Palexia® (tapentadol hydrochloride)

Lynn Lambert, BPharm
Amayeza Information Services

Palexia® is an analgesic containing the active ingredient tapentadol hydrochloride.[1,2] Tapentadol is a novel, dual-acting central analgesic working as a mμ-opioid receptor (MOR) agonist and noradrenaline reuptake inhibitor (NRI).[3,4]

Two tapentadol-containing preparations are currently available in South Africa[5]:

- Palexia® tablets contain 50 mg or 100 mg tapentadol hydrochloride. Palexia® is indicated for the short-term relief of acute, moderately severe postoperative pain in patients aged 18 years and older. The duration of therapy should not exceed 10 days.[1,5]
- Palexia® SR prolonged release tablets contain 50 mg, 100 mg and 200 mg tapentadol hydrochloride. Palexia® SR is indicated in the management of moderate to severe chronic pain that is unresponsive to non-narcotic analgesia in patients 18 years and older.[2,5]

Pharmacokinetic properties

The pharmacokinetic properties of Palexia® and Palexia® SR are listed in Table I.

Dosing

The dose of tapentadol should be individualised based on the severity of pain being treated, previous treatment regimens and the ability to monitor the patient.[1,2]

Palexia® [1]

- Depending on the initial pain intensity, the recommended dose of Palexia® is 50 to 100 mg every four to six hours.
- Palexia® should be taken whole with sufficient liquid, with or without food.
- On the first day of treatment: a second dose may be taken as little as one hour after the initial dose, if pain persists. Thereafter, the recommended dose should be adjusted for pain control and tolerability.
- The maximum daily dose should not exceed 600 mg.

Palexia® SR

It should be taken twice a day, every 12 hours. Palexia® should be taken whole with sufficient liquid, with or without food.2

Initiating treatment[2]:

- Patients not currently using opioid analgesics:
- The recommended dose is 50 mg twice a day
- Patients currently using opioid analgesics:
- When switching from opioids to Palexia® SR and choosing

Table I. Pharmacokinetic properties of tapentadol[1,2]

	Palexia®	Palexia® SR
Absorption	Following a single-dose of tapentadol in a fasting state, the mean absolute bioavailability is approximately 32%. Steady state serum concentrations of tapentadol are reached on the second day of a six-hourly treatment regimen.	
*Cmax	Approximately 1.25 hours after administration.	Between three and six hours after administration of prolonged release tablets.
Distribution	Tapentadol is distributed throughout the body, with low serum protein binding (20%).	
Metabolism	Tapentadol is extensively metabolised via glucuronidation (97% of the parent compound). The metabolites do not contribute to its analgesic activity.	
Elimination	Tapentadol and its metabolites are excreted almost exclusively (99 %) via the kidneys.	
**t1/2 (average)	Four hours	Five to six hours

*Cmax = maximum serum concentration
**t1/2 = elimination half-life

the initial dose, the nature of the previous medication, administration and the mean daily dose should be taken into account.

Titration and maintenance[2]:

Doses should be titrated individually under the doctor's supervision, according to the patient's needs, i.e. adequate pain relief with minimal side-effects.

Palexia® SR should be titrated in increments of 50 mg twice daily every three days, if necessary.

The maximum daily dose should not exceed 500 mg.

Efficacy

The affinity of tapentadol for MOR is lower than that of morphine. Although tapentadol offers highly effective analgesia, it has a two to three times lower analgesic potency than morphine. However, tapentadol is a selective and rapid-acting NRI, which contributes to the analgesic potency. Tapentadol as an NRI offers pain suppression by increasing noradrenaline and activating alpha-2-adrenergic receptors in the brain and spinal column. The dual mechanism of action of tapentadol contributes to its opioid-sparing effects providing comparable analgesia to oxycodone.[3,4]

Three randomised, double-blind, phase three studies have evaluated the efficacy of tapentadol for moderate to severe acute pain[3]:

- Tapentadol was compared to oxycodone and placebo in two studies for postoperative pain (bunionectomy). Similar improvements in pain intensity were seen with tapentadol and oxycodone.
- Compared to morphine, ibuprofen and placebo, single doses of tapentadol 75 mg or more were effective in reducing postsurgical dental pain and showed a better tolerability profile than morphine.

Efficacy of short-term use of tapentadol in chronic inflammatory pain in patients with end-stage degenerative joint disease was found to be non-inferior to oxycodone in a double-blind placebo-controlled study.[3]

Randomised controlled studies have demonstrated effective pain control for moderate to severe chronic pain in patients with osteoarthritis, low back pain and neuropathic pain. Although results showed that tapentadol was non-inferior to oxycodone in terms of efficacy, it offered better gastrointestinal tolerability than oxycodone.[6]

In a phase 3/4b study in patients with severe chronic low back pain with a neuropathic component, tapentadol prolonged release (PR) demonstrated 37 % greater pain reduction versus oxycodone/naloxone PR. During the treatment period, the incidence of constipation was 40 % lower and that of vomiting was 53 % lower with tapentadol PR than with oxycodone/naloxone PR. Tapentadol PR therefore provided a significantly greater improvement in quality of life and 77 % more patients completed the study. [7]

Compared to tramadol, which is a prodrug and a weak opioid that also inhibits noradrenaline and serotonin reuptake, tapentadol does not require activation by metabolism and works primarily by NRI. In addition, tapentadol has a relatively strong opioid activity. These differences offer potential advantages of tapentadol over tramadol, such as a lower abuse potential and improved tolerability.[8]

Safety (special precautions, drug interaction, adverse effects)

See Table II.

Table II. Special precautions with tapentadol

Abuse potential	Due to the potential for abuse, tapentadol should be carefully considered before use in patients where there is a risk for misuse or abuse. In addition, patients treated with tapentadol should be monitored for signs of abuse or addiction.
Respiratory depression	Patients with compromised respiratory function should not be treated with tapentadol as it may cause dose-related respiratory depression.
Head injury and increased intracranial pressure	Tapentadol should not be taken by patients with increased intracranial pressure, impaired consciousness or coma. Tapentadol may adversely affect the progression of patients with head injury.
Seizures	Since tapentadol has not been studied in patients with seizures, it should be prescribed under careful consideration to patients with a history or risk of seizures.
Renal impairment	Tapentadol should not be used in patients with severe renal impairment due to lack of clinical efficacy studies in this population.
Hepatic impairment	Patients with hepatic impairment being treated with tapentadol had a higher serum concentration, compared to those with normal hepatic function. As a result, tapentadol should be used with caution in patients with moderate hepatic impairment. However, due to lack of studies, tapentadol should not be used in patients with severe hepatic impairment.
Use in pancreatic/biliary tract disease	Due to the risk of spasms of the sphincter of Oddi, tapentadol should be used with caution in patients with biliary tract disease. Tapentadol should not be used in patients with acute pancreatitis.
Lactose warning	Due to the lactose content in tapentadol, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Effects on ability to drive and use machines	Tapentadol may adversely affect central nervous system functions, especially at the start of treatment, including change of dose or concomitant use with alcohol or tranquilisers. Patients should be cautioned regarding driving or using machinery while on tapentadol.

Table II. Special precautions with tapentadol		
Body system	Frequency	Adverse effect
General disorders and administration site conditions	Common	Asthenia, fatigue, feeling of body temperature change
	Uncommon	Drug withdrawal syndrome, oedema, abnormal feeling, feeling drunk, irritability, feeling of relaxation
Renal and urinary disorders	Uncommon	Urinary hesitation, pollakiuria
Musculoskeletal and connective tissue disorder	Common	Muscle spasms
	Uncommon	Sensation of heaviness
Skin and subcutaneous tissue disorders	Common	Pruritus, hyperhidrosis, rash
	Uncommon	Urticaria
Gastrointestinal disorders	Very common	Nausea, vomiting
	Common	Constipation, diarrhoea, dyspepsia, dry mouth
	Uncommon	Abdominal discomfort
	Rare	Impaired gastric emptying
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression, decreased oxygen saturation, dyspnoea
Vascular disorders	Common	Flushing
	Uncommon	Decreased blood pressure
Cardiac disorders	Uncommon	Increased heart rate, palpitations
	Rare	Decreased heart rate
Eye disorders	Uncommon	Visual disturbance
Nervous system disorders	Very common	Dizziness, somnolence, headache
	Common	Tremor
	Uncommon	Disturbance in attention, memory impairment, presyncope, sedation, ataxia, dysarthria, hypoaesthesia, paraesthesia, involuntary muscle contractions
	Rare	Convulsion, depressed level of consciousness, abnormal coordination
Psychiatric disorders	Common	Anxiety, confusional state, hallucinations, sleep disorder, abnormal dreams
	Uncommon	Depressed mood, disorientation, agitation, nervousness, restlessness, euphoric mood
	Rare	Abnormal thinking
Metabolism and nutrition disorders	Common	Decreased appetite
Immune system disorders	Rare	Hypersensitivity
Angioedema, anaphylaxis, anaphylactic shock and increased blood pressure have been reported in post-marketing studies. Suicidal ideation has also been reported.		

Drug interactions

- The weak serotonergic activity of tapentadol is not considered to affect the analgesic properties of the drug. Due to its minimal serotonergic activity, tapentadol is unlikely to cause serotonin syndrome. [9] However, serotonin syndrome has been associated with the concomitant use of tapentadol and serotonergic medicines such as the selective serotonin reuptake inhibitors (SSRIs). Confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea are signs indicative of possible serotonin syndrome. Withdrawing the serotoninergic product results in improvement. [1, 2]
- A lack of clinical data on the concomitant use of tapentadol with mixed opioid agonist/antagonists (such as pentazocine, nalbuphine) or partial μ-opioid agonists are available. However, the analgesic effect provided by the μ-opioid component of tapentadol may be reduced in such circumstances. Therefore, care should be taken when combining tapentadol with these medicines.[1,2]
- Patients receiving other μ-opioid receptor agonist analgesics, general anaesthetics, phenothiazines or other tranquilisers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with tapentadol, may exhibit additive CNS depression. As a result, respiratory depression, hypotension, profound sedation, or coma may occur. When such combined therapy is contemplated, a reduction of dose of one or both medicines should be considered. Tapentadol should not be used in patients taking monoamine oxidase inhibitors (MAO-Is) or who have taken MAO-Is within 14 days, due to potential additive effects on noradrenaline levels, which may result in adverse cardiovascular events.[1,2]

Adverse effects

The most common adverse effects with tapentadol involve the gastrointestinal and central nervous systems (nausea, dizziness, vomiting, somnolence, and headache).[1,2]

Table III describes the adverse effects experienced in clinical trials and post-marketing studies with tapentadol.

Important prescribing points

- Discontinuation of treatment: Treatment with tapentadol should not be abruptly discontinued due to withdrawal symptoms. When discontinuing treatment, it is advised that the dose should be gradually tapered to prevent withdrawal symptoms. Medical practitioners should be vigilant for symptoms of withdrawal and treat patients accordingly, should they occur.[1,2]
- Paediatric patients: Tapentadol is not recommended for use in children younger than 18 years of age due to insufficient data on safety and efficacy in this population.
- Elderly patients (persons aged 65 years and over): The dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Since elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended.

References

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