AUSTRALIAN PRODUCT INFORMATION – PALEXIA® SR (TAPENTADOL (as hydrochloride)) SUSTAINED RELEASE TABLETS

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, PALEXIA® SR should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Hazardous and harmful use

PALEXIA® SR poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see *section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of PALEXIA® SR. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking PALEXIA® SR.

1 NAME OF THE MEDICINE

Tapentadol (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PALEXIA® SR tablet contains 25, 50, 100, 150, 200 or 250 mg tapentadol (as hydrochloride).

PALEXIA® SR tablets contain lactose.

For the full list of excipients, see *Section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

There are six (6) distinct strengths of PALEXIA® SR sustained release tablets:

- PALEXIA® SR 25 mg tapentadol (as hydrochloride) sustained release tablets: slightly brownish-orange film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H9” engraving on the other side
- PALEXIA® SR 50 mg tapentadol (as hydrochloride) sustained release tablets: white film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H1” engraving on the other side.
- PALEXIA® SR 100 mg tapentadol (as hydrochloride) sustained release tablets: pale yellow film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H2” engraving on the other side.
- PALEXIA® SR 150 mg tapentadol (as hydrochloride) sustained release tablets: pale pink film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H3” engraving on the other side.
- PALEXIA® SR 200 mg tapentadol (as hydrochloride) sustained release tablets: pale orange film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H4” engraving on the other side.
- PALEXIA® SR 250 mg tapentadol (as hydrochloride) sustained release tablets: brownish red film-coated oblong shaped tablets with Grünenthal logo engraving on one side and “H5” engraving on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PALEXIA® SR is indicated for the management of severe pain where:

- other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- the pain is opioid-responsive, and
- requires daily, continuous, long-term treatment.

PALEXIA® SR is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

PALEXIA® SR is not indicated as an as-needed (PRN) analgesia.

4.2 DOSE AND METHOD OF 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.

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

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 may not be digested completely and therefore it can be eliminated and seen in the patient's stool. However, this finding has no clinical relevance, since the active substance of the tablet will have already been absorbed.

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 daily.

b) Initiation of therapy in 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 minimizes side effects under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50 mg PALEXIA® SR twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients. For dose adjustments 25 mg PALEXIA® SR may also be used.

Total daily doses of PALEXIA® SR tablets 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 tapentadol. When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment (see *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® SR 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 *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment (see *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 25 mg or 50 mg PALEXIA® SR and not be administered more frequently than once every 24 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE* and also *Section 5.2 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 (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

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 patients with severe respiratory disease, acute respiratory disease and respiratory depression
- 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 *Section 4.5 INTERACTIONS 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 *Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION*)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

PALEXIA® SR contains the opioid tapentadol (as hydrochloride) and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed PALEXIA® SR at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed PALEXIA® SR.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see *section 6.4 – SPECIAL PRECAUTIONS FOR STORAGE* and *section 6.6 – SPECIAL PRECAUTIONS FOR DISPOSAL*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share PALEXIA® SR with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of PALEXIA® SR but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with moderate hepatic impairment or existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see *section 4.2 -DOSE AND METHOD OF ADMINISTRATION*). The use of opioid is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see *section 4.3 -CONTRAINDICATIONS*).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, in opioid naïve patients and when used concomitantly with other CNS depressants. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

PALEXIA® SR should be employed only under careful medical supervision at the lowest effective dose. If respiratory depression occurs, it should be treated as any mu-opioid receptor agonist-induced respiratory depression (see *Section 4.9 OVERDOSE*).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these

risks, concomitant prescribing of PALEXIA® SR with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe PALEXIA® SR concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking PALEXIA® SR.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see *Hazardous and harmful use*, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive

and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see *Ceasing Opioids*).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (eg. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

In a study conducted over 12 months, 22.4% of patients given PALEXIA® SR had objective signs of opioid withdrawal compared with 27.3% given oxycodone CR when assessed between 2 - 5 days after the last dose of study drug. Only 4.8% of patients given PALEXIA® SR and 4.5% given oxycodone CR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

When discontinuing PALEXIA® SR in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids* and *section 4.2 – DOSE AND METHOD OF ADMINISTRATION*).

Accidental ingestion/exposure

Accidental ingestion or exposure of PALEXIA® SR, especially by children, can result in a fatal overdose of tapentadol. Patients and their caregivers should be given information on safe storage and disposal of unused PALEXIA® SR (see *section 6.4 – SPECIAL PRECAUTIONS FOR STORAGE* and *section 6.6 – SPECIAL PRECAUTIONS FOR DISPOSAL*).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see *Tolerance, dependence and withdrawal*). If opioid induced

hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see *section 4.2 – DOSE AND METHOD OF ADMINISTRATION*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Sleep-related breathing disorders

Drugs with mu-opioid receptor agonist activity, such as PALEXIA® SR, can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Use of these drugs increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Head Injury and Increased Intracranial Pressure

Like other drugs with mu-opioid receptor agonist activity, PALEXIA® SR 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® SR should be used with caution in patients with head injury and brain tumors.

Seizures

PALEXIA® SR 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® 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. In addition, tapentadol may increase the seizure risk in patients taking other medicinal products that lower the seizure threshold (see *Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).*

Renal Impairment

For patients with mild or moderate renal impairment, no dosage adjustment is recommended (see *Section 4.2 DOSE AND METHOD OF ADMINSTRATION*).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, therefore use in this population is not recommended (see *Section 4.2 DOSE AND METHOD OF ADMINSTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Hepatic Impairment

For patients with mild hepatic impairment, no dosage adjustment is recommended (see *Section 4.2 DOSE AND METHOD OF ADMINSTRATION*).

A study of tapentadol (PALEXIA® IR) 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 *Section 4.2 DOSE AND METHOD OF ADMINSTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see *Section 4.2 DOSE AND METHOD OF ADMINSTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Use in Pancreatic/Biliary Tract Disease

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

Paediatric use

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.

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 *Section 4.2 DOSE AND METHOD OF ADMINSTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Only a small amount of tapentadol is metabolised by oxidative pathways (see *Section 5.2 PHARMACOKINETIC PROPERTIES*). 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.

Mixed opioid agonists/antagonists

Care should be taken when combining PALEXIA SR with mixed mu-opioid agonist/antagonists (e.g. pentazocine, nalbuphine) or partial mu-opioid agonists (e.g. buprenorphine).

PALEXIA SR 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.

CNS depressants

Patients receiving other mu-opioid receptor agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, benzodiazepines, gabapentinoids, cannabis, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA® SR 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® SR. When such combined therapy is contemplated, the reduction of dose of one or both agents should be considered (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol*).

Monoamine oxidase (MAO) inhibitors

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 noradrenaline levels which may result in adverse cardiovascular events (see *Section 4.3 CONTRAINDICATIONS*).

Serotonin Syndrome

PALEXIA® SR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake 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 serotoninergic medicinal products 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. 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – Pregnancy Category C

There are no adequate and well controlled studies of tapentadol in pregnant women. PALEXIA® SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Long-term maternal use of opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NOWS).

The effect of tapentadol 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 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® SR should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Like drugs with mu-opioid receptor agonist activity, PALEXIA® SR may have a major influence on the ability to drive and use machines, due to the fact that it may cause sedation and adversely affect central nervous system functions (see *Section 4.8 ADVERSE EFFECTS (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 tranquilizers (see *Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION*). Patients should be cautioned as to whether driving or use of machines is permitted.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Treatment emergent adverse events in the double-blind Phase 2/3 studies (osteoarthritis, low back pain, diabetic peripheral neuropathy)

In the pooled Phase 2/3 PALEXIA® SR studies, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 71.7%. This was higher when compared with the placebo group (54.5%) and lower than the oxycodone CR group (86.3%) (Table 1).

Compared with oxycodone CR there was better gastrointestinal tolerability with PALEXIA® SR. The incidence of nausea (19.5%), vomiting (7.4%) and constipation (13.6%) was lower with PALEXIA® SR than oxycodone CR (36.1%, 19.8% and 31.5%, respectively) (Table 1). PALEXIA® SR also had a beneficial safety profile over that of oxycodone CR for somnolence (11.3% vs 16.3%), dizziness (13.7% vs 19.8%), and pruritus (4.9% vs 12.4%). This suggests that the adverse event profile for PALEXIA® SR is similar to those of other opioid agonists, while at the same time exhibiting a lower incidence of a number of adverse events.

The majority of subjects in all treatment groups in the pooled all Phase 2/3 PALEXIA® SR studies experienced TEAEs that were mild to moderate in intensity. Less subjects in the all PALEXIA® SR group reported severe adverse events compared to those in the oxycodone CR group.

Table 1 TEAEs in at least 5% of subjects in any pooled treatment group (all studies) (PALEXIA® formulation Phase 2/3 studies integrated summary of safety: safety analysis set)[a]

System organ class/preferred term	Placebo	All PALEXIA® SR (n=3613) n (%)	All oxycodone CR (n=1472) n (%)
Number (n (%)) of subjects with TEAE	817 (54.5)	2589 (71.7)	1271 (86.3)
Gastrointestinal disorders	**370 (24.7)**	**1464 (40.5)**	**952 (64.7)**
Nausea	128 (8.5)	704 (19.5)	531 (36.1)
Constipation	85 (5.7)	493 (13.6)	464 (31.5)
Vomiting	44 (2.9)	269 (7.4)	292 (19.8)
Dry mouth	26 (1.7)	217 (6.0)	66 (4.5)
Diarrhoea	78 (5.2)	199 (5.5)	78 (5.3)
Nervous system disorders	**288 (19.2)**	**1308 (36.2)**	**662 (45.0)**
Dizziness	77 (5.1)	495 (13.7)	291 (19.8)
Headache	170 (11.3)	427 (11.8)	174 (11.8)
Somnolence	44 (2.9)	408 (11.3)	240 (16.3)
General disorders and administration site conditions	**138 (9.2)**	**583 (16.1)**	**290 (19.7)**
Fatigue	48 (3.2)	253 (7.0)	139 (9.4)
Skin and subcutaneous tissue disorders	80 (5.3)	481 (13.3)	332 (22.6)
Pruritus	20 (1.3)	176 (4.9)	183 (12.4)
Hyperhidrosis	16 (1.1)	160 (4.4)	75 (5.1)

a: This summary of clinical safety includes clinical studies that vary in design (controlled dose adjustment, fixed dose, and open label) and subject population (lower back pain, pain due to OA, and pain due to peripheral neuropathy). Studies included: KF5503/09, KF5503/10, KF5503/19, KF5503/20, KF5503/24, KF5503/11, KF5503/12, KF5503/23, KF5503/36

MedDRA version 11.0 was used for coding.

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

Treatment emergent adverse events in the Phase IIIb/IV lower back pain with neuropathic component open-label study

The percentage of subjects with at least 1 TEAE during the whole treatment period was 76.9% in the PALEXIA® SR group and 83.6% in the oxycodone/naloxone PR group (Table 2).

The majority of TEAEs in both groups were mild to moderate in intensity.

Table 2 TEAEs in at least 5% of subjects (KF5503/60 – safety analysis set).

	PALEXIA® SR (n=130) n (%)	**Oxycodone/Naloxone PR** (n=128) n (%)
Number of subjects with TEAE	100 (76.9)	107 (83.6)
General Disorders	**40 (30.8)**	**35 (27.3)**
Fatigue	39 (30.0)	31 (24.2)
Gastrointestinal disorders	**58 (44.6)**	**66 (51.6)**
Nausea	29 (22.3)	23 (18.0)
Constipation	20 (15.4)	33 (25.8)
Vomiting	10 (7.7)	21 (16.4)
Dry mouth	9 (6.9)	7 (5.5)
Nervous System Disorders	**38 (29.2)**	**35 (27.3)**
Dizziness	24 (18.5)	22 (17.2)
Headache	10 (7.7)	5 (3.9)
Skin and subcutaneous tissue disorders	**16 (12.3)**	**24 (18.8)**
Hyperhidrosis	8 (6.2)	13 (10.2)
Pruritus	8 (6.2)	11 (8.6)
Infections and Infestations	**19 (14.6)**	**11 (8.6)**
Nasopharyngitis	8 (6.2)	5 (3.9)

Treatment emergent adverse events in the double-blind Phase III cancer pain studies

The safety analyses for the pooled Phase III cancer trials (KF5503/15 and KF5503/16) were performed for the titration phases and maintenance phases separately. All groups could receive rescue medication (morphine IR).

For the titration phase, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 52.0% compared to 64.0% for those administered morphine PR. Compared to morphine PR, there was better gastrointestinal tolerability with PALEXIA® SR. The incidence of nausea (12.3%), vomiting (7.0%), dry mouth (1.5%) and constipation (13.5%) was lower with PALEXIA® SR than morphine PR (22.2%, 14.3%, 5.8%, and 16.4% respectively) (Table 3).

For the maintenance phase, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 62.0%. This was higher when compared with the placebo group (57.1%) and lower than the morphine PR group (64.6%). Compared to morphine PR, there was better gastrointestinal tolerability with PALEXIA® SR (30.7% versus 27.3% respectively) (Table 3). The incidence of diarrhoea (0.8%) was lower with PALEXIA® SR than morphine PR (6.3%) (Table 3).

During the titration and maintenance phases, the intensity of TEAEs was mild or moderate in most subjects in all treatment groups. There was no notable difference between the groups, or any notable differences for each of the system organ classes or TEAEs with the exception of neoplasms benign, malignant and unspecified in the maintenance phase. The higher incidence of neoplasms in the PALEXIA® SR group was classified as unrelated to tapentadol and due to the underlying disease.

Table 3 TEAEs in at least 5% of subjects in titration and maintenance phases of pooled Phase III cancer pain trials - (KF5503/15 and KF5503/16a – safety analysis set).

System Organ Class/preferred term	Placebo n (%)	PALEXIA® SR n (%)	Morphine PR n (%)
Titration phase	-	**n=400**	**n=189**
Number (n (%)) of subjects with TEAE	-	208 (52.0)	121 (64.0)
Gastrointestinal disorders	-	**120 (30.0)**	**84 (44.4)**
Constipation	-	54 (13.5)	31 (16.4)
Nausea	-	49 (12.3)	42 (22.2)
Vomiting	-	28 (7.0)	27 (14.3)
Dry mouth	-	6 (1.5)	11 (5.8)
Nervous system disorders	-	**57 (14.3)**	**28 (14.8)**
Dizziness	-	21 (5.3)	11 (5.8)
Somnolence	-	16 (4.0)	12 (6.3)
Maintenance phase	**n=126**	**n=121**	**n=127**
Number (n (%)) of subjects with TEAE	72 (57.1)	75 (62.0)	82 (64.6)
Gastrointestinal disorders	40 (31.7)	33 (27.3)	39 (30.7)
Nausea	19 (15.1)	17 (14.0)	14 (11.0)
Constipation	13 (10.3)	13 (10.7)	14 (11.0)
Vomiting	4 (3.2)	10 (8.3)	9 (7.1)
Diarrhoea	5 (4.0)	1 (0.8)	8 (6.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	8 (6.3)	15 (12.4)	6 (4.7)
Neoplasm malignant	6 (4.8)	11 (9.1)	5 (3.9)
Metabolism and nutrition disorders	9 (7.1)	10 (8.3)	9 (7.1)
Decreased appetite	7 (5.6)	8 (6.6)	8 (6.3)
Skin and subcutaneous tissue disorder	2 (1.6)	7 (5.8)	13 (10.2)
Hyperhidrosis	1 (0.8)	4 (3.3)	7 (5.5)

[a] This study was terminated due to poor recruitment and an FDA recall of rescue medication

The following adverse drug reactions (ADRs) were reported from clinical trials performed with PALEXIA® SR:

Very Common (≥ 1/10)

Nervous system disorders:	Dizziness, Somnolence, Headache
Gastrointestinal disorders:	Nausea, Constipation

Common (≥ 1/100 to < 1/10)

Metabolism and nutrition disorders:	Decreased appetite
Psychiatric disorders:	Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness
Nervous system disorders:	Disturbance in attention, Tremor, Muscle contractions involuntary
Vascular disorders:	Flushing
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Gastrointestinal disorders:	Vomiting, Diarrhoea, Dyspepsia
Skin and subcutaneous tissue disorders:	Pruritus, Hyperhidrosis, Rash
General disorders and administration site conditions:	Asthenia, Fatigue, Feeling of body temperature change, Mucosal dryness, Oedema

Uncommon (≥ 1/1,000 to < 1/100)

Immune system disorders:	Drug hypersensitivity
Metabolism and nutrition disorders:	Weight decreased
Psychiatric disorders:	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams, Euphoric mood
Nervous system disorders:	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia
Eye disorders:	Visual disturbance

Cardiac disorders:	Heart rate increased, Heart rate decreased, palpitations
Vascular disorders:	Blood pressure decreased
Gastrointestinal disorders:	Abdominal discomfort
Skin and subcutaneous tissue disorders:	Urticaria
Renal and urinary disorders:	Urinary hesitation, Pollakiuria
Reproductive system and breast disorders:	Sexual dysfunction
General disorders and administration site conditions:	Drug withdrawal syndrome, Feeling abnormal, Irritability

Rare (≥ 1/10,000 to < 1/1,000)

Psychiatric disorders:	Drug dependence, Thinking abnormal
Nervous system disorders:	Convulsion, Presyncope, Coordination abnormal
Respiratory, thoracic and mediastinal disorders:	Respiratory depression
Gastrointestinal disorders:	Impaired gastric emptying
General disorders and administration site conditions:	Feeling drunk, Feeling of relaxation

Treatment emergent adverse events with prolonged treatment

A total of 894 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® SR (100 mg to 250 mg twice daily) in a 1 year safety study (KF5503/24). The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The overall incidence of TEAEs was lower in the PALEXIA® SR group (85.7%) compared to oxycodone CR (20 mg to 50 mg) (90.6%).

The most common TEAEs (incidence >10% in either treatment group) were constipation, nausea, vomiting, somnolence, dizziness, headache, fatigue and pruritus. Subjects administered PALEXIA® SR had a lower incidence of constipation, nausea, vomiting, dizziness, fatigue and pruritus compared to oxycodone CR (22.6% vs 38.6%, 18.1% vs 33.2%, 7.0% vs 13.5%, 14.8% vs 19.3%, 9.7% vs 10.3%, and 5.4% vs 10.3% respectively).

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®. 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 and hallucinations have been reported during post approval use of PALEXIA®.

Post-marketing rare events of angioedema, anaphylaxis and anaphylactic shock have been reported. Post marketing cases of delirium have also been observed in patients with additional risk factors such as cancer and advanced age.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience with PALEXIA® SR 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® 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 drug. 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.

Contact the Poisons Information Centre on 13 11 26 for further advice on the management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 ECG 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 supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Clinical trials

Osteoarthritis and low back pain

The efficacy and safety of PALEXIA® SR in the treatment of moderate to severe chronic pain has been investigated in three pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in patients with moderate to severe chronic pain from osteoarthritis of the knee (clinical trials KF5503/11 and KF5503/12) and one in patients with moderate to severe chronic low back pain (clinical trial KF5503/23). Efficacy and safety in patients with severe chronic lower back pain, with a neuropathic component, has also been investigated in a Phase IIIb/IV randomised, open-label, parallel-

arm multicentre study (clinical trial KF5503/60). These pain conditions were chosen as they usually present with moderate to severe pain that is often treated with opioids.

Clinical Trials KF5503/11, KF5503/12 and KF5503/23

In the three pivotal studies, subjects were initially randomised to receive PALEXIA® SR (50 mg twice daily), placebo or oxycodone CR (10 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 3 weeks (increments of PALEXIA® SR 50 mg, oxycodone CR 10 mg, or placebo twice daily) to achieve a stable optimum dose. Subjects were allowed paracetamol as rescue medication during the titration period. Subjects received the following maximum (minimum) doses: PALEXIA® SR 250 mg (100 mg) twice daily, oxycodone CR 50 mg (20 mg) twice daily, or placebo twice daily. The study drug was taken with or without food.

To enter the 12-week maintenance period, subjects had to be on a stable dose of the study drug for the last 3 days of the titration period without any rescue medication. If needed, subjects could request controlled adjustment of their dose based on their individual analgesia requirements and/or tolerability experience however adjustments were to be kept to a minimum during the maintenance period.

All three studies had the same primary endpoints - change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point numerical rating scale (NRS), and change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point NRS. Secondary endpoints included 30% and 50% responder rates and Patient Global Impression of Change scale.

The results for these endpoints for all three studies are summarised in Table 4.

A pre-specified meta-analysis of the data generated in these three clinical trials was also undertaken. The two main objectives of the meta-analysis were to assess the superior safety of PALEXIA® SR compared to oxycodone CR with regards to constipation (gastrointestinal tolerability), and to assess the non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

PALEXIA® SR was superior to oxycodone CR with regards to constipation, nausea and vomiting (gastrointestinal tolerability) ($p<0.001$). The non-inferiority of PALEXIA® SR to oxycodone CR in relation to the primary endpoint (change from baseline of the average pain intensity over the 12-week maintenance period or at Week 12) (using LOCF) was also demonstrated (both p-values ≤ 0.001) (Table 4).

Clinical Trial KF5503/60

A randomized, multicentre, open-label, active-controlled study was conducted to evaluate the effectiveness, safety and tolerability of PALEXIA® SR in patients with uncontrolled severe chronic low back pain with a neuropathic pain component. PALEXIA® SR provided

significant reductions in pain intensity from baseline to final evaluation on the primary effectiveness endpoint.

Change in PAC-SYM total score was a second primary endpoint included to evaluate patient's experience of bowel dysfunction. There was no significant change in PAC-SYM score from baseline to final evaluation with PALEXIA® SR ($p = 0.235$).

Table 4 Meta-analysis of data generated in studies KF5503/11, KF5503/12 and KF5503/23 (ITT, LOCF); non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

	KF5503/11 (n=1023), Osteoarthritis			KF5503/12 (n=987), Osteoarthritis			KF5503/23 (n=958), Lower back pain			Meta-analysis		
	Placebo (n=336)	**PALEXIA® SR (n=344)**	**Oxycodone CR (n=342)**	**Placebo (n=336)**	**PALEXIA® SR (n=319)**	**Oxycodone CR (n=331)**	**Placebo (n=316)**	**PALEXIA® SR (n=312)**	**Oxycodone CR (n=323)**	**Placebo (n=991)**	**PALEXIA® SR (n=978)**	**Oxycodone CR (n=999)**
Baseline pain Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)	7.6 (1.32)	7.5 (1.32)	7.5 (1.22)	7.4 (1.25)	7.4 (1.26)	7.3 (1.21)
Wk 12 maintenance Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)	5.5 (2.57)	4.6 (2.66)	4.6 (2.56)	5.1 (2.56)	4.5 (2.54)	4.8 (2.45)
LS Means diff from placebo Baseline vs Wk 12[a]		-0.7 (0.18)	-0.3 (0.18)		-0.3 (0.18)	0.2 (0.18)		-0.8 (0.19)	-0.9 (0.19)		-0.6 (0.11)	-0.3 (0.11)
p-value 95% CI[b]		<0.001 (-1.04, -0.33)	0.069 (-0.68, 0.02)		0.152 (-0.61, 0.09)	0.279 (-0.16, 0.54)		<0.001 (-1.22, -0.47)	<0.001 (-1.24, -0.49)		<0.001 (-0.80, -0.39)	0.002 (-0.53, -0.12)
Overall maintenance Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)	5.5 (2.46)	4.7 (2.52)	4.6 (2.38)	5.2 (2.40)	4.6 (2.40)	4.8 (2.32)
LS Means diff from placebo Baseline vs overall[a]		-0.7 (0.17)	-0.3 (0.17)		-0.2 (0.16)	0.1 (0.16)		-0.7 (0.18)	-0.8 (0.18)		-0.5 (0.10)	-0.3 (0.10)
p-value 95% CI[b]		<0.001 (-1.00, -0.33)	0.049 (-0.67, -0.00)		0.135 (-0.55, 0.07)	0.421 (-0.18, 0.44)		<0.001 (-1.06, -0.35)	<0.001 (-1.16, -0.46)		<0.001 (-0.73, -0.34)	<0.001 (-0.52, -0.14)
30% responder rate	35.9%	43.0%[c]	24.9%[c]	40.9%	41.1%	26.0%[d]	27.1%	39.7%[c]	36.5%	34.8%	41.3%[c]	27.0%[d]
50% responder rate	24.3%	32.0%[c]	17.3%[d]	27.0%	31.0%	22.1%	18.9%	27.0%[c]	17.4%	23.5%	30.1%[c]	20.8%
PGIC assessment of very much improved & much improved	35.5%	58.5%[c]	47.0%[c]	43.2%	56.0%[c]	42.5%	32.7%	55.5%[c]	60.0%[c]	37.4%	56.7%[c]	49.8%[c]

a: Change from baseline in average pain intensity scores based on numerical rating scale (NRS)[a], ITT population**;** LOCF = last observation carried forward Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).

b: Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled centre and baseline pain intensity as covariate (type III SS) unadjusted p-value.

c:Indicates statistically significant over placebo

d: Indicates statistical significance of placebo over active

LS = least square

Painful diabetic peripheral neuropathy

A randomised withdrawal Phase III clinical trial (KF5503/36 evaluating the efficacy and safety of orally administered PALEXIA® SR (100 to 250 mg twice daily) compared PALEXIA® SR to placebo in subjects with painful diabetic peripheral neuropathy.

The study consisted of two phases: an open label phase (n=588) during which all subjects received PALEXIA® SR and were titrated to an optimal dose, and a double-blind phase (n=389) during which subjects were randomised to receive PALEXIA® SR (n=196) or placebo (n=193).

During the open-label titration phase, subjects initially received PALEXIA® SR (50 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 3 weeks (increments of PALEXIA® SR 50 mg twice daily) to achieve a stable optimum dose. The maximum (minimum) doses administered were: PALEXIA® SR 250 mg (100 mg) twice daily. The study drug was taken with or without food.

Following completion of the open-label titration phase, subjects who had at least a 1-point improvement on an 11-point NRS in average pain intensity score were randomised into the double-blind maintenance phase to receive their individually determined open-label PALEXIA® SR dose or placebo for 12 weeks.

Subjects were allowed paracetamol as rescue medication during the titration period. Subjects were allowed PALEXIA® SR as supplemental analgesia during the double-blind maintenance phase (25 mg, twice daily for the first 4 days and 25 mg once daily for the remainder of the maintenance phase).

The primary efficacy endpoint was change from baseline at randomisation in average pain intensity over the last week (Week 12) of the double-blind maintenance period, as determined by twice-daily measurements on an 11-point NRS.

For the primary efficacy analysis, PALEXIA® SR showed a statistically significant difference in average pain intensity compared to placebo at Week 12 of the double-blind maintenance period ($p<0.001$, an LS mean difference compared to placebo: -1.3) (Table 5).

Table 5 Change in average pain intensity scores based on numerical rating scale (NRS)[a]- from start of double-blind phase to week 12 of double-blind phase baseline, ITT population

	Placebo	PALEXIA® SR
Start DB		
n	192	193
Mean (SD)	3.4 (1.88)	3.6 (1.90)
Median (Range)	3.3 (0 to 9)	3.8 (0 to 9)
Week 12 of Maintenance		
n	192	196
Mean (SD)	4.7 (2.46)	3.5 (2.13)
Median (Range)	4.8 (0 to 10)	3.2 (0 to 10)
Change from Start DB to Week 12 of Maintenance Period		
n	192	193
Mean (SD)	1.3 (2.41)	-0.1 (1.69)
Median (Range)	1.0 (-7 to 9)	-0.1 (-7 to 5)
LS Mean Change	1.4	0.0
LS Mean Difference versus Placebo (SE)		-1.3 (0.20)
95% CI (verses Placebo)		(-1.70, -0.92)
p value (versus Placebo)[b]		<0.001

[a]: LOCF=last observation carried forward

[b]: Test for no treatment difference based on the ANCOVA model with treatment, country, dose category and prior opioid use as factors and Start DB pain intensity as a covariate.

Average pain scores are the averages of all scores recorded during the 72-hour period before randomisation or during each week.

Daily pain intensity is the average of pain scores over a 24-hour period, starting from time of randomization.

DB=double-blind

Cancer pain

A randomised withdrawal active and placebo controlled double-blind Phase III trial (KF5503/15 evaluated the efficacy and safety of orally administered PALEXIA® SR tablets given twice daily over 4 weeks (Maintenance Phase) in subjects with moderate to severe chronic malignant tumour-related pain in comparison to placebo.

The study consisted of two phases: a titration phase (n= 505) where subjects were randomised to receive PALEXIA® SR (n = 345) or morphine PR (n= 160) and were titrated to an optimal dose, and a maintenance phase (n = 328). Subjects who received PALEXIA® SR in the titration phase were re-randomised to PALEXIA® SR (n=107) or placebo (n=112) in the maintenance phase. Subjects who received morphine PR in the titration phase continued to take morphine PR (n = 109) in the maintenance phase.

During the titration phase, subjects initially received PALEXIA® SR (100 mg twice daily) or morphine PR (40 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 2 weeks (increments of PALEXIA® SR 50 mg or morphine PR 20 mg twice daily at minimum 3-day intervals). The maximum (minimum) doses administered were: PALEXIA® SR 250 mg (100 mg) twice daily or morphine PR 100 mg (40 mg) twice daily. The mean (standard deviation [sd]) daily dose was 276.1 mg (66.66 mg) for PALEXIA® SR and 101.8 mg (29.06 mg) for morphine PR.

Following completion of the titration phase, subjects who had met the stabilisation criteria (mean pain intensity <5 points/day (11-point NRS)) and mean consumption of rescue medication ≤ 20 mg morphine IR per day) during the last 3 days of the titration phase were re-randomised into the maintenance phase to receive their individually determined titration phase dose of PALEXIA® SR or placebo for 4 weeks. A similar percentage of subjects in the Palexia® SR (216/279 [77%]) and morphine PR (107/129 [83%]) treatment groups completed the titration phase and met the stabilisation criteria.

Subjects were allowed morphine IR (10 mg) as rescue medication during the titration phase. No maximum dose was defined.

The primary efficacy endpoint was the proportion of subjects classified as responders at the end of the 4 week maintenance phase. Responders were defined as subjects who completed 28 days of the maintenance phase, had mean pain intensity in the maintenance phase <5 points (11-point NRS) and had mean consumption of ≤ 20 mg morphine IR rescue medication per day during the maintenance period. During the maintenance phase the mean (sd) daily dose of PALEXIA® SR and morphine PR was 336.8 mg (107.61 mg) and 121.1 mg (43.64 mg), respectively.

For the primary efficacy analysis, PALEXIA® SR showed a statistically significant difference in responder rate compared to placebo at the end of the 4 week maintenance phase (p = 0.020) (Table 6).

Table 6 Responder rates in the maintenance phase from KF5503/15 (Full Analysis Set) comparing PALEXIA® SR to placebo

Primary Endpoint – Maintenance Phase			
Observed Rates[a]			
Responders	**Placebo n (%)**	**PALEXIA® SR n (%)**	**Morphine SR n (%)**
No	56 (50.5)	40 (38.1)	34 (31.2)
Yes	55 (49.5)	65 (61.9)	75 (68.8)
Total	111	105	109
PALEXIA® SR versus Placebo: From logistic regression model[b]			
Odds Ratio	**95% confidence intervals**		**p-value**[c]
	Lower Limit	Upper Limit	
2.018	1.12	3.65	0.020

[a] Odds Ratio for observed (uncorrected) results = 1.65

[b] From logistic regression model with factors treatment and pooled centre and Start of Maintenance pain intensity as covariate

[c] Wald chi-square test

5.2 PHARMACOKINETIC PROPERTIES

The tapentadol SR formulation is a hydrophilic hypromellose-based matrix formulation that provides pH-independent in-vitro release of the drug substance over a time period of approximately 12 hours. An initial drug substance release of about 20% occurs over the first 30 minutes with ongoing drug release over the ensuing 12-hour period.

Absorption

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

Dose proportional increases for AUC (the most relevant exposure parameter for sustained-release formulations) have been observed after administration of PALEXIA® SR tablets over the therapeutic dose range. Steady state serum concentrations of tapentadol are reached on the second day of the treatment regimen.

A multiple dose study with twice daily dosing using 86 mg and 172 mg tapentadol administered as SR tablets showed an accumulation ratio of about 1.5 for the parent drug which is primarily determined by the dosing interval and apparent half-life of tapentadol.

Food Effect

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

Distribution

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

Metabolism 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 contribute to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

The terminal half-life is on average 5-6 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.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients in the tablet core (all strengths) are:

- hypromellose 100,000 mPa-s, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Excipients in the film coating are:

- hypromellose 6 mPa-s, lactose monohydrate, purified talc, macrogol 6000, titanium dioxide (E171), propylene glycol (50, 100, 150, 200 and 250 mg tablets only), macrogol 400 (25 mg tablets only), iron oxide yellow (E172) (25, 100, 150, 200 and 250 mg tablets only), iron oxide red (E172) (25, 150, 200 and 250 mg tablets only), and iron oxide black (E172) (250 mg tablets only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister Packs of 7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets.

Not all tablet strengths or pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

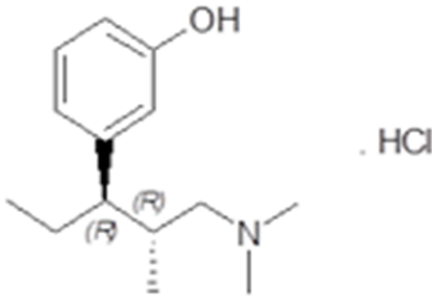
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

PALEXIA® SR sustained 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 pKa_1 is 9.36 and pKa_2 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 ± 0.01. The chemical name for tapentadol HCl is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is $C_{14}H_{23}NO \bullet HCl$.

Chemical structure

The structural formula of tapentadol HCl is:



CAS number

The Chemical Abstracts Service (CAS) Registry Number of tapentadol HCl is 175591-09-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug, S8

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

19 January 2011

10 DATE OF REVISION

1 March 2022

Section Changed	Summary of new information
4.8	Addition of the adverse event 'hallucinations' to the Post Marketing Experience section.
4.4	Update to the information on seizures.
4.5	Change of subsection heading from Mu-opioid agonists/antagonists to Mixed opioid agonists/antagonists. Update of information on interaction with Mixed opioid agonists/antagonists.