SCHEDULING STATUS

Schedule 6

1. NAME OF THE MEDICINE

PALEXIA® 50 mg tablets

PALEXIA® 75 mg tablets

PALEXIA® 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PALEXIA 50 mg tablet contains 50 mg tapentadol (as hydrochloride).

Each PALEXIA 75 mg tablet contains 75 mg tapentadol (as hydrochloride).

Each PALEXIA 100 mg tablet contains 100 mg tapentadol (as hydrochloride).

Excipient with known effect

Contains sugar (lactose monohydrate)

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 full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

PALEXIA 50 mg: White round biconvex film coated tablets engraved with the Grűnenthal logo on one side and H6 on the other side.

PALEXIA 75 mg: Pale yellow round biconvex film coated tablets engraved with the Grűnenthal logo on one side and H7 on the other side.

PALEXIA 100 mg: Pale pink round biconvex film coated tablets engraved with the Grűnenthal logo on one side and H8 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALEXIA is indicated for the short-term relief of acute moderately severe post-operative pain in patients aged 18 years and older. The duration of therapy should not exceed 10 days.

In clinical pharmacokinetic interaction studies with naproxen and probenecid there was an increase in AUC of tapentadol by 17 % and 57 %, respectively.

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.

The recommended oral dose is 50 to 100 mg PALEXIA 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 every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.

Total daily doses greater than PALEXIA 600 mg have not been studied and are therefore, not recommended.

Discontinuation of treatment

Withdrawal symptoms could occur after abrupt discontinuation of treatment with PALEXIA (See Special warnings and precautions for use). When a patient no longer requires therapy with PALEXIA, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Special populations

Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment *(*See Pharmacokinetic properties*)*. PALEXIA has not been studied in patients with severe renal impairment, therefore the use in this population is not recommended *(*See Special Warnings and precautions for use and Pharmacokinetic properties and Contraindications*)*.

Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment *(*See Pharmacokinetic properties*)*. PALEXIA should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at PALEXIA 50 mg 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 Special Warnings and precautions for use and Pharmacokinetic properties).

PALEXIA has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (See Contraindications*)*.

Elderly Patients (persons aged 65 years and over)

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 Pharmacokinetic properties*)*.

Paediatric Patients

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

Method of administration

PALEXIA should be taken whole with sufficient liquid. PALEXIA may be administered with or without food.

4.3 Contraindications

PALEXIA is contraindicated:

- in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product;
- in situations where medicines with μ-opioid receptor agonist activity, such as PALEXIA, are contraindicated, i.e. patients with respiratory depression and patients with acute or severe bronchial asthma or hypercapnia;
- in patients with head injury;

- in severe renal impairment (CrCl < 30 ml/min);
- in severe hepatic impairment;
- in acute pancreatitis;
- 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 medicine (See Interaction with other medicines and other forms of interaction);
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (See Interaction with other medicines and other forms of interaction);
- in pregnancy and lactation (See Fertility, Pregnancy and Lactation).

4.4 Special warnings and precautions for use

Potential for Abuse

PALEXIA has a potential for abuse. This should be considered when prescribing or dispensing PALEXIA in situations where there is concern about an increased risk of misuse, abuse, or diversion. Patients treated with PALEXIA should be carefully monitored for signs of abuse and addiction.

Respiratory Depression

PALEXIA may produce dose-related respiratory depression. Therefore, PALEXIA should not be administered to patients with impaired respiratory function (See Contraindications).

Head Injury and Increased Intracranial Pressure

PALEXIA should not be used in patients who may be susceptible to the intracranial effects of carbon dioxide retention, such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. PALEXIA may obscure the clinical course of patients with head injury.

Seizures

PALEXIA has not been evaluated in patients with a seizure disorder. PALEXIA 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. In addition, PALEXIA may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold.

Renal impairment

PALEXIA has not been studied in efficacy studies in patients with severe renal impairment, therefore the use in this population is contraindicated (See Posology and method of administration and Pharmacokinetic properties).

Hepatic impairment

A study of PALEXIA in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA should be used with caution in patients with moderate hepatic impairment (See Posology and method of administration and Pharmacokinetic properties).

PALEXIA has not been studied in patients with severe hepatic impairment and, therefore, use in this population is contraindicated (See Posology and method of administration and Pharmacokinetic properties).

Use in Pancreatic/Biliary Tract Disease

PALEXIA may cause spasm of the sphincter of Oddi. PALEXIA should be used with caution in patients with biliary tract disease. PALEXIA should not be used in patients with acute pancreatitis (See Contraindications).

Sleep-related breathing disorders

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

Lactose warning

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

4.5 Interaction with other medicinal products and other forms of interaction

There have been reports of serotonin syndrome associated with the therapeutic use of PALEXIA in combination with serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs),

serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants.

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

• Spontaneous clonus

• Inducible or ocular clonus with agitation or diaphoresis

• Tremor and hyperreflexia

• Hypertonia and body temperature > 38°C and inducible clonus or ocular clonus.

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.

There is no clinical data on the concomitant use of PALEXIA with mixed opioid agonist/antagonists (such as pentazocine, nalbuphine) or partial μ-opioid agonists. The analgesic effect provided by the μ-opioid component of PALEXIA may be reduced in such circumstances. Therefore, care should be taken when combining PALEXIA with these medicinal products.

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.

Patients receiving other μ-opioid receptor agonist analgesics, general

anaesthetics, phenothiazines or other tranquilisers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these substances are taken in combination with PALEXIA. When such combined therapy is contemplated, a reduction of dose of one or both medicines should be considered.

PALEXIA 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 norepinephrine (noradrenaline) levels which may result in adverse cardiovascular events (See Contraindications).

4.6 Fertility, pregnancy and lactation

Pregnancy

PALEXIA should not be used during pregnancy (See Contraindications). Studies in animals have shown CNS depressive effects and delayed post-natal development. Long term maternal use of opioids during pregnancy co-exposes the foetus. The newborn may experience subsequent neonatal withdrawal syndrome (NOWS).

Labour and Delivery

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

Lactation

PALEXIA should not be used by mothers who are breastfeeding their infants. PALEXIA is excreted in milk.

4.7 Effects on ability to drive and use machines

PALEXIA 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 Undesirable 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 tranquilisers. Patients should be cautioned as to whether driving or use of machines is permitted.

4.8 Undesirable effects

Clinical Trial Data

Approximately 65 % of PALEXIA treated patients in the placebo controlled studies experienced adverse reactions. The most frequent adverse reactions were in the gastrointestinal and central nervous system (nausea, dizziness, vomiting, somnolence, and headache).
Approximately 9 % of PALEXIA treated patients with adverse reactions discontinued from clinical studies.

The information below lists adverse reactions that were identified from clinical trials performed with PALEXIA and from post-marketing environment. They are listed by system organ class and frequency. The following terms and frequencies are applied: *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); and *not known* (cannot be estimated from the available data).

ADVERSE DRUG REACTIONS					
System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Unknown**
Immune system disorders				Medicine 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	Abnormal thinking	
Nervous system disorders	Dizziness, somnolence, headache	Tremor	Disturbance in attention, memory impairment, presyncope, sedation, ataxia, dysarthria, hypoaesthesia, paraesthesia, involuntary muscle,	Convulsion, depressed level of consciousness, abnormal coordination.	

			contractions		
Eye disorders			Visual disturbance.		
Cardiac disorders			Increased heart rate, palpitations.	Decreased heart rate	
Vascular disorders		Flushing	Decreased blood pressure		
Respiratory, thoracic and mediastinal disorders			Respiratory depression, decreased oxygen saturation, 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,	Drug withdrawal		

		feeling of body temperature change.	syndrome, oedema, abnormal feeling, feeling drunk, irritability, feeling of relaxation		

Medical practitioners should be vigilant for symptoms of withdrawal and treat patients accordingly, should they occur.

Post-Marketing experience

Postmarketing data

Adverse Reactions Identified During Postmarketing Experience

Angioedema, anaphylaxis, anaphylactic shock, delirium and increased blood pressure have been reported.
Suicidal ideation has been reported.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of PALEXIA.

4.9 Overdose

Symptoms include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of Overdosage

Management of overdose should be focused on treating the symptoms of μ-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 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 medicine. Gastrointestinal decontamination with activated charcoal 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

Pharmacologic classification: A.2.9 Other Analgesics

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to μ-opioid receptor agonist activity and the inhibition of norepinephrine (noradrenaline) reuptake.

Tapentadol is an analgesic with μ-agonistic opioid and norepinephrine (noradrenaline) reuptake inhibition properties. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

5.2 Pharmacokinetic properties

Absorption

Tapentadol is completely absorbed after oral administration of PALEXIA. Mean absolute bioavailability after single-dose oral 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. Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed over the therapeutic dose range.

A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed an accumulation ratio between 1,4 and 1,7 for the parent compound and between 1,7 and 2,0 for the major metabolite tapentadol-O-glucuronide. Steady state serum concentrations of

tapentadol are reached on the second day of the treatment regimen of 6 hourly administration.

Food Effect

The AUC and C_{max} increased by 25 % and 16 %, respectively, when IR tablets were administered after a high-fat, high-calorie breakfast.

Distribution

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

Biotransformation

In humans, the metabolism of tapentadol is extensive. About 97 % of the parent compound is metabolised. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration, approximately 70 % of the dose is excreted in urine in the conjugated form (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 tapentadol was excreted in urine as unchanged. 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.
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 1 530 ± 177 ml/min. Terminal half-life is on average 4 hours.

Special populations

Elderly

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 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.

PALEXIA was not studied in patients with severe hepatic impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolised by glucuronidation, and only a small amount is metabolised by oxidative pathways.

No changes in the pharmacokinetic parameters of tapentadol were observed when paracetamol and aspirin (acetylsalicylic acid) were given concomitantly.

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes.

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 interactions by displacement from the protein binding site is low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, opadry white, opadry yellow, opadry pink, povidone.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Blisters must be kept in the cartons until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

PALEXIA Tablets are packed in white opaque PVC/PVDC blisters, sealed to aluminium foil.

Each carton contains 28 or 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg.No. 1980/011122/07)

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8. REGISTRATION NUMBER(S)

PALEXIA® 50 mg tablets: 47/2.9/0994

PALEXIA® 75 mg tablets: 47/2.9/0995

PALEXIA® 100 mg tablets: 47/2.9/0996

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- PALEXIA® 50 mg tablets – 02 June 2017
- PALEXIA® 75 mg tablets – 02 June 2017
- PALEXIA® 100 mg tablets – 02 June 2017

10. DATE OF REVISION OF THE TEXT

25 October 2022