

## **NAME OF THE MEDICINE**

PALEXIA® IR 50 mg tapentadol (as hydrochloride) immediate release, film coated tablets

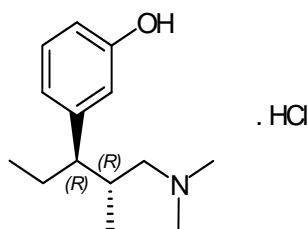
PALEXIA® IR 75 mg tapentadol (as hydrochloride) immediate release, film coated tablets

PALEXIA® IR 100 mg tapentadol (as hydrochloride) immediate release, film coated tablets

## **DESCRIPTION**

PALEXIA® IR immediate release tablets contain tapentadol hydrochloride (HCl) which is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake inhibition activity in a single molecule. Tapentadol is a white to off-white powder; freely soluble in water and methanol, and soluble in ethanol. The  $pK_{a1}$  is 9.36 and  $pK_{a2}$  is 10.37 determined in 0.15 M KCl solution. The partition coefficient is defined as the ratio of the equilibrium concentrations of a single neutral molecular species in a 1-octanol/aqueous buffered solution 2-phase system. The value of log P for tapentadol hydrochloride in 1-octanol/water is  $2.89 \pm 0.01$ . The chemical name for tapentadol HCl is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is  $C_{14}H_{23}NO \cdot HCl$ .

The structural formula of tapentadol HCl (CAS number: 175591-09-0) is:



PALEXIA® IR tablets contain 50, 75 or 100 mg tapentadol (as hydrochloride).

Excipients in the table core are: microcrystalline cellulose, lactose, croscarmellose sodium, povidone (K30) and magnesium stearate.

Excipients in the film coating are: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172) (75 and 100 mg tablets only), iron oxide red (E172) (75 and 100 mg tablets only), and iron oxide black (E172) (100 mg tablets only).

## **PHARMACOLOGY**

### **Pharmacodynamics**

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. It has 18 times less binding affinity than morphine to the human mu-opioid receptor but was only 2-3 times less potent in producing analgesia in animal models (on a dose per body weight basis). This low *in-vivo* potency difference is consistent with its two mechanisms of action. Tapentadol has been shown to inhibit noradrenaline reuptake in the brains of rats resulting in increased

noradrenaline concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonised by selective mu-opioid receptor antagonists (e.g., naloxone), whereas the noradrenaline reuptake inhibition is sensitive to noradrenaline modulators. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

Effects on the cardiovascular system: In repeat dose toxicity studies in conscious dogs, non-persistent QT/QTc interval prolongation was observed at exposures similar to or lower than the clinical plasma  $C_{max}$ . These effects were not observed in safety pharmacology studies with repeated ECG measurements. Heart rate was increased in conscious rats and dogs at peak plasma concentrations at least twice the clinical plasma  $C_{max}$ , but there was no clear effect on other ECG parameters (PR interval, QRS duration, T-wave or U-wave morphology). In a thorough QT trial in healthy subjects, no effect of multiple therapeutic and suprathreshold doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

## **Pharmacokinetics**

### *Absorption*

Tapentadol is rapidly and completely absorbed after oral administration of PALEXIA<sup>®</sup> IR. 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 PALEXIA<sup>®</sup> IR tablets. Dose-proportional increases in the  $C_{max}$  and AUC values of tapentadol have been observed after administration of PALEXIA<sup>®</sup> IR tablets over the oral therapeutic dose range. Steady state serum concentrations of tapentadol are reached on the second day of the treatment regimen.

A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol administered as immediate release tablets showed an accumulation ratio between 1.4 and 1.7 for the parent drug 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.

### *Food Effect*

The AUC and  $C_{max}$  increased by 25% and 16%, respectively, when PALEXIA<sup>®</sup> IR tablets were administered after a high-fat, high-calorie breakfast. PALEXIA<sup>®</sup> IR tablets may be given with or without food.

### *Distribution*

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

### *Metabolism and Elimination*

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% (55% glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of drug was excreted in urine as unchanged drug.

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, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

#### *Elderly patients*

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, 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 was 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 ratios 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 Phase 2 glucuronidation, and only a small amount is metabolised by Phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, any clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. This has been evidenced by clinical pharmacokinetic drug-drug interaction studies with probe drugs naproxen and probenecid with increases in AUC of tapentadol by 17% and 57%, respectively. No changes in the pharmacokinetic parameters of tapentadol were observed when paracetamol and acetylsalicylic acid were given concomitantly. Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro* but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide,

respectively.

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.

## CLINICAL TRIALS

The efficacy and safety of PALEXIA<sup>®</sup> IR tablets in the treatment of moderate to severe pain has been investigated in four pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in in-patients following bunionectomy (clinical trials KF5503/32 and KF5503/37), one in in-patients following abdominal hysterectomy (clinical trial KF5503/35), and one in out-patients with end stage degenerative joint disease of the hip or knee (clinical trial KF5503/33).

### Orthopaedic Surgery – Bunionectomy

The first bunionectomy clinical trial (KF5503/32) (n=603) investigated the efficacy of PALEXIA<sup>®</sup> IR tablets (50, 75 and 100 mg) against placebo and active comparator (oxycodone HCl IR 15 mg). The primary objective was to determine the efficacy of PALEXIA<sup>®</sup> IR tablets using the sum of pain intensity difference (SPID) over 48 hours compared to placebo, and to assess the safety and tolerability of repeat doses of PALEXIA<sup>®</sup> IR tablets over the double-blind treatment period.

PALEXIA<sup>®</sup> IR (50, 75 or 100 mg), (n=119, 120 and 118 respectively), placebo (n=121) or oxycodone HCl IR (15 mg) (n=125) were administered as a single dose, once every 4 to 6 hours over the 72 hours following randomisation.

The results for SPID<sub>48</sub> for the ITT population are provided in Table 1. All PALEXIA<sup>®</sup> IR treatment groups showed a statistically significant (p<0.001) improvement in pain compared to placebo (mean SPID<sub>48</sub>: 119.1, 139.1, 167.2 in the 50, 75 and 100 mg groups respectively). There was a numerical trend of increasing efficacy with increasing dose of PALEXIA<sup>®</sup> IR. Oxycodone HCl (mean SPID<sub>48</sub>: 172.3) also showed a statistically significant (p<0.001) difference to placebo (mean SPID<sub>48</sub>: 24.5).

**Table 1. Sum of Pain Intensity Difference (SPID) at 48h<sup>a</sup>, ITT population**

	Placebo (n=120)	PALEXIA <sup>®</sup> IR 50 mg (n=119)	PALEXIA <sup>®</sup> IR 75 mg (n=120)	PALEXIA <sup>®</sup> IR 100 mg (n=118)	Oxycodone IR HCl 15 mg (n=125)
<b>Mean SPID<sub>48</sub> (SD)</b>	24.5 (120.93)	119.1 (125.86)	139.1 (118.93)	167.2 (98.99)	172.3 (110.86)
<b>LS Means (diff from placebo)</b>		88.2	113.5	141.4	142.4
<b>95% CI</b>		60.71, 115.59	86.12, 140.81	113.98, 168.90	115.28, 169.47
<b>p-value<sup>b</sup></b>		<0.001	<0.001	<0.001	

a: the summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief.

b: adjusted p-value vs placebo; based on analysis of covariance model with factors of treatment, centre, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.

LS = least square

The second bunionectomy clinical trial (KF5503/37) (n=291) investigated the efficacy of PALEXIA® IR 75 mg against placebo and active comparator (morphine IR 30 mg). The primary objective was to determine the efficacy of PALEXIA® IR 75 mg using the sum of pain intensity difference (SPID) over 48 hours compared to placebo, and to assess the efficacy and safety of PALEXIA® IR 75 mg compared to morphine IR 30 mg.

PALEXIA® IR 75 mg (n=96), placebo (n=99) or morphine IR 30 mg (n=96) were administered as a single dose, once every 4 to 6 hours over the 72 hours following randomisation.

In the ITT population, for SPID<sub>48</sub>, PALEXIA® IR 75 mg showed a statistically significant improvement in pain relief compared to placebo (LS Mean difference to placebo of 70.8, p<0.0001). Morphine IR 30 mg also demonstrated a statistically significant improvement in pain relief compared to placebo (LS Mean difference to placebo of 109.4; p-value < 0.0001) (Table 2).

**Table 2. Sum of Pain Intensity Difference (SPID) at 48h<sup>a</sup>, ITT population**

	Placebo (n=96)	PALEXIA® IR 75 mg (n=96)	Morphine IR 30 mg (n=93)
<b>Mean SPID<sub>48</sub> (SD)</b>	-17.5 (111.27)	46.2 (130.83)	102.5 (153.26)
<b>LS Means (diff from placebo)</b>		70.8	109.4
<b>95% CI</b>		35.9, 105.6	74.2, 144.6
<b>p-value</b>		<0.0001	<0.0001

a: the summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief. LS = least square

### **Abdominal Surgery - Hysterectomy**

The abdominal hysterectomy clinical trial (KF5503/35) (n=854) investigated the efficacy and tolerability of PALEXIA® IR (50, 75 and 100 mg) against placebo and active comparator (morphine IR 20 mg). The primary objective was to determine the efficacy of PALEXIA® IR using the sum of pain intensity difference (SPID) over 24 hours compared to placebo, and to assess the safety and tolerability of repeat doses of PALEXIA® IR over the double-blind treatment period.

PALEXIA® IR (50, 75 or 100 mg) (n=168, 171 and 176 respectively), placebo (n=169) or morphine IR (20 mg) (n=170) were administered as a single dose, once every 4 to 6 hours over the 72 hours following randomisation.

In the ITT population, all PALEXIA® IR treatment groups showed statistically significant improvement in pain relief compared to the placebo group for the primary variable, SPID<sub>24</sub> (p<0.0001) (Table 3). There was a numerical trend of increasing efficacy with increasing dose of PALEXIA® IR (LS Means difference to placebo for SPID<sub>24</sub>: 18.1, 20.8 and 23.3 in the 50, 75 and 100 mg groups respectively). Morphine IR 20 mg (LS Means difference to placebo for SPID<sub>24</sub>: 20.6) also showed a statistically significant (p<0.0001) difference to placebo.

**Table 3. Sum of Pain Intensity Difference (SPID) at 24h<sup>a</sup>, ITT population**

	Placebo (n=166)	PALEXIA <sup>®</sup> IR 50 mg (n=163)	PALEXIA <sup>®</sup> IR 75 mg (n=167)	PALEXIA <sup>®</sup> IR 100 mg (n=172)	Morphine IR 20 mg (n=164)
<b>Mean SPID<sub>24</sub></b> (SD)	29.0 (44.98)	49.0 (39.87)	52.4 (41.85)	52.9 (40.95)	48.8 (41.00)
<b>LS Means</b> (diff from placebo)		18.1	20.8	23.3	20.6
<b>95% CI</b>		10.9, 25.3	13.7, 28.0	16.3, 30.4	13.4, 27.8
<b>p-value</b>		<0.0001	<0.0001	<0.0001	<0.0001

a: the summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief. LS = least square

### End-Stage Degenerative Joint Disease

The clinical trial in subjects with end stage degenerative joint disease of the hip or knee (clinical trial KF5503/33) (n=674) investigated the efficacy and tolerability of PALEXIA<sup>®</sup> IR (50 and 75 mg) against placebo and active comparator (oxycodone HCl IR 10 mg). The primary objective was to determine the efficacy of PALEXIA<sup>®</sup> IR using the sum of pain intensity difference (SPID) over 5 days compared to placebo, and to assess the safety and tolerability of repeat doses of PALEXIA<sup>®</sup> IR over the double-blind treatment period.

PALEXIA<sup>®</sup> IR (50 or 75 mg) (n=161 and 169 respectively), placebo (n=172) or oxycodone HCl IR (10 mg) (n=172) were administered as a single dose, once every 4 to 6 hours over 10 days following randomisation.

In the ITT population, both PALEXIA<sup>®</sup> IR 50 mg and 75 mg treatment groups showed a significant improvement in pain compared to placebo for the primary efficacy variable of SPID at 5 days (all p values <0.001) (Table 4). There was no numerical trend of increasing efficacy with increasing dose of PALEXIA<sup>®</sup> IR (LS Means difference to placebo for SPID<sub>5 days</sub>: 101.2 and 97.5 respectively). Oxycodone HCl IR (10 mg) also showed a statistically significant (p<0.001) difference to placebo (Table 4).

**Table 4. Sum of Pain Intensity Difference (SPID) at 5 days<sup>a</sup>, ITT population**

	Placebo (n=169)	PALEXIA <sup>®</sup> IR 50 mg (n=153)	PALEXIA <sup>®</sup> IR 75 mg (n=166)	Oxycodone HCl IR (10 mg) (n=171)
<b>Mean SPID<sub>5 days</sub></b> (SD)	130.6 (182.77)	229.2 (228.92)	223.8 (217.76)	236.5 (222.82)
<b>LS Means</b> (diff from placebo)		101.2	97.5	111.9
<b>95% CI</b>		54.58, 147.89	51.81, 143.26	66.49, 157.38
<b>Raw p-value</b>		<0.001	<0.001	<0.001

a: the summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief. LS = least square

This study also included the pre-specified assessment of the non-inferiority of Palexia<sup>®</sup> IR (50 and 75 mg) compared to oxycodone HCl IR (10 mg) with respect to efficacy (based on 5-day SPID) and tolerability (based on incidence of the reported evaluation of nausea and vomiting as adverse events of nausea and/or vomiting and

constipation). For 5 day SPID, both PALEXIA<sup>®</sup> IR 50 mg and PALEXIA<sup>®</sup> IR 75 mg were non-inferior to oxycodone HCl IR 10 mg.

## INDICATIONS

PALEXIA<sup>®</sup> IR is indicated for the relief of moderate to severe pain.

## CONTRAINDICATIONS

PALEXIA<sup>®</sup> IR is contraindicated:

- in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product,
- in situations where drugs 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 drugs (see **INTERACTIONS WITH OTHER MEDICINES**),
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see **INTERACTIONS WITH OTHER MEDICINES**).

## PRECAUTIONS

### Potential for Abuse

As with other drugs that have mu-opioid receptor agonist activity, PALEXIA<sup>®</sup> IR has a potential for abuse. This should be considered when prescribing or dispensing PALEXIA<sup>®</sup> IR in situations where there is concern about an increased risk of misuse, abuse, or diversion.

Drugs that have mu-opioid receptor agonist activity may be abused by crushing, chewing, snorting or injecting the product. Such practices pose a significant risk to the abuser and may result in overdose or death.

All patients treated with drugs that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

### Drug Dependence

**Tolerance:** Repeated administration of opioids may lead to tolerance. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia, in the absence of disease progression or other external factors.

**Withdrawal symptoms:** Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see **DOSAGE and ADMINISTRATION**). In a study conducted over 3 months, 17.3% of patients given PALEXIA<sup>®</sup> IR had objective signs of opioid withdrawal compared with 26.1 % given oxycodone IR when assessed between 2 - 5 days after the last dose of study drug. Only 0.3% of patients given PALEXIA<sup>®</sup> IR and 3% given oxycodone IR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

### **Respiratory Depression**

At high doses or in mu-opioid receptor agonist sensitive patients, PALEXIA<sup>®</sup> IR may produce dose-related respiratory depression. Therefore, PALEXIA<sup>®</sup> IR should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and PALEXIA<sup>®</sup> IR 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 **OVERDOSAGE**).

### **Head Injury and Increased Intracranial Pressure**

Like other drugs with mu-opioid receptor agonist activity, PALEXIA<sup>®</sup> IR 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<sup>®</sup> IR should be used with caution in patients with head injury and brain tumours.

### **Seizures**

PALEXIA<sup>®</sup> IR has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. However, like other analgesics with mu-opioid receptor agonist activity PALEXIA<sup>®</sup> IR should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

### **Renal Impairment**

For patients with mild or moderate renal impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

PALEXIA<sup>®</sup> IR has not been studied in controlled efficacy studies in patients with severe renal impairment, therefore use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

### **Hepatic Impairment**

For patients with mild hepatic impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

A study of PALEXIA<sup>®</sup> IR in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA<sup>®</sup> IR should be used with caution in patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

PALEXIA<sup>®</sup> IR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

### **Use in Pancreatic/Biliary Tract Disease**

Drugs with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. PALEXIA<sup>®</sup> IR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

### **Effects on fertility**

There were no apparent effects on the fertility of male rats at intravenous doses up to 12 mg/kg/day, although histopathology analyses were not conducted. In female rats, the



numbers of corpora lutea and implantations were reduced, and pre- and post-implantation losses were increased, at intravenous tapentadol doses associated with maternal toxicity. The clinical relevance of these findings is unknown.

### **Use in pregnancy (Category C)**

There are no adequate and well controlled studies of tapentadol in pregnant women. PALEXIA® IR should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

The effect of tapentadol on labour and delivery in humans is unknown. PALEXIA® IR is not recommended for use in women during and immediately prior to labour and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, neonates whose mothers have been taking tapentadol should be monitored for respiratory depression.

Tapentadol crosses the placenta in pregnant rats. Tapentadol was evaluated for teratogenic effects in rats and rabbits following intravenous and subcutaneous administration during organogenesis. Embryofetal toxicity such as delays in skeletal maturation and cerebral ventricular dilation was observed in rats concomitant with maternal toxicity at subcutaneous doses of 10 mg/kg/day or greater (plasma AUC exposure less than maximum anticipated clinical exposure). Subcutaneous administration of tapentadol to rabbits revealed embryofetal toxicity at doses of 10-24 mg/kg/day (AUC exposure 1 to 2 fold the maximum anticipated human exposure), along with reduced fetal viability, skeletal delays and other variations, and multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia and cleft palate at 10-24 mg/kg/day, and ablepharia, encephalopathy and spina bifida at 24 mg/kg/day. There were no teratogenic effects observed in similar studies conducted in rats and rabbits via the intravenous route (up to 15 mg/kg/day). Embryofetal toxicity, including malformations, may be secondary to maternal toxicity in these species.

### **Use in lactation**

There is limited information on the excretion of tapentadol in breast milk. Tapentadol is excreted into milk in lactating rats following oral dosing. Oral tapentadol administration to rats during lactation resulted in increased postnatal pup mortality, at doses lower than those associated with maternal toxicity (exposure (AUC) less than maximum anticipated clinical exposure). The potential relevance to humans is unknown. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. PALEXIA® IR should not be used during breast feeding.

### **Paediatric use**

PALEXIA® IR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

### **Use in the elderly (persons aged 65 years and over)**

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

### **Carcinogenicity**

Tapentadol was administered to rats (diet) and mice (oral gavage) for two years. A significant trend towards increased hepatocellular tumours (adenoma and carcinoma)

was observed in mice at oral doses of 100 mg/kg/day or greater. A dose-related increased incidence of hepatocellular hypertrophy (but not tumours) was observed in rats at dietary doses of 125 mg/kg/day or greater. Exposures (plasma AUC) in both species were less than that at the maximum recommended clinical dose. These findings may derive from adaptive changes following hepatic enzyme induction. The potential clinical relevance is unknown.

### **Genotoxicity**

Tapentadol did not induce gene mutations in bacteria, but was clastogenic at cytotoxic concentrations in an *in vitro* chromosomal aberration test with metabolic activation in Chinese hamster V79 cells in 1 of 2 assays. The one positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, at extrapolated exposures (AUC) similar to the maximum anticipated human exposure. The weight of evidence indicates that tapentadol presents no significant genotoxic potential at clinical doses.

### **Effects on Ability to Drive and Use Machines**

Like drugs with mu-opioid receptor agonist activity, PALEXIA<sup>®</sup> IR may have a major influence on the ability to drive and use machines, due to the fact that it may adversely affect central nervous system functions (see **ADVERSE EFFECTS**). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers (see **INTERACTIONS WITH OTHER MEDICINES**). Patients should be cautioned as to whether driving or use of machines is permitted.

## **INTERACTIONS WITH OTHER MEDICINES**

Tapentadol is mainly metabolised by glucuronidation, a system with a very high capacity which is not easily saturated even in disease. As therapeutic concentrations of drugs that are subject to glucuronidation are generally well below the concentrations needed for potential inhibition of glucuronidation, the risk of clinically relevant interaction between these drugs is generally low. The following substances have been included in a set of interaction studies without any clinically significant finding: paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole and metoclopramide (see **Pharmacokinetics**).

Only a small amount of tapentadol is metabolised by oxidative pathways (see **Pharmacokinetics**). Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro* but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.

### Mu-opioid agonists/antagonists

There is no clinical data on the concomitant use of PALEXIA<sup>®</sup> IR with mixed opioid agonist/antagonists or partial mu-opioid agonists. As with pure mu-opioid agonists, the analgesic effect provided by the mu-opioid component of PALEXIA<sup>®</sup> IR may be theoretically reduced in such circumstances. Therefore, care should be taken when combining PALEXIA<sup>®</sup> IR with these medicinal products.

### CNS depressants

Patients receiving other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA<sup>®</sup> IR may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with PALEXIA<sup>®</sup> IR. When such combined therapy is contemplated, the reduction of dose of one or both agents should be considered.

### Monoamine oxidase (MAO) inhibitors

PALEXIA<sup>®</sup> IR is contraindicated 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 noradrenaline levels which may result in adverse cardiovascular events (see **CONTRAINDICATIONS**).

### **Serotonin Syndrome**

PALEXIA<sup>®</sup> IR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline reuptake inhibition activity

A causal relationship between tapentadol and serotonin syndrome has not been established, however, in isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tapentadol in combination with serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), MAOIs and triptans. Signs of serotonin syndrome may include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

## **ADVERSE EFFECTS**

### **Treatment emergent adverse events in the double-blind Phase 2/3 studies**

In the Phase 2/3 multiple-dose double-blind studies, the percentage of subjects administered PALEXIA<sup>®</sup> IR with at least 1 TEAE was 71.9%. This was higher when compared with the placebo group (47.8%), lower than in the oxycodone HCl IR group (84.0%) (Table 5).

Compared with oxycodone HCl IR there was better gastrointestinal tolerability with PALEXIA<sup>®</sup> IR. In the Phase 2/3 multiple-dose double-blind studies, the incidence of nausea (27.8%), vomiting (16.4%), and constipation (7.8%) was lower with PALEXIA<sup>®</sup> IR than with oxycodone HCl IR (44.1%, 30.8%, and 19.7%, respectively) (Table 5).

Fewer PALEXIA<sup>®</sup> IR subjects discontinued treatment due to gastrointestinal events compared to oxycodone HCl IR (3.8% vs 12.1%, respectively).

**Table 5. TEAEs in at least 5% of subjects in any treatment group: Phase 2/3 multiple dose double-blind safety analysis set<sup>a</sup>**

<b>System organ class/preferred term</b>	<b>Placebo (n=788) n (%)</b>	<b>All PALEXIA<sup>®</sup> IR (n=2694) n (%)</b>	<b>All oxycodone HCl IR (n=675) n (%)</b>	<b>All morphine IR (n=266) n (%)</b>
<b>Number (n (%)) of subjects with TEAE</b>	<b>377 (47.8)</b>	<b>1937 (71.9)</b>	<b>567 (84.0)</b>	<b>185 (69.5)</b>
<b>Gastrointestinal disorders</b>	<b>171 (21.7)</b>	<b>1166 (43.3)</b>	<b>432 (64.0)</b>	<b>138 (51.9)</b>
Nausea	101 (12.8)	750 (27.8)	298 (44.1)	96 (36.1)
Vomiting	30 (3.8)	442 (16.4)	208 (30.8)	67 (25.2)
Constipation	25 (3.2)	210 (7.8)	133 (19.7)	26 (9.8)
<b>Nervous system disorders</b>	<b>151 (19.2)</b>	<b>1003 (37.2)</b>	<b>276 (40.9)</b>	<b>81 (30.5)</b>
Dizziness	56 (7.1)	552 (20.5)	167 (24.7)	30 (11.3)
Somnolence	22 (2.8)	348 (12.9)	87 (12.9)	27 (10.2)
Headache	77 (9.8)	263 (9.8)	69 (10.2)	37 (13.9)
<b>General disorders and administration site conditions</b>	<b>61 (7.7)</b>	<b>344 (12.8)</b>	<b>110 (16.3)</b>	<b>37 (13.9)</b>
Pyrexia	27 (3.4)	92 (3.4)	16 (2.4)	16 (6.0)
<b>Skin and subcutaneous tissue disorders</b>	<b>37 (4.7)</b>	<b>294 (10.9)</b>	<b>135 (20.0)</b>	<b>54 (20.3)</b>
Pruritus	7 (0.9)	119 (4.4)	70 (10.4)	23 (8.6)
Pruritus generalised	5 (0.6)	54 (2.0)	26 (3.9)	18 (6.8)
<b>Investigations</b>	<b>55 (7.0)</b>	<b>163 (6.1)</b>	<b>35 (5.2)</b>	<b>30 (11.3)</b>

a: Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

MedDRA version 11.0 was used for coding.

TEAE = treatment emergent adverse events; Flex = Tapentadol flexible dose of 50 mg or 100 mg; IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total, per category).

The following adverse drug reactions (ADRs) were reported from clinical trials performed with PALEXIA<sup>®</sup> IR:

**Very Common (≥ 1/10)**

Nervous system disorders:

Dizziness, Somnolence, Headache

Gastrointestinal disorders:

Nausea, Vomiting

**Common (≥1/100 to <1/10)**

Metabolism and nutrition disorders:

Decreased appetite

Psychiatric disorders:

Anxiety, Confusional state,  
Hallucination, Sleep disorder,  
Abnormal dreams

Nervous system disorders:

Tremor

Vascular disorders:

Flushing

Gastrointestinal disorders:

Constipation, Diarrhoea, Dyspepsia,  
Dry mouth

Skin and subcutaneous tissue disorders:

Pruritus, Hyperhidrosis, Rash

Musculoskeletal and connective tissue disorder:

General disorders and administration site conditions:

Muscle spasms

Asthenia, Fatigue, Feeling of body temperature change

**Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )**

Psychiatric disorders:

Nervous system disorders:

Eye disorders:

Cardiac disorders:

Vascular disorders:

Respiratory, thoracic and mediastinal disorders:

Gastrointestinal disorders:

Skin and subcutaneous tissue disorders:

Musculoskeletal and connective tissue disorder:

Renal and urinary disorders:

General disorders and administration site conditions:

Depressed mood, Disorientation, Agitation, Nervousness, Restlessness, Euphoric mood

Disturbance in attention, Memory impairment, Presyncope, Sedation, Ataxia, Dysarthria, Hypoaesthesia, Paraesthesia, Muscle contractions involuntary

Visual disturbance

Heart rate increased, Palpitations

Blood pressure decreased

Respiratory depression, Oxygen saturation decreased, Dyspnoea

Abdominal discomfort

Urticaria

Sensation of heaviness

Urinary hesitation, Pollakiuria

Drug withdrawal syndrome, Oedema, Feeling abnormal, Feeling drunk, Irritability, Feeling of relaxation

**Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )**

Immune system disorders:

Psychiatric disorders:

Nervous system disorders:

Cardiac disorders:

Gastrointestinal disorders:

Drug hypersensitivity

Thinking abnormal

Convulsion, Depressed level of consciousness, Coordination abnormal

Heart rate decreased

Impaired gastric emptying

**Treatment emergent adverse events with prolonged treatment**

A total of 679 subjects with moderate to severe pain from low back pain or osteoarthritis of the knee or hip were treated with a flexible dosing regimen of PALEXIA<sup>®</sup> IR (50 mg or 100 mg every 4 hours to 6 hours, as needed) in a 90-day safety study (KF5503/34). The dosing regimen is considered to mimic the clinical use of mu-opioid receptor agonists in an outpatient setting. There were 318 subjects who received treatment for at least 90 days, and the maximum duration of treatment with PALEXIA<sup>®</sup> IR was 105 days.

The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The percentage of subjects with at least 1 TEAE was 76.3% in the PALEXIA<sup>®</sup> IR (50 mg or 100 mg) and 82.9% in the oxycodone HCl IR (10 mg or 15 mg) groups (Table 6). Subjects administered PALEXIA<sup>®</sup> IR had a lower incidence of

gastrointestinal events compared to oxycodone HCl IR (44.2% vs 63.5% respectively) (Table 6).

Discontinuations due to TEAEs occurred less frequently in the PALEXIA<sup>®</sup> IR treated group compared with oxycodone IR (20.8% and 30.6%).

Discontinuations due to gastrointestinal TEAEs also occurred less frequently in the PALEXIA<sup>®</sup> IR treated group compared with oxycodone IR (8.8% and 21.2%).

**Table 6. TEAEs during prolonged treatment in at least 5% of subjects: KF5503/34 safety analysis set**

System organ class/preferred term	PALEXIA <sup>®</sup> IR (n=679) n (%)	Oxycodone HCl IR (n=170) n (%)
<b>Number (n (%)) of subjects with TEAE</b>	518 (76.3)	141 (82.9)
<b>Gastrointestinal disorders</b>	300 (44.2)	108 (63.5)
Nausea	125 (18.4)	50 (29.4)
Vomiting	115 (16.9)	51 (30.0)
Constipation	87 (12.8)	46 (27.1)
Diarrhoea	45 ( 6.6)	10 ( 5.9)
Somnolence	36 ( 5.3)	5 ( 2.9)
<b>Nervous system disorders</b>	249 (36.7)	63 (37.1)
Dizziness	123 (18.1)	29 (17.1)
Somnolence	78 (11.5)	17 (10.0)
Headache	69 (10.2)	16 ( 9.4)
<b>General disorders and administration site conditions</b>	100 (14.7)	18 (10.6)
Fatigue	38 ( 5.6)	4 ( 2.4)
<b>Skin and subcutaneous tissue disorders</b>	58 ( 8.5)	27 (15.9)
Pruritus	29 ( 4.3)	20 (11.8)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events. All adverse events are coded using MedDRA version 10.0.

IR = immediate release; N, n = number of subjects (total; per category); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

### Post marketing experience

In addition to adverse events reported in clinical trials, the following adverse events have been observed during post approval use of PALEXIA<sup>®</sup>. As these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Suicidal ideation has been reported during post approval use of PALEXIA<sup>®</sup>.

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

### DOSAGE AND ADMINISTRATION

As with many centrally acting analgesic medications, 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.

The recommended oral starting dose is 50, 75, or 100 mg PALEXIA<sup>®</sup> IR every 4 to 6 hours depending upon the initial pain intensity. On the first day of dosing, a second dose may be taken as soon as one hour after the initial dose, if pain control is not achieved. Thereafter, the usual recommended dose is 50 to 100 mg PALEXIA<sup>®</sup> IR every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.

PALEXIA<sup>®</sup> IR should be taken whole with sufficient liquid.  
PALEXIA<sup>®</sup> IR may be administered with or without food.

Total starting daily doses greater than 700 mg PALEXIA<sup>®</sup> IR and maintenance daily doses greater than 600 mg PALEXIA<sup>®</sup> IR have not been studied and are therefore, not recommended.

### **Discontinuation of treatment**

Withdrawal symptoms could occur after abrupt discontinuation of treatment with PALEXIA<sup>®</sup> IR. When a patient no longer requires therapy with PALEXIA<sup>®</sup> IR it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see **PRECAUTIONS**).

### **Renal Impairment**

No dosage adjustment is recommended in patients with mild or moderate renal impairment (see **Pharmacokinetics**).

PALEXIA<sup>®</sup> IR has not been studied in controlled efficacy studies in patients with severe renal impairment and its use is not recommended. A pharmacokinetic study showed an increased level of an inactive metabolite in subjects with renal impairment (see **PRECAUTIONS** and also **Pharmacokinetics**).

### **Hepatic Impairment**

No dosage adjustment is recommended in patients with mild hepatic impairment (see **Pharmacokinetics**).

PALEXIA<sup>®</sup> IR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg PALEXIA<sup>®</sup> IR and not be administered more frequently than once every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval (see **PRECAUTIONS** and also **Pharmacokinetics**).

PALEXIA<sup>®</sup> IR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

### **Elderly Patients (persons aged 65 years and over)**

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

## Paediatric Patients

PALEXIA<sup>®</sup> IR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population (see **PRECAUTIONS**).

## OVERDOSAGE

Experience with PALEXIA<sup>®</sup> IR overdose 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 the clinical setting, these symptoms may include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of overdose should be focused on treating symptoms of mu-opioid receptor agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of PALEXIA<sup>®</sup> IR is suspected.

Pure opioid 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 antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. 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.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management.

## PRESENTATION AND STORAGE CONDITIONS

- PALEXIA<sup>®</sup> IR 50 mg tapentadol (as hydrochloride) immediate release tablets: white round shape biconvex film-coated tablets with Grünenthal logo embossed on one side and “H6” engraving on the other side.
- PALEXIA<sup>®</sup> IR 75 mg tapentadol (as hydrochloride) immediate release tablets: Pale yellow round shape biconvex film-coated tablets with Grünenthal logo embossed on one side and “H7” engraving on the other side.
- PALEXIA<sup>®</sup> IR 100 mg tapentadol (as hydrochloride) immediate release tablets: Pale pink round shape biconvex film-coated tablets with Grünenthal logo embossed on one side and “H8” engraving on the other side.

Blister packs of 5, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets  
Not all tablet strengths or pack sizes may be available.

PALEXIA<sup>®</sup> IR 50 mg, 75 mg and 100 mg immediate release tablets have a shelf-life of 36 months when stored below 30°C.



**NAME AND ADDRESS OF SPONSOR**

Seqirus Pty Ltd  
ABN 26 160 735 035  
63 Poplar Road  
Parkville, VIC 3052  
Australia

**POISON SCHEDULE OF THE MEDICINE**

Controlled Drug, S8

**Date of first inclusion in the Australian Register of Therapeutic Goods:**

22 November 2010

**Date of most recent amendment:**

27 March 2017

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