AUSTRALIAN PRODUCT INFORMATION – PALEXIA® IR (TAPENTADOL (as hydrochloride)) Immediate Release Tablets

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, PALEXIA® IR 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® IR 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® IR. 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® IR.

1 NAME OF THE MEDICINE

Tapentadol (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

PALEXIA® IR tablets contain lactose.

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

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PALEXIA® IR is indicated for the short-term management of severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain.

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.

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

adjusted to maintain adequate analgesia with acceptable tolerability.

PALEXIA® IR should be taken whole with sufficient liquid.

PALEXIA® IR may be administered with or without food.

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

Discontinuation of treatment

Withdrawal symptoms could occur after abrupt discontinuation of treatment with PALEXIA® IR. When a patient no longer requires therapy with PALEXIA® IR it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

Duration of treatment

As with all symptomatic treatments, the continued use of tapentadol must be evaluated on an ongoing basis.
PALEXIA® IR should not be used longer than necessary.

Renal Impairment

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

PALEXIA® IR has not been studied in controlled efficacy studies in patients with severe renal impairment and its use is not recommended. A pharmacokinetic study showed an increased level of an inactive metabolite in subjects with renal impairment (see *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® IR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg PALEXIA® IR and not be administered more frequently than once every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® IR 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® IR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population (see *Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

4.3 CONTRAINDICATIONS

PALEXIA® IR 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 INTERACTIONS*),
- 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 INTERACTIONS*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

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

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® IR 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® IR 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 opioids 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® IR 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® IR 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® IR 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® IR.

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 3 months, 17.3% of patients given PALEXIA® IR had objective signs of opioid withdrawal compared with 26.1 % given oxycodone IR when assessed between 2 - 5 days after the last dose of study drug. Only 0.3% of patients given PALEXIA® IR and 3% given oxycodone IR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

When discontinuing PALEXIA® IR 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® IR, 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® IR (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® IR, 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® IR should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide

retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. PALEXIA® IR should be used with caution in patients with head injury and brain tumours.

Seizures

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

Use in renal impairment

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

PALEXIA® IR 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 ADMINISTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Use in hepatic impairment

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

A study of PALEXIA® IR in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA® IR should be used with caution in patients with moderate hepatic impairment (see *Section 4.2 DOSE AND METHOD OF ADMINISTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

PALEXIA® IR 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 ADMINISTRATION* 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® IR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

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 ADMINISTRATION* and also *Section 5.2 PHARMACOKINETIC PROPERTIES*).

Paediatric use

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

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 IR with mixed mu-opioid agonist/antagonists (e.g. pentazocine, nalbuphine) or partial mu-opioid agonists (e.g. buprenorphine).

PALEXIA IR 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 anaesthetics, 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® IR may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with PALEXIA® IR. 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® IR is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on noradrenaline levels which may result in adverse cardiovascular events (see *Section 4.3 CONTRAINDICATIONS*).

Serotonin Syndrome

PALEXIA® IR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline reuptake inhibition activity.

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

Anticholinergics

Concomitant administration of opioids with anticholinergics or medications with anticholinergic activity may result in increased anticholinergic adverse effects.

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

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

malformations, may be secondary to maternal toxicity in these species.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Like drugs with mu-opioid receptor agonist activity, PALEXIA® IR 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 INTERACTIONS*). Patients should be cautioned as to whether driving or use of machines is permitted.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

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

Compared with oxycodone HCl IR there was better gastrointestinal tolerability with PALEXIA® IR. In the Phase 2/3 multiple-dose double-blind studies, the incidence of nausea (27.8%), vomiting (16.4%), and constipation (7.8%) was lower with PALEXIA® IR than with oxycodone HCl IR (44.1%, 30.8%, and 19.7%, respectively) (Table 1).

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

Table 1 TEAEs in at least 5% of subjects in any treatment group: Phase 2/3 multiple dose double-blind safety analysis set[a]

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

[a] Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.
MedDRA version 11.0 was used for coding.

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

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

Very Common (≥ 1/10)

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

Common (≥1/100 to <1/10)

Metabolism and nutrition disorders:	Decreased appetite
Psychiatric disorders:	Anxiety, Confusional state, Hallucination, Sleep disorder, Abnormal dreams
Nervous system disorders:	Tremor
Vascular disorders:	Flushing
Gastrointestinal disorders:	Constipation, Diarrhoea, Dyspepsia, Dry mouth
Skin and subcutaneous tissue disorders:	Pruritus, Hyperhidrosis, Rash
Musculoskeletal and connective tissue disorder:	Muscle spasms
General disorders and administration site conditions:	Asthenia, Fatigue, Feeling of body temperature change

Uncommon (≥1/1,000 to <1/100)

Psychiatric disorders:	Depressed mood, Disorientation, Agitation, Nervousness, Restlessness, Euphoric mood
Nervous system disorders:	Disturbance in attention, Memory impairment, Presyncope, Sedation, Ataxia, Dysarthria, Hypoaesthesia, Paraesthesia, Muscle contractions involuntary
Eye disorders:	Visual disturbance
Cardiac disorders:	Heart rate increased, Palpitations
Vascular disorders:	Blood pressure decreased
Respiratory, thoracic and mediastinal disorders:	Respiratory depression, Oxygen saturation decreased, Dyspnoea
Gastrointestinal disorders:	Abdominal discomfort
Skin and subcutaneous tissue disorders:	Urticaria

Uncommon (≥1/1,000 to <1/100) (cont.)

Musculoskeletal and connective tissue disorder:	Sensation of heaviness
Renal and urinary disorders:	Urinary hesitation, Pollakiuria
General disorders and administration site conditions:	Drug withdrawal syndrome, Oedema, Feeling abnormal, Feeling drunk, Irritability, Feeling of relaxation

Rare (≥1/10,000 to <1/1,000)

Immune system disorders:	Drug hypersensitivity
Psychiatric disorders:	Thinking abnormal
Nervous system disorders:	Convulsion, Depressed level of consciousness, Coordination abnormal
Cardiac disorders:	Heart rate decreased
Gastrointestinal disorders:	Impaired gastric emptying

Treatment emergent adverse events with prolonged treatment

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

The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The percentage of subjects with at least 1 TEAE was 76.3% in the PALEXIA® IR (50 mg or 100 mg) and 82.9% in the oxycodone HCl IR (10 mg or 15 mg) groups (Table2). Subjects administered PALEXIA® IR had a lower incidence of gastrointestinal events compared to oxycodone HCl IR (44.2% vs 63.5% respectively) (Table 2).

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

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

Table 2 TEAEs during prolonged treatment in at least 5% of subjects: KF5503/34 safety analysis set

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

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
All adverse events are coded using MedDRA version 10.0.
IR = immediate release; N, n = number of subjects (total; per category); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

Post marketing experience

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

Suicidal ideation has been reported during post approval use of PALEXIA®. 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® IR overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In the clinical setting, these symptoms may include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions, respiratory depression up to respiratory arrest and death.

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® IR is suspected.

Pure opioid antagonists such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

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

Orthopaedic Surgery – Bunionectomy

The first bunionectomy clinical trial (KF5503/32) (n=603) investigated the efficacy of PALEXIA® IR tablets (50, 75 and 100 mg) against placebo and active comparator (oxycodone HCl IR 15 mg). The primary objective was to determine the efficacy of

PALEXIA® IR tablets using the sum of pain intensity difference (SPID) over 48 hours compared to placebo, and to assess the safety and tolerability of repeat doses of PALEXIA® IR tablets over the double-blind treatment period.

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

The results for $SPID_{48}$ for the ITT population are provided in Table 3. All PALEXIA® IR treatment groups showed a statistically significant ($p<0.001$) improvement in pain compared to placebo (mean $SPID_{48}$: 119.1, 139.1, 167.2 in the 50, 75 and 100 mg groups respectively). There was a numerical trend of increasing efficacy with increasing dose of PALEXIA® IR. Oxycodone HCl (mean $SPID_{48}$: 172.3) also showed a statistically significant ($p<0.001$) difference to placebo (mean $SPID_{48}$: 24.5).

Table 3 Sum of Pain Intensity Difference (SPID) at 48h[a], ITT population

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

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

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

LS = least square

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

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

In the ITT population, for $SPID_{48}$, PALEXIA® IR 75 mg showed a statistically significant improvement in pain relief compared to placebo (LS Mean difference to placebo of 70.8, p<0.0001). Morphine IR 30 mg also demonstrated a statistically significant improvement in pain relief compared to placebo (LS Mean difference to placebo of 109.4; p-value < 0.0001) (Table 4).

Table 4 Sum of Pain Intensity Difference (SPID) at 48h[a], ITT population

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

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

LS = least square

Abdominal Surgery - Hysterectomy

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

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

In the ITT population, all PALEXIA® IR treatment groups showed statistically significant improvement in pain relief compared to the placebo group for the primary variable, $SPID_{24}$ (p<0.0001) (Table 5). There was a numerical trend of increasing efficacy with increasing dose of PALEXIA® IR (LS Means difference to placebo for $SPID_{24}$: 18.1, 20.8 and 23.3 in the 50, 75 and 100 mg groups respectively). Morphine IR 20 mg (LS Means difference to placebo for $SPID_{24}$: 20.6) also showed a statistically significant (p<0.0001) difference to placebo.

Table 5 Sum of Pain Intensity Difference (SPID) at 24h[a], ITT population

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

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

LS = least square

End-Stage Degenerative Joint Disease

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

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

In the ITT population, both PALEXIA® IR 50 mg and 75 mg treatment groups showed a significant improvement in pain compared to placebo for the primary efficacy variable of SPID at 5 days (all p values <0.001) (Table 6). There was no numerical trend of increasing efficacy with increasing dose of PALEXIA® IR (LS Means difference to placebo for $SPID_5$ days: 101.2 and 97.5 respectively). Oxycodone HCl IR (10 mg) also showed a statistically significant (p<0.001) difference to placebo (Table 6).

Table 6 Sum of Pain Intensity Difference (SPID) at 5 days[a], ITT population

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

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

This study also included the pre-specified assessment of the non-inferiority of -PALEXIA® IR (50 and 75 mg) compared to oxycodone HCl IR (10 mg) with respect to efficacy (based on 5-day SPID) and tolerability (based on incidence of the reported evaluation of nausea and vomiting as adverse events of nausea and/or vomiting and constipation). For 5 day SPID, both PALEXIA® IR 50 mg and PALEXIA® IR 75 mg were non-inferior to oxycodone HCl IR 10 mg.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Tapentadol is rapidly and completely absorbed after oral administration of PALEXIA® IR. Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after administration of PALEXIA® IR tablets. Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed after administration of PALEXIA® IR tablets over the oral therapeutic dose range. Steady state serum concentrations of tapentadol are reached on the second day of the treatment regimen.

A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol administered as immediate release tablets showed an accumulation ratio between 1.4 and 1.7 for the parent drug and between 1.7 and 2.0 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite.

Food Effect

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

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.

Excretion

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

Elderly patients

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment

AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In

subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratios of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolised by Phase 2 glucuronidation, and only a small amount is metabolised by Phase 1 oxidative pathways.

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

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

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

5.3 PRECLINICAL SAFETY DATA

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

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

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of 5, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets.

Not all tablet strengths or pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

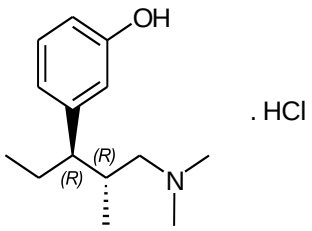
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

PALEXIA® IR immediate release tablets contain tapentadol hydrochloride (HCl) which is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake inhibition activity in a single molecule. Tapentadol is a white to off-white powder; freely soluble in water and methanol, and soluble in ethanol. The 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-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is $C_{14}H_{23}NO \bullet HCl$.

Chemical structure

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



CAS number

(CAS number: 175591-09-0)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug, S8

8 SPONSOR

Seqirus Pty Ltd
ABN 26 160 735 035
655 Elizabeth Street
Melbourne VIC 3000
Australia

www.cslseqirus.com.au

9 DATE OF FIRST APPROVAL

22 November 2010

10 DATE OF REVISION

10 February 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Addition of 'Duration of treatment' paragraph
4.5	Anticholinergics interaction added
4.9	Overdose section – addition of death to symptoms.
8.0	Change to Sponsor physical address and inclusion of sponsor website address