SUMMARY OF PRODUCT CHARACTERISTICS PALEXIA®

1. NAME OF THE MEDICINAL PRODUCT[a,b]

Palexia® 50 mg film-coated tablets
Palexia® 75 mg film-coated tablets
Palexia® 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg tapentadol (as hydrochloride).
Each film-coated tablet contains 75 mg tapentadol (as hydrochloride).
Each film-coated tablet contains 100 mg tapentadol (as hydrochloride).

Excipient(s) with known effect:
Palexia® 50 mg contains 24.74 mg lactose.
Palexia® 75 mg contains 37.11 mg lactose.
Palexia® 100 mg contains 49.48 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

[50 mg]: White round shaped film-coated tablets of 7 mm diameter, marked with Grünenthal logo on one side and “H6” on the other side.

[75 mg]: Pale yellow round shaped film-coated tablets of 8 mm diameter, marked with Grünenthal logo on one side and “H7” on the other side.

[100 mg]: 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

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.

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

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

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by either shortening or lengthening the dosing interval (see sections 4.4 and 5.2).
Palexia® 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 Palexia® in children and adolescents below 18 years of age has not yet been established. Therefore Palexia® is not recommended for use in this population.

Method of administration
Palexia® should be taken with sufficient liquid. Palexia® can 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 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
Palexia® has a potential for abuse and addiction. This should be considered when prescribing or dispensing Palexia® in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.
All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, Palexia® may 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
Palexia® 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. Palexia® should be used with caution in patients with head injury and brain tumors.

Seizures
Palexia® 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 Palexia® is not recommended in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
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 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. Palexia® should 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.

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 de-

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pendence, 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, 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

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

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).

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

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.

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.

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.

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.

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.

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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).

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ADVERSE DRUG REACTIONS

	Frequency			
System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**
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
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.*

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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[c].

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 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

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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%.

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 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 C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. 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

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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

[50 mg]:
Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Povidone K30
Magnesium stearate
Tablet coat:
Polyvinylalcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc

[75 mg]:
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)

[100 mg]:
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)

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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[d]
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[e]
Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Germany.

8. MARKETING AUTHORISATION NUMBER(S)[f]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION[g]
Date of first authorisation: 19. August 2010
Date of last renewal: 28. July 2015

10. DATE OF REVISION OF THE TEXT[g]
August 2015

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SUMMARY OF PRODUCT CHARACTERISTICS PALEXIA®

1. NAME OF THE MEDICINAL PRODUCT[a,b]

Palexia® 4 mg/ml oral solution
Palexia® 20 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 4 mg tapentadol (as hydrochloride)
1 ml oral solution contains 20 mg tapentadol (as hydrochloride)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Clear, colourless solution
pH 3.5 to 4.5

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

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 oral solution 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 oral solution is 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.

Calculation table for Palexia® **4 mg/ml** oral solution:

Single dose of tapentadol prescribed	Volume (ml) to be administered
25 mg	6.25 ml
50 mg	12.5 ml
75 mg	18.75 ml
100 mg	25 ml

Calculation table for Palexia® **20 mg/ml** oral solution:

Single dose of tapentadol prescribed	Volume (ml) to be administered
20 mg	1.25 ml
50 mg	2.5 ml
75 mg	3.75 ml
100 mg	5 ml

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

Renal Impairment
In patients with mild or moderate renal impairment a dosage adjustment is not required (see section 5.2).
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 25 mg tapentadol as oral solution and not be administered more frequently than once every 8 hours. At initiation of therapy a daily dose greater than 150 mg tapentadol 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).

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Palexia® 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 Palexia® in children and adolescents below 18 years of age has not yet been established. Therefore Palexia® is not recommended for use in this population.

Method of administration
Palexia® can be taken with or without food.
Palexia® oral solution can be taken either undiluted or diluted in water or any non-alcoholic drink. There is an oral syringe with an attached adaptor in the pack which is recommended to be used to take the exact volume needed from the bottle corresponding to the prescribed single dose of tapentadol.

Palexia® can be taken via enteral tubes, e.g. nasogastric or percutaneous endoscopic gastrostomy (PEG) tubes.

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 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
Palexia® has a potential for abuse and addiction. This should be considered when prescribing or dispensing Palexia® in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.
All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, Palexia® may 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
Palexia® 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. Palexia® should be used with caution in patients with head injury and brain tumors.

Seizures
Palexia® 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 Palexia® is not recommended in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
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 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. Palexia® should 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.

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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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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).

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

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.

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.

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.

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.

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.

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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 another immediate release formulation of tapentadol (Palexia®film-coated 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).

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ADVERSE DRUG REACTIONS

	Frequency			
System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**
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
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.*

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Clinical trials performed using another immediate release formulation of tapentadol (Palexia® film-coated tablets) 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[c].

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 another immediate-release formulation of 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

The bioavailability as assessed by C_{max} and AUC and all other pharmacokinetic parameters determined for tapentadol after administration of 100 mg tapentadol as oral solution were similar compared to a 100 mg film-coated tablet (another oral immediate-release formulation). Therefore the information given below based on trials with film-coated tablets is also applicable to the oral solution.

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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%.

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 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 patients (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 $t_{1/2}$.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

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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

[4 mg/ml]:
Sodium benzoate (E211)
Citric acid monohydrate
Sucralose (E955)
Raspberry flavor (containing propylene glycol)
Purified water

[20 mg/ml]:
Citric acid monohydrate
Sucralose (E955)
Raspberry flavor (containing propylene glycol)
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
After first opening of the bottle, the solution should not be used for longer than six weeks.

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special storage conditions.
After first opening: Store in an upright position.

6.5 Nature and contents of container[d]

High density polyethylene (HDPE)-bottles sealed with aluminium foil liner and closed with a high density polyethylene (HDPE) / polypropylene (PP) child-resistant cap.

Each bottle of the oral solution is provided with an oral syringe and an adapter. The syringe is scaled in 0.25 milliliter increments with a minimum volume of 0.25 ml and a maximum volume of 5 ml.

[4 mg]
100 ml bottles

[20 mg]
100 ml bottles and 200 ml bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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7. MARKETING AUTHORISATION HOLDER[e]

Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Germany.

8. MARKETING AUTHORISATION NUMBER(S)[f]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION[g]

Date of first authorisation: 04. October 2012
Date of last renewal: 28. July 2015

10. DATE OF REVISION OF THE TEXT[g]

August 2015

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SUMMARY OF PRODUCT CHARACTERISTICS PALEXIA® RETARD

1. NAME OF THE MEDICINAL PRODUCT[a,b]

Palexia® retard 25 mg prolonged-release tablets
Palexia® retard 50 mg prolonged-release tablets
Palexia® retard 100 mg prolonged-release tablets
Palexia® retard 150 mg prolonged-release tablets
Palexia® retard 200 mg prolonged-release tablets
Palexia® retard 250 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 25 mg tapentadol (as hydrochloride).
Each prolonged-release tablet contains 50 mg tapentadol (as hydrochloride).
Each prolonged-release tablet contains 100 mg tapentadol (as hydrochloride).
Each prolonged-release tablet contains 150 mg tapentadol (as hydrochloride).
Each prolonged-release tablet contains 200 mg tapentadol (as hydrochloride).
Each prolonged-release tablet contains 250 mg tapentadol (as hydrochloride).

Excipient(s) with known effect:
Palexia® retard 25 mg contains 1.330 mg lactose.
Palexia® retard 50 mg contains 3.026 mg lactose.
Palexia® retard 100 mg contains 3.026 mg lactose.
Palexia® retard 150 mg contains 3.026 mg lactose.
Palexia® retard 200 mg contains 3.026 mg lactose.
Palexia® retard 250 mg contains 3.026 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

[25 mg]: Slightly brownish-orange film-coated oblong shaped tablets (5.5 mm x 10 mm) marked with Grünenthal logo on one side and “H9” on the other side.

[50 mg]: White film-coated oblong shaped tablets (6.5 mm x 15 mm) marked with Grünenthal logo on one side and “H1” on the other side.

[100 mg]: Pale yellow film-coated oblong shaped tablets (6.5 mm x 15 mm) marked with Grünenthal logo on one side and “H2” on the other side.

[150 mg]: Pale pink film-coated oblong shaped tablets (6.5 mm x 15 mm) marked with Grünenthal logo on one side and “H3” on the other side.

[200 mg]: Pale orange film-coated oblong shaped tablets (7 mm x 17 mm) marked with Grünenthal logo on one side and “H4” on the other side.

[250 mg]: Brownish red film-coated oblong shaped tablets (7 mm x 17 mm) marked with Grünenthal logo on one side and “H5” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Palexia® retard 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.
Palexia® retard 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 50 mg tapentadol as prolonged-release tablet administered twice daily.

Initiation of therapy in patients currently taking opioid analgesics

When switching from opioids to Palexia® retard 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 Palexia® retard for patients currently taking opioids compared to those not having taken opioids before initiating therapy with Palexia® retard.

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

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pain control in most of the patients. The 25 mg tapentadol prolonged-release tablet can also be used for dose adjustments to meet individual patient requirements.

Total daily doses of Palexia® retard 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).
Palexia® retard 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
*I*n patients with mild hepatic impairment a dosage adjustment is not required (see section 5.2).
Palexia® retard 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. 25mg 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).
Palexia® retard 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 Palexia® retard in children and adolescents below 18 years of age has not yet been established. Therefore Palexia® retard is not recommended for use in this population.

Method of administration
Palexia® retard has to be taken whole, not divided or chewed, to ensure that the prolonged-release mechanism is maintained. Palexia® retard should be taken with sufficient liquid. Palexia® retard can be taken with or without food.

4.3 Contraindications
Palexia® retard 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
Palexia® retard has a potential for abuse and addiction. This should be considered when prescribing or dispensing Palexia® retard in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.
All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, Palexia® retard may produce dose-related respiratory depression. Therefore, Palexia® retard should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and Palexia® retard 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
Palexia® retard 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. Palexia® retard should be used with caution in patients with head injury and brain tumors.

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Seizures
Palexia® retard 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 Palexia® retard is not recommended in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
Palexia® retard 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. Palexia® retard should be used with caution in patients with moderate hepatic impairment (see section 4.2 and 5.2), especially upon initiation of treatment.
Palexia® retard 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® retard should be used with caution in patients with biliary tract disease, including acute pancreatitis.

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

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

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

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® retard 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.

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

4.7 Effects on ability to drive and use machines
Palexia® retard 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 occurs as well as in connection with 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® retard 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 Palexia® retard 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).

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ADVERSE DRUG REACTIONS

	Frequency			
System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**
Immune system disorders			Drug hypersensitivity+	
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
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 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.*

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Clinical trials performed with Palexia® retard 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[c].

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 European Medicines Agency has deferred the obligation to submit the results of studies with Palexia® retard 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 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.

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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 Palexia® retard 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. Palexia® retard may be given with or without food.

Distribution

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

Metabolism

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 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_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. 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 probe-

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necid, 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 post partum already at dosages that did not provoke maternal toxicities. There were no effects on neurobehavioral parameters.
Excretion into breast milk was investigated in rat pups suckled by dams dosed with tapentadol. Pups were dose-dependently exposed to tapentadol and tapentadol O-glucuronide. It was concluded that tapentadol is excreted in milk.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[25 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 400
Macrogol 6000
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

[50 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 6000
Propylene glycol
Titanium dioxide (E 171)

[100 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 6000
Propylene glycol
Titanium dioxide (E 171)
Yellow iron oxide (E 172)

[150 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 6000
Propylene glycol
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

[200 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 6000
Propylene glycol
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

[250 mg]:
Tablet core:
Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Tablet coat:
Hypromellose
Lactose monohydrate
Talc
Macrogol 6000
Propylene glycol
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

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6.2 Incompatibilities
Not applicable

6.3 Shelf life
[25 mg]:
2 years

[50 mg, 100 mg, 150 mg, 200 mg, 250 mg]:
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[d]
[25 mg]:
PVC/PVDC-aluminium blisters
Packs with 7, 10, 14, 20, 24, 28, 30, 40, 50, 54, 56, 60, 90, 100 prolonged-release tablets.

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

[50 mg, 100 mg, 150 mg, 200 mg, 250 mg]:
PVC/PVDC-aluminium/paper/PET blisters.
Packs with 7, 10, 14, 20, 24, 28, 30, 40, 50, 54, 56, 60, 90, 100 prolonged-release tablets.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER[e]
Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Germany.

8. MARKETING AUTHORISATION NUMBER(S)[f]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION[g]
Palexia® retard 25 mg
Date of first authorisation: 07. May 2012
Date of last renewal: 28. July 2015

Palexia® retard 50 mg, 100 mg, 150 mg, 200 mg, 250 mg
Date of first authorisation: 19. August 2010
Date of last renewal: 28. July 2015

10. DATE OF REVISION OF THE TEXT[g]
July 2016

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