Appropriate use of opioids for chronic pain in primary care

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Current state of play

Chronic pain affects approximately 28 million adults in the UK, with this number likely increasing as the population ages.[1] This places a significant demand on both primary and secondary care services.

The coronavirus pandemic has highlighted pressures and blockage points within the healthcare system in the UK and the impact of the pandemic is likely to be felt for some time to come. There were over 28 million fewer outpatient attendances between April 2020 and June 2021.[2] In primary care, there were also 31 million fewer appointments booked between April 2020 and March 2021.[3] This backlog is likely to be exacerbated further as the impact of long COVID becomes apparent.[2]

The delay in accessing specialist care will put further emphasis on the assessment and management of pain conditions in primary care. Therefore, a detailed understanding of the recommended management strategies for pain conditions is vital. Opioid prescribing can be part of the management plan, as long as the principles of safe opioid management are followed.

This article outlines the indications for opioid use, details of initiation and rotation, and implications of opioid prescribing for patients.

Definition of chronic pain

There are varying definitions of chronic pain but multiple surveys demonstrate the impact this condition has upon our patients and their quality of life. The International Classification of Diseases 11th Revision (ICD-11)[4] states that chronic pain is 'pain that persists past normal healing time and hence lacks the acute warning function of physiological nociception.' Chronic pain is then divided into chronic primary and secondary pain.

Chronic primary pain is defined as pain that persists for longer than three months and is associated with significant emotional distress or functional disability and that cannot be explained by another chronic condition.[4] This new definition applies to chronic pain syndromes that are best conceived as health conditions in their own right. Examples of chronic primary pain conditions include fibromyalgia, complex regional pain syndrome, chronic migraine, irritable bowel syndrome, and non-specific low-back pain.

Chronic secondary pain syndromes are defined as pain that may initially be regarded as a symptom of other diseases having said disease being the underlying cause. However, a diagnosis of chronic secondary pain marks the stage when the chronic pain becomes a problem in its own right. In many cases, the chronic pain may continue beyond successful treatment of the initial cause; in such cases, the pain diagnosis will remain, even after the diagnosis of the underlying disease is no longer relevant. Examples of chronic secondary pain are chronic pain related to cancer, surgery, injury, internal disease, disease in the muscles, bones or joints, headaches, or nerve damage.

It is important to note that patients can have a mixed picture of both chronic primary and secondary pain; patients with an initial diagnosis of chronic primary pain may develop mixed or secondary pain, based upon new investigations or the progression of symptoms.

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NICE estimates that only 1–6% of the population may have chronic primary pain, with a background chronic pain prevalence of approximately 40%.[5]

Epidemiology of chronic pain

The varying definitions of chronic pain can hamper the understanding of the epidemiology of chronic pain. Public Health England included nearly 8000 adults and 2000 children in a health survey focusing on chronic pain.[6] The prevalence of chronic pain ranged from 18% in 16–34 year olds to 53% in the over-75 age group. The incidence was higher in women, those in the Black ethnic group, and in people living in more deprived areas.

The impact of chronic pain can be felt in multiple facets of a person's life. It is associated with poor general health (physical, psychological, social)[6] and an increased mortality.[7]

Challenges of chronic pain management

Patients with chronic pain can provide a challenge to all healthcare professionals, from primary to tertiary care services. The reasons are multitude but include:

1. Interplay between chronic pain and mental health
2. Polypharmacy and drug interactions/side effects
3. Impact on motivation for exercise
4. Impact on family life and relationships
5. Impact on employment and finances
6. Impact on education
7. Social isolation
8. Limitations of diagnostic testing.

The complexity of chronic pain requires a multidisciplinary approach, and this should be embedded in primary care as well as the hospital setting. The role of the Primary Care Network is crucial in this regard, and as the prevalence of chronic pain increases, further funding of community pharmacy, physiotherapy, and psychology services may be required.

National guidance for the management of chronic pain

There are several NICE guidelines that focus on the management of patients with chronic pain, with the most recent guidance addressing chronic primary pain management specifically.[5] The definition of chronic primary pain adopted by NICE is pain that has 'no clear underlying condition or the pain (or its impact) appears to be out of proportion to any observable injury or disease.'

The guidance promotes the use of exercise and psychology, as well as acupuncture. With regards to medication, the guidance recommends the off-label use of antidepressants but highlights multiple medications that are not recommended, from gabapentinoids to local anaesthetic injections.

Opioids are not recommended by NICE for the management of chronic primary pain.[5] However, NICE recommends shared decision making for patients with chronic primary pain who are already established on opioids. One should explain the lack of evidence and agree a shared plan to continue safely (if the benefits outweigh the risks) or to reduce the medication and eventually stop it. This is an important principle as patients may be concerned that this guideline will result in widespread cessation of opioids without appropriate consultation. Firstly, it is important to note that this guidance applies only to chronic primary pain and not chronic secondary pain or mixed pain conditions. Secondly, the guidance highlights that a discussion is needed between the patient and healthcare professional to decide on the risk/benefit profile of continuing and stopping opioid medication.

Initiating opioid medication

A number of steps are needed before a decision to commence opioid treatment in a patient with chronic pain can be made. A comprehensive history of the symptoms and their impact upon the patient is needed, along with the therapies already tried and their relative

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impacts. Whilst mental health disorders are not a contraindication to opioid prescribing, it is important to recognise they are a risk factor for opioid addiction. There are specific tools to screen for the potential risk of opioid misuse, such as the Opioid Risk Tool.[8] Discussion with the patient's mental health team may be useful.

There is no optimum 'time' to start opioid therapies – they should not be the first step of a management plan – but equally delaying them may be denying patients a potentially useful medication. Input from a multidisciplinary team is likely to be beneficial, and will ensure that 'non-opioid' strategies are explored first, such as physiotherapy and psychology input.

Shared decision making is key when initiating opioids,[9] and patients need to understand the lack of evidence for long-term benefit in chronic pain; however it is accepted that some patients do benefit from opioids.[9] The patient should be counselled that 'curing' chronic pain with medication is not the goal and is often unachievable, even with high doses; opioid medications are part of a wide management plan that focuses on improving quality of life within the context of pain. The discussion should also cover the potential for side effects (e.g. constipation, nausea, pruritus) and long-term complications, such as addiction.

Opioid initiation should begin with an opioid trial, during which an opioid medication is started for a period of time (usually 2–4 weeks) followed by an assessment according to pre-agreed demonstrable objectives (e.g. 25% reduction in pain scores, ability to complete physiotherapy sessions, discontinuation of another medication). A patient diary can help inform the assessment. This approach further highlights the role that opioids can play in pain management and tries to focus on improved quality of life, rather than a focus purely on pain scores. If the opioid medication did not help the patient achieve the objectives or the side effects outweighed any benefits, then the patient may not benefit from opioids and alternative strategies should be explored. The choice of opioid for the trial is dependent upon the patient history and the characteristics of the pain; in most circumstances, a suitable choice would be oral morphine.

If the patient benefitted from opioid therapy during the trial, a further discussion about long-term opioid use is needed. The discussion should focus on the evidence base for opioids, the problems with opioid use (including addiction) and the potential benefits, as informed by the opioid trial. It is important to identify functional outcomes that opioid therapy will assist with, as well as the potential for reduced pain scores.

Once an opioid is started, the patient should be reviewed within 4 weeks to ensure appropriate use, identify side effects and assess the benefits of the drug. Once a stable regime is implemented, the patient should be reviewed every 6 months. Reviews should focus on the 6As:[10]

- analgesic efficacy
- adverse effects
- aberrant behaviours
- activities
- affect
- accurate records.

A ceiling dose of total oral equivalent morphine should be agreed and documented in the clinic notes. The Faculty of Pain Medicine recommends a maximum of 120 mg of daily oral morphine.[9]

Choice of opioid and starting dose

There is no 'first choice' opioid for chronic pain use; each opioid has advantages and disadvantages and the choice is an interplay of patient factors, pain characteristics, and drug profiles. Often, oral morphine is chosen, as it is familiar and easily titrated. If a patient has constant pain during the day, slow release formulations are useful. If the pain is more episodic and short lived, immediate release oral morphine may be preferred. Patients with swallowing problems would benefit from transdermal patches. Injectable opioids, orally administered fentanyl, and pethidine are not recommended for chronic pain.

The starting dose of opioid will vary dependent upon what medication the

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patient currently takes or has taken in the past. Generally, opioid medication should be started at a low dose and titrated upwards based upon efficacy and side effects.

Stopping opioid medication

If the opioid trial does not result in improvements in the outcomes identified, then reduction and cessation should occur. This is likely to be accepted by the patient if there was an agreement made at the beginning of the trial.

Opioid reduction and cessation may be necessary in patients who have been established on opioids if there is no longer any benefit or if the side effects are unmanageable. It is important to discuss alternative management strategies with the patient to allay any fear. An assessment by the multidisciplinary team is useful to ensure that a comprehensive appraisal of potential strategies is made and discussed with the patient.

Opioid reduction should be decided with the patient, backed up with an explanation of the rationale. The dose reduction should be gradual and complemented with regular reviews to assess for withdrawal symptoms. For very high opioid doses or complex opioid regimes, admission to an inpatient hospital bed for the weaning period may be needed.

A 10% weekly or monthly reduction in opioid dose is usually appropriate. This will need to be reviewed regularly. Complete cessation of the opioid may not be feasible in the first instance, and may require several rounds of opioid reduction. Patients with mental health disorders may need more intensive support during the opioid reduction period.

Opioid withdrawal

Opioid withdrawal describes a cluster of symptoms and signs (e.g. sweating, shaking, diarrhoea, loss of appetite, tachycardia) associated with a reduction in opioid blood levels, sometimes seen with opioid reduction regimes. A 10% reduction in opioid does not usually cause withdrawal but is likely to be associated with anxiety, which can mimic withdrawal. The Clinical Opiate Withdrawal Scale is a useful tool to identify true opioid withdrawal.[11] Regular assessments and support for the patient is needed. Occasionally, a slower reduction regime is needed.

Addressing patient concerns about opioids

Often patients will have concerns about starting morphine-type drugs and it is important to address them. This should form part of the shared decision making process, and patients should be reassured that the rate of addiction is likely to be low.[8] There are no accurate prevalence figures for the prevalence of addiction amongst patients in the UK who are taking opioids for the management of chronic pain. We can identify patients at higher risk of developing addiction, using questionnaires such as the Opioid Risk Tool.[8] Urine drug screening is rarely used within clinical practice in the UK for this cohort of patients. Opioids Aware is an online resource created by the Faculty of Pain Medicine, aimed at providing patient (and professional) information and this has a useful section on addiction.[9]

Opioids and driving

Patients who are started on opioid therapy need to be informed about the implications on driving. All opioid medications have the potential to impair driving and high doses are more likely to do so; if a patient is taking more than 220 mg of morphine a day, their driving may be impaired as much as someone who drives while above the legal alcohol limit.[12] At such doses, the patient should be informed that they are unlikely to be fit to drive. If their driving is impaired as a result of taking opioids, it is illegal to drive. It is unsafe to drive in the first few days after starting or changing a dose of an opioid. Also, there is an interaction between alcohol and opioid medications that may result in unsafe driving at a lower opioid dose.

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Case study 1 (fictional)

Background: Patient discharged from hospital with tapentadol for severe chronic pain related to a back surgery procedure performed a year ago. On review, the GP continues the prescription of tapentadol on the same dose and asks to see the patient in 4 weeks for a review …

Commentary and next steps: Tapentadol is an opioid drug that has two mechanisms of action – mu opioid agonism (similar to classical opioids) and noradrenaline re-uptake inhibition.[13] It is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.[14] It is considered a strong opioid but has fewer gastrointestinal side effects compared with classical opioids such as morphine, due to significantly less opioid agonism. Despite the potential for fewer gastrointestinal side effects, tapentadol still has activity at the opioid receptor and so the side effect profile will reflect this and include constipation, nausea, pruritus, sedation, and respiratory depression.[14]

Discharge planning and communication is vital to ensure safe opioid prescribing. The discharge summary should document the indication for tapentadol, the dose and intended duration. Ideally, a plan for maintenance, weaning, or dose titration should be documented. When patients are discharged from hospital on opioids, an assessment needs to be made according to the 6As criteria discussed above, including the use of an opioid risk tool. If the patient has benefits in terms of pain scores and functional outcomes, it may be appropriate to continue tapentadol.

The dose may need to be altered depending on analgesia, functional outcomes, and side effects. Typically, the dose of tapentadol is altered in steps of 50 mg per dose (e.g. 50 mg BD is increased to 100 mg BD).[14] It is recommended that dose increments are made every 3 days, however in practice this may be too frequent and often changes are made every few weeks.[14] Opioid dose changes may be associated with new side effects or interactions with other medication; regular reviews are needed during this period, particularly if dose changes are made frequently (e.g. weekly). Once the dose is established, the patient can be reviewed every 6 months.

If the patient reports no analgesic benefits, or has intolerable side effects, the dose should be reduced in 50 mg steps as above. Reductions should be continued at appropriate time intervals (usually weekly) and the drug stopped. Again, regular reviews will be needed to support the patient and monitor for withdrawal.

It is important to see opioid therapy as part of the overall management strategy, and this patient should continue post-operative physiotherapy and exercise as dictated by the discharging team.

If the daily dose of tapentadol exceeds 150 mg BD (morphine equivalent of 120 mg/day), consider referring the patient to the secondary care pain service.

Case study 2 (fictional)

Background: Patient has been suffering from severe back pain for 15 months but has recently suffered rapid and significant functional decline. Current treatment is paracetamol and codeine (6 months). Patient has high reliance on functional ability for daily activities and responsibilities. Imaging does not appear to correlate with level of pain and functional impairment and the patient is not deemed a good candidate for surgery. GP initiates tapentadol as well as non-pharmacological modalities that have recently become available in the PCN …

Commentary and next steps: There is NICE guidance on the management of low back pain and this stresses the importance of a multidisciplinary approach, with an emphasis on physiotherapy/exercise and psychological strategies to enhance self-management.[5] It is important to identify opioids as one part of the management plan, rather than them being the sole management plan moving forward.

The initiation of tapentadol should be done on a trial basis, over 2–4 weeks, starting with a dose of 50 mg BD.[14] The consultation should identify specific objectives that the tapentadol trial should assist with. Objectives could include a reduction and cessation of codeine intake and engagement with a physiotherapy rehabilitation plan. The maximum dose of tapentadol is 500 mg per day.[14]

If tapentadol is unsuccessful at helping to manage this debilitating pain, referral on to secondary care services would be indicated.

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Case study 3 (fictional)

Background: Elderly patient who was being managed by a care of the elderly specialist for severe chronic pain as a result of osteoarthritis. GP initiates tapentadol for a trial period …

Commentary and next steps: Opioid therapy, such as tapentadol, can be useful in the management of chronic pain as a result of osteoarthritis, particularly if surgery is not part of the management plan. In the elderly population, it is important to consider the potential impact of opioid related side effects such as drowsiness and constipation. Elderly patients may be on multiple medications and it is important to note interactions between opioids and other potentially sedating drugs, as well as interactions between tapentadol and serotonin reuptake inhibitors. It is also important to consider age-related organ function, as tapentadol is not recommended in patients with severe liver and kidney impairment, with a dose reduction needed for moderate liver impairment.[14]

After a trial of tapentadol 50 mg BD for 4 weeks, an assessment should be made of the potential benefits based upon functional improvements. In this population, dose changes should be made slowly and at longer intervals (e.g. 50 mg/day increase every 4 weeks) to reduce the risks of side effects.

When to refer patients who are on opioids to secondary care services

1. Above 120 mg of oral morphine (equivalent) per day[9]
2. Potential opioid misuse
3. Complex opioid prescribing – multiple opioids, organ failure
4. Complex psychological and mental health disorders.

Summary

The burden and impact of chronic pain on the patient, their family and the health infrastructure cannot be underestimated. Opioid therapy remains an option for patients who suffer from chronic pain, but only as part of a holistic approach that includes non-pharmacological therapies such as physiotherapy and psychology. A full discussion with patients about the benefit and potential harm of opioid therapy are necessary, including a discussion about driving.

Opioid choice and dose vary, but often morphine is considered an appropriate starting point. Close monitoring of opioid use if necessary using the 6As approach, with more than 120 mg daily morphine equivalent use prompting referral to secondary care.[9] Opioid rotation often requires a 25–50% reduction in the equivalent dose to avoid opioid related side effects and complications.[15] It is important to link opioid use to functional objectives, and not just a reduction in pain scores. Failure to achieve these agreed upon objectives should prompt consideration of opioid cessation.

Key points

1. Opioids are an option for patients who are not managing despite non-opioid medications and input from other disciplines (e.g. physiotherapy).
2. Shared decision making is needed before opioids are started, including a discussion about potential benefits and risks.
3. An opioid trial should have clear documented objectives that can identify potential benefit.
4. Use the 6As approach during regular assessments for patients on opioids.
5. When rotating opioids, consider reducing the equivalent dose by 25–50%.
6. More than 120 mg daily oral morphine equivalent should prompt referral to secondary care services.

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General considerations for the management of pain with any medication that contains an opioid mechanism of action

The following general aspects should be considered:

- An individualised, patient-centred approach for the diagnosis and treatment of pain is essential to establish a therapeutic alliance between patient and clinician
- Consider patient variables that may affect opioid dose for each patient prior to opioid use[1]
- In patients with acute pain e.g. post-surgery pain, the use of medication should be for the shortest necessary time[1]
- All patients should be carefully selected, abuse risk factors evaluated and regular monitoring and follow up implemented to ensure that opioids are used appropriately[3,4] and in alignment with treatment goals (pain intensity and functionality) as agreed with the patient[3,4]
- Patients should be made aware of the potential side effects of opioids and the potential for developing tolerance, dependence, and addiction[3,4]
- It is important to optimally use multimodal, non-opioid approaches in acute and chronic pain before escalating to opioids or in conjunction with opioid therapy[1]
- Addiction is possible even when opioids are taken as directed. The exact prevalence of abuse in patients treated with opioids for chronic pain is difficult to determine[5]
- Regular clinical reviews are required for long-term opioid treatment to assess pain control, impact on lifestyle, physical and psychological well-being, side effects, and continued need for treatment[2]
- Any long term treatment with opioids should be monitored and re-evaluated regularly, including tapering down the dose or discontinuing treatment[3,4]
- Signs of opioid use disorder should be monitored and addressed[3,4]
- Patients and the general public can benefit from clear educational materials and awareness interventions to support the responsible use of opioids.[6]

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PALEXIA® SR (tapentadol hydrochloride) Prolonged Release Tablets Prescribing Information

Refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** 50 mg (white), 100 mg (pale yellow), 150 mg (pale pink), 200 mg (pale orange) and 250 mg (brownish red) prolonged-release tablets contain 50 mg, 100 mg, 150 mg, 200 mg and 250 mg of tapentadol (as hydrochloride) respectively. **Indication:** Palexia SR is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. **Dosage and method of administration:** Individualise according to severity of pain, the previous treatment experience and the ability to monitor the patient. Swallowed whole with sufficient liquid, not divided or chewed, with or without food. The tablet shell may not be completely digested and eliminated / seen in the patient's stool which has no clinical significance as the active substance will have already been absorbed. Initial dose 50 mg twice a day. Switching from other opioids may require higher initial doses. Titrate in increments of 50 mg twice a day every 3 days for adequate pain control. Total daily doses greater than 500 mg not recommended. *Discontinuation of treatment:* Taper dose gradually to prevent withdrawal symptoms. *Renal/ hepatic impairment:* Not recommended in severe patients. Moderate hepatic impairment, exercise caution, at initiation do not exceed 50mg SR once daily. *Elderly:* May need dose adjustments. *Children below 18 years:* Not recommended. **Contraindications:** Hypersensitivity to ingredients, suspected or having paralytic ileus, acute intoxication with alcohol, hypnotics, centrally acting analgesics or psychotropics. Not for use when mu-opioid receptor agonists are contraindicated (e.g. significant respiratory depression, acute or severe bronchial asthma or hypercapnia). **Special warnings and precautions:** Abuse and addiction potential of Palexia SR should be considered where there is increased risk of misuse, abuse, addiction or diversion. All patients should be carefully monitored for signs of abuse and addiction. Concomitant use with sedating medicinal products such as benzodiazepines or related substances may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If used concomitantly, reduction of dose of one or both agents should be considered and the duration of the concomitant treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. It is strongly recommended to inform patients and caregivers to be aware of these symptoms. At high doses or in mu-opioid receptor agonist sensitive patients, dose-related respiratory depression may occur. Caution and monitoring required with impaired respiratory function. Should not use in patients susceptible to intracranial effects of carbon dioxide retention (e.g. increased intracranial pressure, impaired consciousness or coma). Use with caution in head injury, brain tumors, moderate hepatic impairment and biliary tract disease including acute pancreatitis. Not recommended if history of or at risk of seizures. May increase the seizure risk in patients taking other medicinal products that lower the seizure threshold. Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage. Care should be taken when combining with mixed mu-opioid agonists/antagonists (e.g. pentazocine, nalbuphine) or partial mu-opioid agonists (e.g. buprenorphine). Should not use with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. **Interactions:** The concomitant use with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. When combined therapy with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered and the duration of the concomitant use should be limited. 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. 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 SSRIs, SNRIs and tricyclic antidepressants. Use with strong inhibitors of uridine diphosphate transferase isoenzymes (involved in glucuronidation) may increase systemic exposure of Palexia SR. Caution if concomitant administration of strong enzyme inducing drugs (e.g. rifampicin, phenobarbital, St John's Wort) starts or stops as this may lead to decreased efficacy or risk for adverse events, respectively. Avoid use in patients who have taken monoamine oxidase inhibitors (MAOIs) within the last 14 days, due to cardiovascular events. **Pregnancy and Breast-feeding:** Use in pregnancy only if the potential benefit justifies the potential risk to the foetus. Long term maternal opioid use during pregnancy may cause neonatal withdrawal syndrome (NOWS). NOWS can be life threatening. Not recommended during and immediately before labour and delivery. Do not use during breast feeding. New-born infants whose mothers have been taking tapentadol should be monitored for respiratory depression. **Driving and using machines:** May have major effect on ability to drive and use machines, especially at the beginning or change in dosage, in connection with alcohol or tranquilisers. **Undesirable effects:** ***Very common*** *(≥1/10):* dizziness, somnolence, headache, nausea, constipation. ***Common*** *(≥1/100, <1/10):* decreased appetite, anxiety, depressed mood, sleep disorder, nervousness, restlessness, disturbance in attention, tremor, involuntary muscle contractions, flushing, dyspnoea, vomiting, diarrhoea, dyspepsia, pruritus, hyperhidrosis, rash, asthenia, fatigue, feeling of body temperature change, mucosal dryness, oedema. ***Other important undesirable/ serious effects observed in clinical trials and/or post-marketing:*** drug hypersensitivity, depressed level of consciousness, mental impairment, syncope *(uncommon ≥1/1000, <1/100)*, angioedema, anaphylaxis and anaphylactic shock, respiratory depression, convulsion, impaired gastric emptying, drug dependence *(rare ≥1/10,000, <1/1000)*, delirium *(unknown)*. No evidence of increased risk of suicidal ideation or suicide with Palexia SR. Prescribers should consult the SmPC in relation to all adverse reactions. **Overdose:** Seek specialist treatment (see SmPC). **Legal classification:** POM, CD (Schedule II). **Marketing Authorisation numbers, pack sizes and basic NHS cost:** 50 mg: PL 50414/0014, 28 pack (£12.46) and 56 pack (£24.91); 100 mg: PL 50414/0015, 56 pack (£49.82); 150 mg: PL 50141/0016, 56 pack (£74.73); 200 mg: PL 50414/0017, 56 pack (£99.64) and 250 mg: PL 50414/0018, 56 pack (£124.55). **Marketing Authorisation Holder:** Grunenthal Pharma Ltd. 4045 Kingswood Road, Citywest Business Park, Citywest, Co.Dublin, Ireland.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Grünenthal Ltd (telephone 0870 351 8960).