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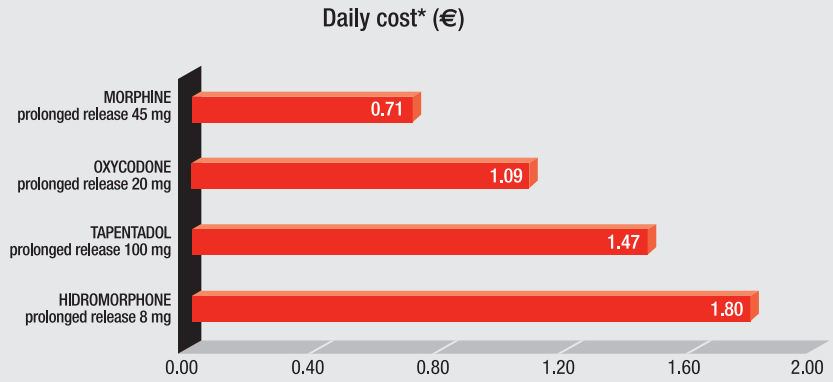
Tapentadol (▲Palexia®) for chronic intense pain

Prolonged release opioid of unknown therapeutic value



*Note: costs calculated with the approximate equipotent doses of available presentations according to conversion factors[2].

When a major opioide is required, then morphine is the elective choice

Indications[1]

Management of chronic severe pain in adults that can only be treated with an opioid.

Mechanism of action and pharmacokinetics[1]

Potent analgesic opioid, with a bioavailability of 32% and maximum concentration between 3-6 hours. It is metabolized fundamentally by conjugation and none of its metabolites present analgesic propertites. Elimination is renal (half-life = 4 hours).

Posology and methods of administration[1]

The tablets should be taken entirely, and should not be masticated or triturated. The drug can be taken with or without food.

Treatment onset: in patients taking opioids, 50 mg twice daily is the recommeded starting dose. Patients with previous treatment with opioids may require higher initial doses[1]. The dose equivalence of tapentadol:morphine is 2.5:1 and tapentadol:oxycodone is 5:1.

Dose adjustments: should be done in increments of 50 mg every 12 hours every 3 days until adequate pain control is achieved. Maximum daily dose: 500 mg.

- Tapentadol has proved more effective than placebo in arthrosis, lumbalgia and pain related to diabetic neuropathy.
- However, the results should be interpreted with caution as there are important limitations.
- No direct comparisons have been made with other opioids. There is only one analysis in which tapentadol did not show any differences when compared to oxycodone.
- No studies are available on its use for pain in cancer patients.
- This drug has the same adverse effect profile as other opioid analgesics. The most frequent are nausea, constipation, dizzyness, somnolence and cefalea.
- There are no rapid release presentations.

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

Suspending treatment: reduce doses gradually to avoid abstinence-related symptoms.

Clinical efficacy

There are no studies directly comparing tapentadol to other major opioids. The EMA assessment report[3] included two studies on knee arthrosis[4] (of which one study remains unpublished), one study on lumbalgia, another on diabetic neuropathy and one study on long term tolerance[7]. A pooled data analysis[8] has also been published which includes individual data of the patients in two published[4,5] studies and of those in the unpublished study.

With respect to knee arthrosis and lumbalgia, tapentadol was compared to placebo and oxycodone as the active comparator (studies were not designed for a direct comparison). After a washout phase and dose adjustments (3 weeks), the maintenance period of treatment lasted 12 weeks. The patients included showed an average score measuring pain intensity at the start of the study of ≥5 points on a scale of 11 points (from "0" = no pain to "10" = worst pain imaginable). The doses employed of tapentadol were 100-250 mg every 12 hours compared to oxycodone 20-50 mg every 12 hours. Both tapentadol and oxycodone proved significantly superior to placebo. The differences for tapentadol were -0.7 (95%CI, -1.00 to -0.33)[4] and -0.7 (95%CI, -1.06 to -0.35)[5] while those for oxycodone were -0.3 (95%CI, -0.67 to -0.00)[4] and -0.8 (95%CI, -1.16 to -0.46)[5]. However in the unpublished study the differences between tapentadol and placebo did not show significant differences[3]. Only one of these studies reports the difference in the average intensity of pain with respect to the baseline scores in each treatment group: -2.8 (tapentadol), -2.9 (oxycodone), and -2.1 (placebo)[5]. These data should be interpreted with precaution as the rates of patients abandoning treatment were very high and unbalanced: placebo (range 39-52%), tapentadol (range 43-48%), oxycodone (range 60-65%). As a result this limits the internal validity of the outcomes.

In the study on patients with peripheral diabetes related neuropathy[6] the efficacy of tapentadol was compared to placebo for 12 weeks, after an initial phase lasting 3 weeks to allow for tapentadol dose titration. Tapentadol proved superior to placebo in the average reduction of pain intensity -1.3 (95%CI, -1.70 to -0.91). In patients treated with tapentadol there was no change in the average intensity of pain with respect to baseline values. However, those treated with placebo showed an increase in the intensity of pain of +1.4 points. The rate of withdrawals was 32% in both groups, which could limit the results of the study. In the pooled data study[8], tapentadol did not show any differences compared to oxycodone.

Safety

Adverse reactions[1]

Similar to the rest of the opioids. Most frequent adverse effects (≥10%): nausea, constipation, dizzyness, somnolence, and cefalea.

Contraindications[1]

Hypersensitivity to the drug or any of its excipients (contains lactose), important respiratory depression, acute or severe bronchial asthma, hypercapnea, paralytic ileum, and severe liver or renal failure.

Warnings and precautions[1]

Potential for abuse and addiction and abstinence syndrome. Precaution is necessary in cases of respiratory dysfunction, head injury and raised intracraneal pressure, history of convulsions and disorders that can increase the risk of convulsions, moderate liver failure and pancreatic or biliary-tract disease.

Use in special situations[1]

Pregnancy: use only if the possible benefits justify the potencial risk to the fetus (class C)[2] **Birth:** it is not recommended during and immediately after delivery. **Lactation, children and adolescents:** its use is not recommended. **Liver failure:** no dose adjustments are required in mild liver failure, although adjustments are necessary in moderate cases. It is not recomended in severe liver failure. **Renal failure:** no dose adjustments are required in mild or moderate renal failure. It is not recommended in cases of severe renal failure. **Elderly:** assess for possible renal and/or liver dysfunction.

Effects on driving capabilities and use of machinery[1]

Tapentadol can reduce the mental and physical capacities to carry out potentially dangerous tasks and therefore patients should be cautioned.

Interactions[1]

Its use with MAO inhibitors is contraindicated. Precaution should be taken when using benzodiazepines, barbiturics, antipsychotic agents, H_1 antagonists, opioids and alcohol given the possible increase of the risk of respiratory depression. The concommitant use of SRSI drugs can provoke a serotoninergic syndrome. The analgesic effect can be reduced when employing pentazocine, nalbuphine, or buprenorphine. If treatment with rifampicine, phenobarbital, or Saint Johns wort is initiated or suspended then a reduction in the efficacy or a greater risk of adverse effects could occur respectively.

Place in therapeutics

With regard to cancer related chronic pain, morphine is the elective choice. However, in non-cancer related chronic pain the use of opioids is considered as a second or third line option, as the harm- benefit balance remains uncertain unlike the case of cancer related pain. Before initiating a chronic treatment with opioids, in the case on non-cancer related pain a careful evaluation of the patient should be carried out and the risk of abuse or dependence should be considered[10].

There are no randomized clinical trials that directly compare tapentadol with either other major opioids (morphine, fentanyl and oxycodone) or tramadol in the management of peripheral diabetic neuropathy. The analgesic effect of tapendatol has been studied in rare clinical situations compared to placebo. In other trials, both tapentadol and oxycodone have proved more effective than placebo in the management of moderate to severe pain in arthrosis, chronic lumbalgia and peripheral diabetic neuropathy. The duration of these studies (12 weeks) is very short to adequately evaluate chronic pain and the exclusion criteria were highly restrictive. Therefore, the selected population for these studies does not adequately represent the profile of patients susceptible to benefit from this treatment. The rates of withdrawals due to any cause (including adverse effects) in all arms of treatment were also considerably high and the clinical relevance of the benefits was limited. Of the studies carried out, it is inferred that tapendatol presents a similar adverse effect profile to other major opioids, as well as similar risks of abuse and dependence.

The absence of direct comparative studies with other standard opioids and the limited internal validity of the results from the available studies does not offer sufficient or conclusive information with regard to tapentadol's level of contribution in terms of efficacy and safety in the management of chronic pain.

Presentations

Palexia retard® (Grünenthal Pharma S.A.) (50, 100, 150, 200, 250) mg 60 sublingual tablets (44.02; 88.05; 132.07; 153.33; 169.17) € respectively. Requires medical and narcotic prescription.

References

A complete report on tapentadol can be found at: http://www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010

NEW DRUGS ASSESSMENT COMMITTEE:
Iñaki Abad, Mª José Ariz, Ana Azparren, Mª Concepción Celaya, Juan Erviti, Javier Garjón, Javier Gorricho, Antonio López, Rodolfo Montoya, Mikel Moreno, Lourdes Muruzábal