release tablets should be considered. As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.

PALEXIA should not be used longer than necessary.

Renal Impairment
In patients with mild or moderate renal impairment a dosage adjustment is not required (see section 5.2).
PALEXIA 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).
PALEXIA 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).
PALEXIAhas 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 PALEXIAin children and adolescents below 18 years of age has not yet been established. Therefore PALEXIAis not recommended for use in this population.

Method of administration
PALEXIA is for oral use.
The tabletshould be taken with sufficient liquid. PALEXIAcan be taken with or without food.

4.3 Contraindications

PALEXIA is contraindicated

- in patients with hypersensitivity to tapentadol or to any of the excipients listed in section 6.1
- in situations whereactive 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 such as PALEXIA. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. 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).
Before initiating treatment with PALEXIA and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.
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.

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

Seizures
PALEXIAhas 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 PALEXIAis 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).

Special populations
Renal Impairment
PALEXIAhas 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. PALEXIAshould be used with caution in patients with moderate hepatic impairment (see section 4.2 and 5.2), especially upon initiation of treatment.
PALEXIA 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. PALEXIA 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 PALEXIA 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.

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

PALEXIA film-coated tablets contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free.

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 PALEXIA 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 PALEXIA 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 PALEXIA with mixed mu-opioid agonist/antagonists (like pentazocine, nalbuphine) or partial mu-opioid agonists (like buprenorphine) (see also section 4.4).

PALEXIA 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 PALEXIA 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*.

Concomitant administration of PALEXIA with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

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

Fertility
No human data on the effect of PALEXIA 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

Palexia 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 changes 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 PALEXIA 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 PALEXIA 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).

ADVERSE DRUG REACTIONS					
System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Unknown**
Immune system disorders				Drug 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	Delirium**
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, Palpitations	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		

** 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 PALEXIA 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
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.

4.9 Overdose

Symptoms
Human experience with overdose of tapentadol is 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 that may be fatal.

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 mu-opioid agonistic 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 Palexia 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 PALEXIA. 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. 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 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 PALEXIA 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 glucoronidation.
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 4 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 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 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.

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 F_1 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:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Povidone K30
Magnesium stearate

Tablet coat:
Polyvinylalcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

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 blisters
Packs with 5, 10, 14, 20, 24, 28, 30, 40, 50, 54, 56, 60, 90, 100 film-coated tablets.

PVC/PVDC aluminium perforated unit-dose blisters
Packs with 10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 90x1, 100x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Grunenthal Pharma Ltd
4045 Kingswood Road
Citywest Business Park
Citywest
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2242/012/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st December 2010
Date of last renewal: 10th August 2015

10 DATE OF REVISION OF THE TEXT

February 2026