PROFFESIONAL INFORMATION FOR PALEXIA SR® RANGE

SCHEDULING STATUS

Schedule 6

1. NAME OF THE MEDICINE

PALEXIA® SR 50 mg prolonged release tablets

PALEXIA® SR 100 mg prolonged release tablets

PALEXIA® SR 150 mg prolonged release tablets

PALEXIA® SR 200 mg prolonged release tablets

PALEXIA® SR 250 mg prolonged release tablets

Contains sugar (lactose monohydrate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PALEXIA® SR 50 mg prolonged release tablet contains tapentadol hydrochloride equivalent to 50 mg tapentadol.

Each PALEXIA® SR 100 mg prolonged release tablet contains tapentadol hydrochloride equivalent to 100 mg tapentadol.

Each PALEXIA® SR 150 mg prolonged release tablet contains tapentadol hydrochloride equivalent to 150 mg tapentadol.

Each PALEXIA® SR 200 mg prolonged release tablet contains tapentadol hydrochloride equivalent to 200 mg tapentadol.

Each PALEXIA® SR 250 mg prolonged release tablet contains tapentadol hydrochloride equivalent to 250 mg tapentadol

Excipient with known effect

Contains sugar (lactose monohydrate).

PALEXIA® SR 50 mg contains 3,026 mg lactose

PALEXIA® SR 100 mg contains 3,026 mg lactose

PALEXIA® SR 150 mg contains 3,026 mg lactose

PALEXIA® SR 200 mg contains 3,026 mg lactose

PALEXIA® SR 250 mg contains 3,026 mg lactose

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

PALEXIA SR 50 mg: White oblong film coated tablets engraved with the Grűnenthal logo on one side and H1 on the other side.

PALEXIA SR 100 mg: Pale yellow oblong film coated tablets engraved with the Grűnenthal logo on one side and H2 on the other side.

PALEXIA SR 150 mg: Pale pink oblong film coated tablets engraved with the Grűnenthal logo on one side and H3 on the other side.

PALEXIA SR 200 mg: Pale orange oblong film coated tablets engraved with the Grűnenthal logo on one side and H4 on the other side.

PALEXIA SR 250 mg: Brownish red oblong film coated tablets engraved with the Grűnenthal logo on one side and H5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALEXIA SR is indicated for the management of moderate to severe chronic pain that is unresponsive to non-narcotic analgesia.

For use in patients aged 18 years and older.

4.2 Posology and method of administration

Posology

The dosing regimen should be individualised according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

PALEXIA SR should be taken twice daily, approximately every 12 hours.

Initiation of therapy:

a) Initiation of therapy in patients currently not taking opioid analgesics

   Patients should start treatment with single doses of 50 mg PALEXIA SR administered twice a day.

b) Initiation of patients currently taking opioid analgesics

   When switching from opioids to PALEXIA SR and choosing the initial dose; the nature of the previous medication, administration and the mean daily dose should be taken into account.

Titration and maintenance

After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimises side effects under the close supervision of the medical practitioner.

A titration regimen in increments of 50 mg PALEXIA SR twice daily every 3 days is appropriate to achieve adequate pain control in most of the patients. Total daily doses of PALEXIA SR greater than 500 mg tapentadol have not been studied and are therefore not recommended.

Discontinuation of treatment

Withdrawal symptoms could occur after abrupt discontinuation of treatment with PALEXIA SR (See Undesirable Effects and Special warnings and precautions for use). When a patient no longer requires therapy with PALEXIA SR, 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 SR 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 SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at PALEXIA SR 50 mg and not be administered more frequently than once every 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 SR 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 SR 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 SR should be taken whole with sufficient liquid.

PALEXIA SR may be administered with or without food.

The shell (matrix) of the tapentadol tablet might not be digested completely and therefore it might still be visible in the patient's stool. This finding has no clinical relevance, since the active ingredient of the tablet will have already been absorbed.

4.3 Contraindications

PALEXIA SR 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 SR, are contraindicated, i.e. patients with respiratory depression 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 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 patients with head injury;
- in severe renal impairment (CrCl < 30 ml/min);
- in severe hepatic impairment;
- in acute pancreatitis;
- in pregnancy and lactation (See Fertility pregnancy and lactation).

4.4 Special warnings and precautions for use

Potential for abuse

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

Respiratory depression

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

Head Injury and increased intracranial pressure

PALEXIA SR 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 SR may obscure the clinical course of patients with head injury.

Seizures

PALEXIA SR has not been evaluated in patients with a seizure disorder. PALEXIA SR 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

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

PALEXIA SR 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 SR may cause spasm of the sphincter of Oddi. PALEXIA SR should be used with caution in patients with biliary tract disease. PALEXIA SR 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 SR 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 SR 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 SR may be reduced in such circumstances. Therefore, care should be taken when combining PALEXIA SR

with these medicinal products.

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 SR 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 SR. When such combined therapy is contemplated, a reduction of dose of one or both medicines should be considered.

PALEXIA SR 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 SR should not be used during pregnancy (See Contraindications). Studies in animals have shown CNS depressive effects and delayed postnatal 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 SR on labour and delivery in humans is unknown. PALEXIA SR 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 SR, neonates whose mothers have been taking PALEXIA SR should be monitored for respiratory depression.

Lactation

PALEXIA SR should not be used by mothers who are breastfeeding their infants.

PALEXIA SR is excreted in milk.

4.7 Effects on ability to drive and use machines

PALEXIA SR 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

Approximately 70 % of PALEXIA SR treated patients in the placebo controlled studies experienced adverse drug reactions. The most frequent adverse drug reactions were in the gastrointestinal and central nervous system (nausea, dizziness, constipation, headache and somnolence).

Approximately 15 % of PALEXIA SR treated patients with adverse drug reactions discontinued from clinical studies in chronic pain.

The information below lists adverse reactions that were identified from clinical trials performed with PALEXIA SR 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	Weight decreased		
Psychiatric disorders		Sleep disorder, anxiety, depressed mood, nervousness, restlessness	Abnormal dreams, perception disturbances, disorientation, agitation, confusional state, euphoric mood	Drug dependence, abnormal thinking	
Nervous system disorders	Dizziness, headache, somnolence,	Involuntary muscle contractions, tremor, disturbances in attention	Paraesthesia, hypoaesthesia, balance disorder, sedation, syncope, memory impairment, mental impairment, depressed level of consciousness, dysarthria	Abnormal coordination, pre-syncope, convulsion	
Eye disorders			Visual disturbance		
Cardiac disorders			Increased heart rate, decreased		

			heart rate, palpitations		
Vascular disorders		Flushing	Decreased blood pressure		
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Respiratory depression	
Gastrointestinal disorders	Nausea, constipation	Vomiting, diarrhoea, dyspepsia	Abdominal discomfort	Impaired gastric emptying	
Skin and subcutaneous tissue disorders		Pruritus, hyperhidrosis, rash	Urticaria		
Renal and urinary disorders			Pollakiuria, urinary hesitation		
Reproductive system and breast disorders			Sexual dysfunction		
General disorders and administration site conditions		Fatigue, mucosal dryness, asthenia, feeling of body temperature change, oedema	Drug withdrawal syndrome, irritability, feeling abnormal	Feeling drunk, feeling of relaxation	

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

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.

4.9 Overdose

Symptoms include miosis, vomiting, and 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 SR 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

Mean absolute bioavailability after single-dose administration (fasting) of tapentadol is approximately 32 % due to extensive first pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of prolonged release tablets.

Dose proportional increases for AUC have been observed after administration of the prolonged release tablets over the therapeutic dose range.

A multiple study with twice daily dosing using 86 mg and 172 mg tapentadol administered as prolonged release tablets showed an accumulation ratio of about 1,5 for the parent medicine which is primarily determined by the dosing interval and apparent half-life of tapentadol.

Steady state serum concentrations of tapentadol are reached on the second day of the treatment regimen.

Food Effect

The AUC and C_{max} increased by 8 % and 18 %, respectively, when prolonged release tablets were administered after a high-fat, high-calorie breakfast. Tapentadol may be given with or without food.

Distribution

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

Biotransformation

In humans, the metabolism of tapentadol is extensive. About 97 % of the parent compound is metabolised. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70 % of the dose is excreted in urine 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 5-6 hours after oral administration of the prolonged release tablets.

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.

Pharmacokinetic Interactions

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

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

Tablet core: Colloidal anhydrous silica, hypromellose, magnesium stearate, microcrystalline cellulose

Tablet coat: Hypromellose, lactose monohydrate, macrogol 6000, propylene glycol, talc

Colourants: Titanium dioxide (E 171), yellow iron oxide (E 172 : 100, 150, 200 and 250 mg tablets only), red iron oxide (E 172 : 150, 200 and 250 mg tablets only), black iron oxide (E 172 : 250 mg tablets only)

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 SR prolonged release tablets are packed in white opaque PVC/PVDC blisters, sealed with a sealing foil consisting of a laminate of paper, polyethylene therephthalate (PET) and aluminium.

Each carton contains 20, 30 or 56 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® SR 50 mg: 48/2.9/0131

PALEXIA® SR 100 mg: 48/2.9/0132

PALEXIA® SR 150 mg: 48/2.9/0133

PALEXIA® SR 200 mg: 48/2.9/0134

PALEXIA® SR 250 mg: 48/2.9/0135

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- Date on the registration certificate: 2 June 2017

10. DATE OF REVISION OF THE TEXT

10 May 2022