

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PALEXIA 4 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

PALEXIA 4 mg/ml oral solution contains propylene glycol, sodium benzoate and sodium.

See section 4.4

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 children from 2 years of age and in adults, which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration

The use of PALEXIA in children is restricted to hospital use where appropriate equipment to enable respiratory support is available.

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.

Adults:

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.

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

Duration of treatment

The oral solution is intended for acute pain situations. If longer term treatment is anticipated or becomes necessary in adults 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 formulation 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.

Special populations

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). 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 population

Dose recommendation for children is dependent on age and body weight. For children and adolescents from 2 years to less than 18 years the recommended single dose is 1.25 mg per kg body weight every 4 hours. The maximum dose per day is 7.5 mg per kg body weight (6 x single dose). The maximum dose for children and adolescents with a high BMI (body mass index) must not exceed the calculated maximum dose for a body weight at the 97.5 percentile for the given age. Dose reductions may be considered over time as acute pain decreases.

For dosages of 20 mg or more (patients with a body weight of more than 16 kg) PALEXIA 20 mg/ml should be used, for dosages of less than 20 mg (patients with a body weight of 16 kg or less) PALEXIA 4 mg/ml is recommended.

The safety and efficacy of PALEXIA in children younger than 2 years have not yet been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made for children younger than 2 years.

Dose recommendation for children with a body weight of less than 16 kg (PALEXIA 4 mg/ml oral solution):

2 years to less than 18 years. Body weight of 16 kg or less			
1.25 mg/kg every 4 hours.			
PALEXIA 4 mg/ml oral solution (dosing with provided 2.5 ml pipette)			
kg (body weight)	ml (Dose Volume)	kg (body weight)	ml (Dose Volume)
9.0 - 9.2	2.8	12.8 - 13.1	4.0
9.3 - 9.5	2.9	13.2 - 13.4	4.1
9.6 - 9.9	3.0	13.5 - 13.7	4.2
10.0 - 10.2	3.1	13.8 - 14.0	4.3

10.3 - 10.5	3.2		14.1 - 14.3	4.4
10.6 - 10.8	3.3		14.4 - 14.7	4.5
10.9 - 11.1	3.4		14.8 - 15.0	4.6
11.2 - 11.5	3.5		15.1 - 15.3	4.7
11.6 - 11.8	3.6		15.4 - 15.6	4.8
11.9 - 12.1	3.7		15.7 - 15.9	4.9
12.2 - 12.4	3.8		16	5.0
12.5 - 12.7	3.9			

Duration of treatment

The oral solution is intended for acute pain situations. As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis. In children the duration of treatment should not exceed 3 days as safety and efficacy of longer treatment are not yet available.

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

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

Hepatic Impairment

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

Method of administration

PALEXIA is for oral use.

PALEXIA can be taken with or without food.

PALEXIA can be taken either undiluted or diluted in water or any non-alcoholic drink. There is a dosing pipette 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 may be taken via enteral tubes, e.g. administered through a nasogastric tube made of polyurethane, silicone, or polyvinyl chloride (these materials were tested and showed no interactions or degradation of tapentadol).

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.

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

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

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

Respiratory Depression

At high doses or in mu-opioid receptor agonist sensitive patients, 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. In addition, tapentadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold (see section 4.5).

Renal Impairment

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 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 4 mg/ml contains sodium benzoate, propylene glycol and sodium

This medicine contains 59 mg sodium benzoate in 25 ml solution (maximum single dose) which is equivalent to 2.36 mg/ml. This medicine contains 48 mg propylene glycol per 25 ml solution (maximum single dose) which is equivalent to 2.0 mg/ml. This medicine contains less than 1 mmol sodium (23 mg) per maximum single dose, that is to say essentially 'sodium-free'.

Paediatric population

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

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

PALEXIA is not recommended in children aged below 2 years (see section 4.1)

PALEXIA has not been systematically evaluated in children and adolescent with obesity, therefore, paediatric patients with obesity should be extensively monitored and the recommended maximum dose for the age should not be exceeded.

PALEXIA is intended for use in acute pain, and was therefore investigated in short-term treatment. Thus, no long-term safety data in children (e.g. for growth or development) are available.

4.5 Interaction with other medicinal products and other forms of interactions

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of PALEXIA with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Therefore, when a combined therapy of PALEXIA with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered and the duration of the concomitant use should be limited (see section 4.4).

Mixed opioid agonists/antagonists

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

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

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

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

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

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

The major elimination pathway for tapentadol is conjugation with glucuronic acid mediated via uridine diphosphate transferase (UGT) mainly UGT1A6, UGT1A9 and UGT2B7 isoforms. Thus, concomitant administration with strong inhibitors of these isoenzymes (e.g. ketoconazole, fluconazole, meclofenamic acid) may lead to increased systemic exposure of tapentadol (see section 5.2).

Due to the major elimination pathway being glucuronide conjugation the potential for interactions in adults is low.

Additionally, *in vitro*, tapentadol was found not to induce or inhibit any of the main CYP enzymes, including CYP3A4.

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*.

Paediatric population

Due to the major elimination pathway being glucuronide conjugation the potential for interactions in children aged more than 5 months is low (see section 4.2).

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.

Breast-feeding

There is no information on the excretion of tapentadol in human milk. From a study in rat pups suckled by dams dosed with tapentadol it was concluded that tapentadol is excreted in milk (see section 5.3). Therefore, a risk to the suckling child cannot be excluded. 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 change of dosage occurs as well as in connection with the use of alcohol or tranquilisers (see section 4.4). Patients should be cautioned as to whether driving or use of machines is permitted.

4.8 Undesirable effects

The adverse drug reactions that were experienced by adult 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 most severe adverse drug reactions are sedation, respiratory depression and allergic reactions.

The table below lists adverse drug reactions that were identified from clinical trials performed in adults with another immediate release formulation of tapentadol (PALEXIA film-coated tablets) and from post-marketing data in adults. They are listed by class and frequency. Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

ADVERSE DRUG REACTIONS

System Organ Class	Frequency			
	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	Depressed mood, Disorientation, Agitation, Nervousness, Restlessness, Euphoric mood	Thinking abnormal

		dreams		
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.

Clinical trials performed in adults 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.

Paediatric population

Frequency, type and severity of adverse reactions in children and adolescents treated with PALEXIA are expected to be the same as in adults treated with PALEXIA. No new safety issues have been identified from completed paediatric trials for any of the age subgroups investigated.

No clinical trial data on withdrawal symptoms in children using IR formulation of tapentadol are available; however physicians should be vigilant for symptoms of withdrawal after repeated administration of tapentadol and its abrupt cessation (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2. Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

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 in adults 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 in adults was similar to that observed with a strong opioid used as comparator.

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

Paediatric population

Efficacy of tapentadol oral solution taken for up to 72 hours has been demonstrated in children and adolescents (age between 2 years and <18 y) with postsurgical pain.

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.

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, 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 (V_z) for tapentadol is 540 +/- 98 l.

The serum protein binding is low and amounts to approximately 20% mainly bound to albumin.

Metabolism

About 97% of the parent compound is metabolised. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% of the dose is excreted in urine as conjugated forms (55% glucuronide and 15% sulfate of tapentadol). Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of active substance is excreted in urine as unchanged active substance. Tapentadol is additionally metabolised to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolised by conjugation. Therefore, active substance metabolism mediated by cytochrome P450 system is of less importance than glucuronidation. None of the metabolites contributes to the analgesic activity.

Elimination

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The total clearance after intravenous administration is 1530 +/- 177 ml/min.

Special populations

Elderly

The mean exposure (AUC) to tapentadol was similar in a trial with elderly subjects (65-78 years of age) compared to young adults (19-43 years of age), with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment

AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild

and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max} ; and 1.2 and 1.4, respectively, for $t_{1/2}$. 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 phase 2 metabolism are unlikely to occur. In a set of drug-drug interaction trials using paracetamol, naproxen, acetylsalicylic acid and probenecid, a possible influence of these active substances on the glucuronidation of tapentadol was investigated. The trials with probe active substances naproxen (500 mg twice daily for 2 days) and probenecid (500 mg twice daily for 2 days) showed increases in AUC of tapentadol by 17% and 57%, respectively. Overall, no clinically relevant effects on the serum concentrations of tapentadol were observed in these trials. Furthermore, interaction trials of tapentadol with metoclopramide and omeprazole were conducted to investigate a possible influence of these active substances on the absorption of tapentadol. These trials also showed no clinically relevant effects on tapentadol serum concentrations.

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

Paediatric population

Absorption

In the paediatric population the maximum serum concentrations were observed at a similar time to adults, with no age related changes.

Food Effect

A dedicated food effect trial has not been performed in children and adolescents. In the phase III trial performed in children and adolescentstapentadol oral solution was given irrespective of food intake.

Based on efficacy data obtained during the phase III trial in children and adolescents, the food effect does not appear to be of clinical relevance. PALEXIA may be given with or without food.

Distribution

The volume of distribution per age group in children following oral administration of tapentadol and derived from population pharmacokinetic modelling (Pop PK) is shown in the following table:

Age group	Apparent volume of distribution (V/F) following oral administration (L) Mean +/- SE
12 years to less than 18 years	923 +/- 36
6 years to less than 12 years	534 +/- 25
2 years to less than 6 years	276 +/- 17

Parameters based on new combined model

Metabolism

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

Elimination

The paediatric clearance of tapentadol following oral administration and derived from Pop PK modelling for the different age groups is shown in the table below.

Age group	Apparent clearance of tapentadol (CL/F) following oral administration (L/h) Mean +/- SD
12 years to less than 18 years	212 +/- 7
6 years to less than 12 years	149 +/- 7
2 years to less than 6 years	80 +/- 5

Parameters based on new combined model

Special populations

Renal and Hepatic Impairment

PALEXIA has not been studied in children and adolescents with renal and hepatic impairment.

Pharmacokinetic Interactions

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

5.3 Preclinical safety data

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

Tapentadol had no influence on male or female fertility in rats but there was reduced *in utero* survival at the high dose. It is not known whether this was mediated via the male or the female. Tapentadol showed noteratogenic 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 (μ -opioid related CNS effects related to dosing above the therapeutic range). After intravenous dosing in rats reduced *in utero* survival was seen. In rats tapentadol caused increased mortality of the F₁ pups that were directly exposed via milk between days 1 and 4 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.

Juvenile rats were treated from post-natal day 6 to day 90, which covered the period of development corresponding to infancy, childhood and adolescence in humans. During the first 3 days of treatment, a numerically higher incidence of mortality was observed at doses of ≥ 25 mg/kg/day with Tapentadol plasma exposure at the LOAEL comparable to the predicted clinical plasma exposure in children. Tapentadol was well tolerated in pups older than 10 days, There were no treatment-related clinical signs, effects on body weight, food consumption, pre-weaning or reproductive development, long-bone growth, motor activity, behaviour or learning and memory. Organ weights and macroscopic or microscopic evaluation showed no treatment-related changes. Tapentadol did not influence sexual development, mating or pregnancy parameters in the treated animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E 211)

Citric acid monohydrate

Sucralose (E 955)

Raspberry flavor containing propylene glycol (E 1520)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 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

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 a dosing pipette and an adapter attached to the dosing pipette. The scale of the 2.5 ml dosing pipette is subdivided in 0.05 ml intervals.

100 ml bottles

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

For other handling details see section 4.2

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA2242/012/010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th January 2013
Date of last renewal: 10th August 2015

10 DATE OF REVISION OF THE TEXT

July 2019