PALEXIA LP 50 mg, prolonged-release tablet
B/28 (unit packaging) (CIP: 3400941924859)
PALEXIA LP 100 mg, prolonged-release tablet
B/28 (unit packaging) (CIP: 3400941925801)
PALEXIA LP 150 mg, prolonged-release tablet
B/28 (unit packaging) (CIP: 3400941927980)
PALEXIA LP 200 mg, prolonged-release tablet
B/28 (unit packaging) (CIP: 3400941928703)
PALEXIA LP 250 mg, prolonged-release tablet
B/28 (unit packaging) (CIP: 3400941929533)

Applicant: GRÜNENTHAL SAS

<table>
<thead>
<tr>
<th>INN</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2014)</td>
<td>N02AX06 (opioid analgesic)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>“PALEXIA LP is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.”</td>
</tr>
<tr>
<td>Actual benefit</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>- low in the management of severe, chronic cancer pain in adults that can be</td>
<td></td>
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<tr>
<td>adequately managed only with opioid analgesics, except for intractable cancer</td>
<td></td>
</tr>
<tr>
<td>pain.</td>
<td></td>
</tr>
<tr>
<td>- insufficient in the management of severe, chronic, non-cancer pain that can</td>
<td></td>
</tr>
<tr>
<td>be adequately managed only with opioid analgesics.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement in Actual Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe, chronic cancer pain</strong></td>
</tr>
<tr>
<td>In light of the comparison between PALEXIA LP proprietary medicinal products and placebo or low-dose oxycodone LP, the Transparency Committee considers that the PALEXIA LP proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of severe, chronic cancer pain in adults, when compared with other available opioid analgesics.</td>
</tr>
<tr>
<td><strong>Severe, chronic non-cancer pain</strong></td>
</tr>
<tr>
<td>Not applicable.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe, chronic cancer pain</strong></td>
</tr>
<tr>
<td>The Transparency Committee considers that the proprietary medicinal products PALEXIA LP are an alternative to available step 3 opioid oral analgesics (morphine, oxycodone, and hydromorphone) in severe, chronic cancer pain, in view of their dosage limitations, but have no place in the management of intractable cancer pain.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)

Initial date: 3 October 2011 by mutual recognition (reference Member State: Germany);

Amendments to the SPC of 30 January 2014: type II variations in sections “4.8 Adverse effects” and “5.1 Pharmacodynamic properties” in the SPC.

Special monitoring: introduction of national risk-management measures in France, in addition to the measures proposed in the European Risk Management Plan.

Prescribing and dispensing conditions/special status

Narcotic

Prescription limited to 28 days

Controlled prescription in accordance with the specifications laid down by the Order of 31 March 1999

ATC Classification

2014

N Nervous system
N02 Analgesics
N02A Opioids
N02AX Other opioids
N02AX06 tapentadol

02 BACKGROUND

This concerns a request for the inclusion of the proprietary medicinal product PALEXIA LP on the list of pharmaceutical medicines refundable by National Health Insurance and on the list of medicines approved for hospital use. The company is only requesting inclusion in the treatment of severe, chronic cancer pain. However, in accordance with Article R.163-18 of the French Social Security Code, the Transparency Committee is obliged to assess the Actual Benefit of PALEXIA in all its indications, including non-cancer pain.

An earlier request for inclusion for this proprietary medicinal product was submitted then withdrawn at the consultation stage, after the Transparency Committee had adopted the draft opinion on 26 June 2013.\(^1\) The Transparency Committee’s view at the time was that: “In light of their negligible clinical efficacy, their adverse effects, the risk of dependency, ideation, and suicidal behaviour, .../... the proprietary medicinal products PALEXIA LP have no place in the treatment of severe, chronic pain, which can only be treated adequately with opioid analgesics”, and it felt that: “the actual benefit is insufficient when compared with other existing therapies”.

PALEXIA LP is an opioid analgesic whose active ingredient is tapentadol. Tapentadol is a strong analgesic with µ-opioid agonistic activity and additional noradrenaline reuptake inhibitory properties. PALEXIA is available in two pharmaceutical forms: immediate- or prolonged-release tablets. Only the inclusion of the SR form is currently being requested by the Applicant.

**03 THERAPEUTIC INDICATION**

“PALEXIA LP is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.”

**04 DOSAGE**

“Dosage
The dosing regimen should be individualised according to the severity of pain, the previous analgesic treatment experience, and the ability to monitor the patient.

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

*Initiation*

*Initiation of therapy in patients currently not taking opioid analgesics*

Patients should start their treatment with a 50 mg dose of tapentadol as prolonged-release tablet twice daily.

*Initiation of therapy in patients already taking opioid analgesics*

When switching from treatment with opioid analgesics to PALEXIA® SR and choosing the initial dose, the nature of the previous medicinal product, administration, and the mean daily dose should be taken into account. This may require higher initial doses of PALEXIA® SR for patients currently taking opioids compared to those not having taken opioids before initiating therapy with PALEXIA® SR.

*Titration and maintenance treatment*

After initiation of therapy, the dose should be titrated individually to a level that provides adequate analgesia and minimises undesirable effects, under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50 mg tapentadol as prolonged-release tablet twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Average daily doses of PALEXIA® SR greater than 500 mg tapentadol have not been investigated and are therefore not recommended.

*Discontinuation of treatment*

Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see section 4.8 of the SPC). When a patient no longer requires therapy with tapentadol, it is advisable to taper the dose gradually to prevent symptoms of withdrawal.

*Renal impairment*

In patients with mild or moderate renal impairment, a dosage adjustment is not required (see section 5.2 of the SPC).

PALEXIA LP has not been assessed in controlled efficacy trials in patients with severe renal impairment and it is therefore not recommended in these patients (see sections 4.4 and 5.2 of the SPC).
Hepatic impairment
In patients with mild hepatic impairment, a dosage adjustment is not required (see section 5.2 of the SPC).

PALEXIA® SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at the lowest available dose strength (e.g. 50 mg tapentadol as prolonged-release tablet) and not be administered more frequently than once every 24 hours. Initiation of therapy with a dose greater than 50 mg tapentadol is not recommended. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see sections 4.4 and 5.2 of the SPC).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and therefore, use in this population is not recommended (see sections 4.4 and 5.2 of the SPC).

Elderly patients (persons aged 65 years and over)
In general, a dose adaptation in elderly patients is not required. However, as elderly patients are more likely to have decreased renal and hepatic function, special care should be taken in dose selection (see sections 4.2 and 5.2 of the SPC).

Paediatric patients
The safety and efficacy of PALEXIA® SR in children and adolescents below 18 years of age has not been established. Therefore PALEXIA® SR is not recommended for use in this population.

05 THERAPEUTIC NEED

According to the IASP (International Association for the Study of Pain), the definition of pain takes into account both the duration and the appropriate nature of the pain: chronic pain is pain that lasts longer than the time usually required for healing (3 months). Chronic pain does not have the “appropriate” nature of acute pain, which is generally the response to an injury (for example, healing after a wounding).²³

Three types of pain are distinguishable by their physiological mechanism:⁴
- pain due to excess of nociception by hyperstimulation of the pain system, caused by persistent peripheral lesions (e.g. rheumatic pain);
- neuropathic pain, associated with an anatomical lesion of the pain system, often in the peripheral nervous system (e.g. diabetic neuropathy and neuralgia after shingles);
- dysfunctional pain, associated with the pain system through a lesion-unrelated nervous system dysfunction.

Pain due to excess of nociception and neuropathic pain respond to a pharmacological approach that constitutes first-line treatment. These two types of pain are closely linked to cancer pain.

Analgesics are conventionally divided into three steps, according to their respective analgesic potencies. This scale is proposed by the World Health Organisation (WHO) for the treatment of cancer pain:⁵
- Step 1, non-opioid (non-morphine-based) analgesics, represented essentially by paracetamol, acetylsalicylic acid, and low-dose non-steroidal anti-inflammatory drugs;

⁴ Fédération Nationale de Centres de Lutte Contre le Cancer : Standards, Options et Recommandations 2002 pour les traitements antalgiques médicamenteux des douleurs cancéreuses par excès de nociception chez l’adulte, mise à jour.
- Step 2 analgesics, weak opioids (weak morphine derivatives), codeine, tramadol, and low-dose opium. They are most often associated with step 1 analgesics, in particular with paracetamol;
- Step 3 analgesics, strong opioids (strong morphine derivatives), are of three types: pure agonists (morphine, fentanyl, oxycodone, hydromorphone), partial agonists (buprenorphine) and agonists-antagonists (nalbuphine, pentazocine).

Non-cancer-related nociceptive pain
Following the withdrawal of the dextropropoxyphene-based combinations, AFSSAPS [French Healthcare Product Safety Agency] published an update in 2010, further updated in 2011, on the management of moderate to intense pain in adults. It states that for intense, acute nociceptive pain (especially post-traumatic, post-surgical, rheumatic, and gynaecological pain) treatment may call for weak or strong opioids for very intense pain, depending on the urgency of obtaining relief and on the clinical situation.

Chronic non-cancer pain (CNCP) involves both medicinal and non-medicinal treatment, treatment of the causal disease, and management of psychological, social, and professional aspects. The use of strong opioids in this type of pain is controversial as there are few published studies confirming their efficacy and on account of their adverse effects, and worries concerning safety and dependency. Thus, in 2004, AFSSAPS stated that the risk/benefit ratio of strong opioids in CNCP would need to be carefully evaluated and that their prescription should not be recommended until after other available treatments (step 1 and 2 analgesics) had failed, while at the same time taking the usual precautions relating to the long-term use of morphine-based products.

Chronic neuropathic pain
Neuropathic pain responds poorly, if at all, to the usual analgesic treatments (NSAIDs, paracetamol, salicylates). Medicinal analgesic treatments for neuropathy rely consensually on the use of tricyclic antidepressants or on the use of antiepileptics acting on the sodium or calcium channels. Since the efficacy of treatments is often only partial, combinations of analgesics with complementary action mechanisms may be proposed.

According to the guidelines issued by the French Society for the Study and Treatment of Pain published in 2010, strong opioids are recommended for the treatment of neuropathic pain after the failure of first-line treatments (tricyclic antidepressants or certain antiepileptics) used either as monotherapy or, if necessary, in combination.

The efficacy of strong opioids (oxycodone, morphine, methadone) has been established in peripheral neuropathic pain, particularly in diabetic neuropathy and neuropathy after shingles. The doses needed to obtain this effectiveness are often high and need to be individually titrated. The risk of abuse has been estimated at 2.6% in a systematic review.

Cancer pain
Management strategy depends, in addition to its mechanism of action, on whether the pain is cancer-related or not. Interregional Reference Frameworks, working with cancer care support groups, recommend that pain management be based on the pain score recorded on a visual analogue scale (VAS), and indeed these scores can offer a useful means of monitoring pain and treatment efficacy. Strong pure opioid agonists are used to treat nociceptive cancer pain:

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7 Mise au point sur le bon usage des opioïdes forts dans le traitement des douleurs chroniques non cancéreuses. AFSSAPS. 2004.
- from the outset with scores above 7/10 (morphine IV is especially indicated in hyperalgesic patients).
- in cases of ineffective step 2 treatment (weak opioids) (reassessment after 24 hours).

The WHO recommends using morphine as a first-line treatment in adults. The ANAES [National Health Accreditation and Assessment Agency] recommends starting with immediate-release, or possibly extended-release, oral morphine sulphate. Supplementary (interdose) analgesia with a fast-acting morphine-based product is recommended. In cases where treatment with oral morphine has failed, the patient must be reassessed with a view to finding a neuropathic mechanism of action or a significant emotional or cognitive factor. In the event of the failure of treatment for nociceptive pain due to unmanageable adverse effects with morphine, it is recommended to either change to a different opioid (opioid rotation), or change the method of administration.

In neuropathic-type cancer pain, morphine is recommended as a third-line treatment in the event of a contraindication or the failure of one of the first-line therapeutic categories used as monotherapy or in combination (tricyclics, lidocaine, gabapentine).

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11 Fédération Nationale des Centres de Lutte Contre le Cancer : Standards, Options et Recommandations 2002 pour les traitements antalgiques médicamenteux des douleurs cancéreuses par excès de nociception chez l’adulte, mise à jour.
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

This refers to proprietary medicinal products containing morphine and other strong opioids (WHO step 3) indicated in the treatment of severe, chronic pain.

Among the comparator drugs, proprietary medicinal products containing morphine are the following:

<table>
<thead>
<tr>
<th>Name (Company)</th>
<th>Indication</th>
<th>Date of Opinion</th>
<th>AB</th>
<th>Reimbursed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolonged-release proprietary medicinal products administered orally</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKENAN LP (morphine sulfate) Bristol-Myers Squibb</td>
<td>Persistent intense pain or pain resistant to other analgesics, particularly cancer pain.</td>
<td>10 Feb 2010 Renewal of inclusion: RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MOSCONTIN / MOSCONTIN LP (morphine sulfate) Mundipharma</td>
<td>Persistent intense pain or pain resistant to weaker analgesics, particularly cancer pain.</td>
<td>27 Apr 2011 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Immediate-release proprietary medicinal products administered orally</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTISKENAN (morphine sulfate) Bristol-Myers Squibb</td>
<td>Intense pain or pain resistant to weaker analgesics, particularly cancer pain.</td>
<td>10 Feb 2010 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>SEVREDOL (morphine sulfate) Mundipharma</td>
<td></td>
<td>27 Apr 2011 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>ORAMORPH (morphine sulfate) L. Molteni &amp; C. dei F.lli Alitti SpA</td>
<td></td>
<td>1 Dec 2010 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Proprietary medicinal products for injection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MORPHINE (SULFATE) LAVOISIER (morphine sulfate) Chaix and Du Marais</td>
<td>1 mg/ml Severe pain and/o pain resistant to weaker analgesics. 50 mg/ml Intense pain and/o pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.</td>
<td>3 Nov 2010 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MORPHINE AGUETTANT (morphine hydrochloride) Aguettant</td>
<td>0.1, 1, 10, 20 mg/ml Intense pain and/o pain resistant to weaker analgesics. 40 mg/ml Intense pain and/o pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.</td>
<td>25 May 2011 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MORPHINE (CHLORHYDRATE) LAVOISIER (morphine hydrochloride) Chaix and Du Marais</td>
<td>Intense pain and/o pain resistant to weaker analgesics.</td>
<td>3 Nov 2010 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MORPHINE (CHLORHYDRATE) RENAUDIN (morphine hydrochloride) Renaudin</td>
<td>1, 10, 20 mg/ml: Intense pain and/o pain resistant to weaker analgesics. 40 mg/ml: Intense pain and/o pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.</td>
<td>30 Nov 2011 Inclusion 2 Mar 2005 Inclusion</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>MORPHINE (CHLORHYDRATE) COOPER (morphine hydrochloride) Cooper</td>
<td>Intense pain and/o pain resistant to weaker analgesics.</td>
<td>25 May 2011 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Proprietary medicinal products containing strong opioids are described in the table below:

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Indication</th>
<th>Date of Opinion</th>
<th>AB</th>
<th>Reimbursed</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXYCONTIN LP</td>
<td>Mundipharma</td>
<td>Treatment of severe pain that cannot be adequately treated other than with strong opioid analgesics, especially the case of cancer pain.</td>
<td>19 Sep 2012 RI</td>
<td>Substantial in these indications: - cancer pain - severe acute non-cancer pain - severe, chronic neuropathic pain (IAB V)</td>
<td>Yes</td>
</tr>
<tr>
<td>OXYNORM</td>
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<tr>
<td>OXYNORM</td>
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<tr>
<td>OXYNORM</td>
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<tr>
<td>OXYNORMORO (oxycodone)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mundipharma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUROGESIC and its generics (fentanyl)</td>
<td>Janssen-Cilag</td>
<td>Treatment of severe, chronic pain that cannot be adequately treated other than with strong opioid analgesics.</td>
<td>15 Dec 2010 RI</td>
<td>Substantial in the indication: chronic cancer pain, intense or resistant to other analgesics, in cases of stable pain.</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MATRIFEN (similar to DUROGESIC) (fentanyl)</td>
<td>Takeda France SAS</td>
<td>Transdermal treatment of intense chronic pain, as a replacement for strong opioids, after their efficacy has been established.</td>
<td></td>
<td>Insufficient in the indication: Non-cancer pain</td>
<td>No</td>
</tr>
<tr>
<td>TEMGESIC (buprenorphine)</td>
<td>RBPharmaceuticals Limited</td>
<td>Intense pain, particularly post-operative pain and tumour pain.</td>
<td>9 May 2012 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>SOPHIDONE LP (hydrodromorphine hydrochloride)</td>
<td>Mundipharma</td>
<td>Treatment of intense cancer pain in cases of resistance to or intolerance of strong opioids.</td>
<td>6 Nov 2013 RI</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>PETHIDINE RENAUDIN (pethidine)</td>
<td>Renaudin</td>
<td>Intense pain and/or pain resistant to weaker analgesics.</td>
<td>18 Jan 2012 Reassessment of AB</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>NALBUPHINE AGUETTANT</td>
<td>Aguetant</td>
<td>Intense pain and/or pain resistant to weaker analgesics.</td>
<td>2 Jul 2003 (inclusion of AGUETTANT)</td>
<td>Substantial</td>
<td>Yes</td>
</tr>
<tr>
<td>NALBUPHINE MYLAN MYlan SAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NALBUPHINE RENAUDIN</td>
<td>Renaudin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NALBUPHINE SERB Serb</td>
<td>(nalbuphine)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGINACT (oxycodone+naloxone)</td>
<td>Mundipharma</td>
<td>Intense pain that cannot be adequately treated other than with opioid analgesics. Naloxone, an opioid antagonist, is added to neutralise the constipation by the opioid by locally inhibiting the action of oxycodone in the intestinal receptors.</td>
<td>7 Dec 2011 Inclusion</td>
<td>Low in the indication: severe cancer pain (IAB V) Insufficient in the indication: Severe non-cancer pain</td>
<td>No</td>
</tr>
</tbody>
</table>

RI: Renewal of Inclusion
SCT: Same therapeutic category as tapentadol

Note: the proprietary medicinal product TARGINACT (oxycodone+naloxone) is not on the market.

Note that the Actual Benefit of morphine-containing strong opioids and some other opioids has been reassessed, specifically in **non-cancer-related and non-neuropathic pain** (Transparency Committee’s opinion of 19 March 2014).
The proprietary medicinal products concerned by the reassessment were: ACTISKENAN, MORPHINE AGUETTANT, MORPHINE COOPER, MORPHINE Lavoisier, MORPHINE RENAUDIN, MOSCONTIN, MOSCONTIN LP, NALBUPHINE AGUETTANT, NALBUPHINE MYLAN, NALBUPHINE RENAUDIN, NALBUPHINE SERB, PETHIDINE RENAUDIN, SEVREDOL, SKENAN LP and TEMGESIC.

The Transparency Committee considered that the Actual Benefit was:
- “substantial in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data”.
- “insufficient in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis”.

The Actual Benefit afforded by proprietary medicinal products containing oxycodone is to be the subject of a forthcoming reassessment.

06.2 Other health technologies

Not applicable.

Conclusion

The comparators listed are all clinically relevant.
### Marketing Authorisation overseas

PALEXIA® LP has received Marketing Authorisation in Europe, Australia, Canada, and the USA.

### Reimbursement abroad

At the present time, PALEXIA LP is reimbursable in nine European countries and is currently under negotiation in Portugal.

<table>
<thead>
<tr>
<th>Country</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date</td>
<td>Scope (indications) and special condition(s)</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes (20/01/2011) 100%</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes (19/08/2010) 100%</td>
</tr>
<tr>
<td>Ireland</td>
<td>Yes (01/07/2011) 100%</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes (19/07/2011) 100%</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes (01/09/2011) 100%</td>
</tr>
<tr>
<td>Portugal</td>
<td>Assessment in progress</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes (13/05/2011) 40% &lt; 65 years; 90% &gt; 65 years</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes (09/06/2011) PALEXIA is reimbursed to patients with severe, chronic pain after intolerance to strong opioid treatment: 100%</td>
</tr>
<tr>
<td>UK</td>
<td>Yes (17/02/2011) SMC*: Recommended for patients in whom modified-release morphine sulfate has not succeeded in providing adequate pain control or is not tolerated: 100%</td>
</tr>
</tbody>
</table>

*Scottish Medicine Consortium.
For this new request for inclusion for PALEXIA, the clinical data provided concerning the efficacy of tapentadol SR in the treatment of various kinds of pain were obtained from:

- phase III clinical studies already examined by the Transparency Committee on the occasion of the previous request for inclusion (studies submitted with the Marketing Authorisation dossier); these data will be included in this document. Namely:
  - three studies (KF5503/11, KF5503/12, KF5503/23) in chronic, non-neuropathic, non-cancer pain (rheumatic),
  - one study (KF5503/36) in chronic neuropathic pain.
- phase III clinical studies already examined by the Transparency Committee on the occasion of the previous request for inclusion (studies not submitted with the Marketing Authorisation dossier):
  - one study (KF5503/56) in chronic neuropathic pain,
  - one study (KF5503/15) in chronic cancer pain,
- one phase III study, JNS024-KAJ-C02 (KAJ-C02), included only with the new submission, in chronic cancer pain.
- one post-inclusion study conducted in Germany in the treatment of severe, chronic pain.

These studies constitute one of the sources of safety data, to which were added data from studies KF5503/24 (phase III comparative study evaluating the safety profile of tapentadol SR) and 18 (an extension of studies KF5503/11, 23, 24, and a study of the conversion of the immediate-release form to the prolonged-release form: KF5503/19).

08.1 Efficacy

8.1.1 Efficacy in chronic cancer pain

Two phase III studies had as their main objective to evaluate the efficacy of tapentadol SR versus placebo in study KF5503/15, and versus oxycodone SR in study KAJ-C02.

8.1.1.1 Study KF5503/15

Methods

Study KF5503/15 is a multicentre, double-blind, controlled, randomised study versus placebo and active treatment\(^{13}\) which took place between 2007 and 2012. The main aim of this study was to evaluate the efficacy and safety of tapentadol SR administered twice daily for four weeks (after a two-week titration phase), in comparison to placebo, in patients with moderate to severe, chronic cancer pain. Comparison of tapentadol SR with the active treatment (morphine sulfate SR) formed part of the secondary objectives and was to be based on the data from the two-week dose titration phase.

Selection criteria

The main inclusion criteria were:

- age 18 years or above,
- man, or non-pregnant, non-lactating woman, or using a method of birth control,
- malignant chronic tumour-related pain,


\(^{13}\) Austria, Bulgaria, Croatia, Czech Republic, France (n = 1 patient), Germany, Hungary, Italy, Moldova, Poland, Romania, Russia, Serbia, Slovakia, Spain, Switzerland.
- patients opioid-naïve or having received a maximum dose equivalent to 160 mg/day of oral morphine and dissatisfied with the previous treatment,
- pain intensity $\geq 5/10$ on an 11-point numeric scale,
- stage of development of the tumour and pain such as to ensure compliance throughout the duration of the study.

Among the non-inclusion criteria:
- history of epilepsy; history of mild to moderate brain injury, stroke, transient ischaemic accident in the year prior to inclusion; history of serious brain injury during the previous 15 years,
- history or existence of a primary or secondary brain tumour.

**Administered treatments**

In all, the treatment consisted of:
- a two-week titration phase, with increases at least every three days when using morphine IR (immediate release) 10 mg higher than two doses per day, or of pain intensity $\geq 5/10$,
- a four-week maintenance phase for patients stabilised at the end of titration (pain intensity $< 5/10$ and a maximum of two daily doses of additional analgesia during the final three days of titration).

On inclusion, patients were randomised (2:1) into the tapentadol SR and morphine SR groups:
- tapentadol SR groups: starting dose of 100 mg twice daily, then in twice-daily 50 mg increments. The maximum dose was 500 mg/day. At the end of the titration phase, patients in this group were again randomised into two groups to proceed with the maintenance phase:
  - tapentadol SR group,
  - placebo group after three days being weaned off tapentadol SR;
- morphine SR groups: starting dose of 40 mg twice daily, then, if necessary, in twice daily 20 mg increments and followed by the maintenance phase. The maximum dose was 200 mg/day. Interdoses of morphine IR were allowed throughout the duration of the study.

**Endpoints**

The primary efficacy endpoint was the percentage of patients responding to the treatment at the end of the 28 days of the maintenance phase, i.e. patients with a pain intensity $< 5/10$ after receiving at most two daily doses of morphine IR 10 mg in the maintenance phase and having completed the 28-day maintenance phase.

The most relevant secondary endpoints were:
- the proportion of responder patients at the end of the titration phase (as part of the secondary objective of comparing tapentadol SR and morphine SR),
- the use of morphine IR,
- the variation in the mean weekly or overall pain score since the start of the maintenance phase,
- time to the first drop-out for reasons of inefficacy or adverse effects,
- change in the scores of the quality of life questionnaires (EQ5D and SF-36).

**Statistical analysis**

The number of subjects needed has been estimated at 108 per group (placebo or tapentadol SR after the second randomisation) assuming a 20 to 25% difference in responders between the two groups (60 to 65% for the tapentadol SR groups and 40% for the placebo group), an alpha error risk of 5% and a power of 80%.

A logistical regression was performed to evaluate the treatment response as a function of the treatment administered (tapentadol SR or placebo) and adjusted on the centres and the pain

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14 No details are provided concerning the definition of the satisfaction criteria relating to analgesic treatment.
15 Numeric scale going from 0 (no pain) to 10 (unimaginably excruciating pain).
intensity score at the start of the maintenance phase. A study of the non-inferiority of tapentadol SR in comparison with morphine SR (secondary endpoint), with a 20% margin and a unilateral test ($\alpha = 0.025$), was planned exclusively for the titration phase.

### Results

#### Treatment exposure

In all, 496 patients were included and randomised in one of the two treatment groups to follow the titration phase. After this titration phase, patients proceeded to the maintenance phase in the three treatment groups defined after a second randomisation of patients in the tapentadol SR groups into two groups (tapentadol SR and placebo) (Table 1). The percentage of treatment discontinuations was similar in both groups in the titration phase, then in the three groups in the maintenance phase. Most discontinuations were adverse events-related. The median treatment duration was 14 days during the titration phase for tapentadol SR and morphine SR, and 28 days during the maintenance phase for the three groups. The median daily doses were 279 mg of tapentadol SR and 97 mg of morphine SR during the titration phase, and 300 mg and 118 mg, respectively, during the maintenance phase.

#### Table 1. Analysis populations and treatment discontinuations

<table>
<thead>
<tr>
<th>Patients included in titration phase (n)</th>
<th>Tapentadol SR n = 338</th>
<th>Morphine SR n = 158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients completing the titration phase n (%)</td>
<td>279 (82.5)</td>
<td>129 (81.6)</td>
</tr>
<tr>
<td>Early treatment discontinuations in the maintenance phase, n (%)</td>
<td>59 (17.5)</td>
<td>29 (18.4)</td>
</tr>
<tr>
<td>- adverse events, n (%)</td>
<td>22 (6.5)</td>
<td>12 (7.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients randomised for the maintenance phase</th>
<th>Placebo n = 112</th>
<th>Tapentadol SR n = 106</th>
<th>Morphine SR n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients completing the maintenance phase, n (%)</td>
<td>95 (84.8)</td>
<td>89 (84.0)</td>
<td>92 (85.3)</td>
</tr>
<tr>
<td>Early treatment discontinuations in the maintenance phase, n (%)</td>
<td>17 (15.2)</td>
<td>17 (16.0)</td>
<td>16 (14.7)</td>
</tr>
<tr>
<td>- adverse events, n (%)</td>
<td>6 (5.4)</td>
<td>5 (4.7)</td>
<td>6 (5.5)</td>
</tr>
</tbody>
</table>

#### Characteristics of the patients

The characteristics of the patients at the start of the maintenance phase (n = 327) were similar to those of the patients present at the start of the titration phase (n = 496). They were also similar between treatment groups. At the start of the maintenance phase (n = 327), the mean age was 60.2 years (± 10.5) ranging from 26 to 91 years, and 46.8% of the patients were female. In all, 85% of the patients had already received treatment with opioid analgesics before the titration phase. The mean pain intensity was 6.1/10 (± 1.5) at the start of the titration phase, with an intensity ≥ 7/10 for 36.4% of patients. The mean intensity was 3/10 (± 1.3) after the maintenance phase. The pain was neuropathic for 64.7% of patients, visceral for 49.2%, and nociceptive for 71.2%.

The most commonly reported cancers were malignant tumours of the breast (16%), prostate (13%), respiratory tract and pleura (10%), as well as non-small-cell carcinomas of the respiratory tract (15%). The presence of metastases was reported in 80% of patients, and 18% of patients had previously undergone chemotherapy. Around 15 to 22% of patients received concomitant chemotherapy during the study.

#### Efficacy with respect to the primary endpoint

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17 Opioids received before the titration phase for the 496 included subjects: tramadol (43%), fentanyl (21%), and morphine (20%).
At the end of the maintenance phase, the percentage of responders to the treatment was higher in the tapentadol SR groups with 61.9% of responders (65/105) than in the placebo group with 49.5% (55/111) responders (OR = 2.0; 95% CI [1.1;3.7]; p = 0.02).

It should be noted that the percentage of treatment responders in the morphine SR groups was 68.8% (75/109). The majority of non-responders relied on a daily intake of morphine IR greater than 20 mg (14% of patients in the tapentadol SR groups, 25% in the placebo group, and 13% in the morphine SR groups) or had not completed 28 days of treatment (14% of the tapentadol SR and placebo groups and 12% of the morphine SR groups).

The sensitivity analysis performed with reference to the consumption of rescue opioids (included in the definition of “treatment response”), based on a count of the remaining tablets rather than on the patients’ declared consumption, found no difference between the groups: 60% of patients were responders in the tapentadol SR groups versus 50.5% in the placebo group (OR = 1.7; 95% CI: [1.0;3.1]; p = 0.07).

Efficacy with respect to the secondary endpoints

At the end of the two-week titration phase, the percentage of treatment responders was 76% (174/229) in the tapentadol SR groups and 83% (83/100) in the morphine SR groups. Assuming a 20% margin, the non-inferiority of tapentadol SR compared with morphine SR was demonstrated over the titration period, with a lower limit for the confidence interval of 15.5 (intergroup difference: -7.0; 95% CI: [-15.5;-1.4]; p = 0.01).

During the titration phase, patients in the tapentadol SR groups used morphine IR more frequently (71.9% of patients in the group with a mean of 25.7 mg per day) than patients in the morphine SR groups (58% with a mean of 24.3 mg per day) (p < 0.01). No significant difference between the groups was observed in the maintenance phase: 71.4% of patients on tapentadol SR (mean dose: 21.6 mg/day versus 72.1% on placebo (mean dose: 22.8 mg/day) and 61.5% under morphine SR (mean dose: 22.6 mg/day).

No difference in pain scores was found between the tapentadol SR groups and the placebo group, between the start of the maintenance phase and the mean weekly assessments.

No difference in terms of quality of life was shown to exist between the groups for the titration and maintenance phases.

8.1.1.2 Study JNS024-KAJ-C02

Methods

Study KAJ-C02 is a multicentre, double-blind, controlled, randomised, non-inferiority study versus active treatment that took place from 2010 to 2012 in Japan and Korea.

The primary objective of this study was to evaluate the efficacy and safety of tapentadol SR administered twice daily for four weeks, in comparison with oxycodone SR, in patients with moderate to severe, chronic cancer pain.

Selection criteria

The main inclusion criteria were:
- age 20 years or above,
- chronic malignant tumour-related pain,
- pain intensity ≥ 4/10 requiring opioid treatment (dissatisfaction with analgesic treatment),
- not having been treated with opioids during the previous 28 days.

Among the non-inclusion criteria:
- planned cancer surgery in the 28 days prior to inclusion and/or chemotherapy, psychiatric disturbances or other symptoms, with pain,
- any condition resulting in increased intracranial pressure.

18 Patients with a pain intensity < 5/11 or not having taken more than two daily doses of rescue analgesic (morphine IR, 2 × 10 mg) on the last three days of the titration period.
Administered treatments
After randomisation into one of the two treatment groups (tapentadol SR or oxycodone SR), patients were treated for a total of 28 days, starting with a titration phase and followed by a maintenance phase. Depending on the group to which they belonged, patients received an initial twice-daily dose of 25 mg tapentadol SR or 5 mg oxycodone SR. From the 3rd day, the dose could, if necessary, be increased in steps, after receiving the same treatment dose four times. The maximum dose of tapentadol SR was 200 mg twice daily and that of oxycodone SR was 40 mg twice daily. Morphine IR 5 mg was allowed throughout the study without limitation of the dose. Patients could enter the maintenance phase if the pain intensity was below or equal to 3/10 and if they were not using additional analgesia more than twice a day in any three days. Dose adjustments were possible, except in the last three days of the study (D26 to D28).

Endpoints
The primary efficacy endpoint was the change in pain intensity assessed by the patient on an 11-point numeric scale between inclusion and the three last days of the study. Among the relevant secondary endpoints:
- percentage of responders in the fourth week: reduction in pain intensity ≥30 and 50% between inclusion and the end of the maintenance phase,
- use of morphine IR.

Statistical analysis
The non-inferiority margin of tapentadol SR compared with oxycodone SR was fixed at 1 point of pain intensity with a common standard deviation of 2.5/10; with an alpha risk of 0.025 and a power of 90%, the number of subjects needed was thus estimated at 133 per group. The difference between the two groups was assessed by covariance analysis (ANCOVA), adjusted for the treatment, country, and pain intensity on inclusion.

Results
Treatment exposure
A total of 343 patients were randomised into two groups:
- of which 171 into the tapentadol SR groups, 168 of whom received the treatment and 113 completed the four treatment weeks (67.7%);
- and 172 into the oxycodone SR groups, 123 of whom completed the four treatment weeks (71.5%).
The percentage of treatment discontinuations was 32.7% in the tapentadol SR groups (n = 55) and 28.5% in the oxycodone SR groups (n = 49). Most of the discontinuations were disease progression-related: 11 patients (7%) versus 15 patients (9%), respectively; and adverse event-related: 12 patients (7%) versus 14 patients (8%). The median treatment duration was 28 days in both groups, including a median duration of titration of 7 days. The median daily doses during the last three days of the maintenance phase were 83.3 mg of tapentadol SR and 16.7 mg of oxycodone SR.

Patient characteristics
Of the 340 patients (intention-to-treat population), 44.1% were women. The mean age was 65.2 years (±11.3) and 45.9% of patients were under 65 years of age. The mean pain intensity on inclusion was 5.4/10 (±1.4) and 21.5% of patients had intense pain. The most commonly reported cancers were gastrointestinal tumours (40%) and respiratory tract and mediastinal tumours (29%). The presence of metastases was reported in 93% of patients.

Efficacy with respect to the primary endpoint
Assuming a non-inferiority margin of 1 pain-intensity point, the non-inferiority of tapentadol SR compared with oxycodone SR was demonstrated (Table 2).
Table 2. Change in patient-assessed pain intensity (per-protocol population)

<table>
<thead>
<tr>
<th>Pain intensity (score / 10)</th>
<th>Tapentadol SR n = 126</th>
<th>Oxycodone SR n = 139</th>
</tr>
</thead>
<tbody>
<tr>
<td>On inclusion, mean (standard deviation)</td>
<td>5.4 (1.5)</td>
<td>5.3 (1.4)</td>
</tr>
<tr>
<td>Difference (value [D26-D28] – inclusion value), mean (standard deviation)</td>
<td>-2.7 (2.2)</td>
<td>-2.6 (2.1)</td>
</tr>
<tr>
<td>Difference versus oxycodone SR, mean (standard deviation)* [95% CI], p-value</td>
<td>-0.1 (0.2) [-0.5;0.4], p = 0.79</td>
<td></td>
</tr>
</tbody>
</table>

*ANCOVA adjusted to the baseline value. Results are expressed as least-squares means (LS means).

Efficacy with respect to the secondary endpoints
The percentage of responders between the two treatment groups was comparable with:
- at least a 30% improvement in pain intensity for 63.5% of patients on tapentadol SR, versus 59% on oxycodone SR;
- at least a 50% improvement in pain intensity for 50% versus 42.4% of patients, respectively.
74% of patients were found to be using morphine IR, with no difference between the two groups.

8.1.2 Efficacy in chronic neuropathic non-cancer pain
Two randomised, double-blind (in the maintenance phase), controlled phase III studies performed in Canada and the United States evaluated the efficacy of tapentadol SR versus placebo in chronic non-cancer-related neuropathic pain. These were study KF5503/36, carried out between 2007 and 2008 and study KF5503/56, carried out between 2009 and 2011.

Methods
The primary aim of these two studies was to evaluate the efficacy and safety of a 12-week maintenance treatment with tapentadol SR in comparison with placebo in patients with moderate to severe chronic pain due to diabetic peripheral neuropathy.

Selection criteria
The inclusion criteria were:
- men and non-pregnant and non-lactating women, aged 18 years or over;
- type 1 or type 2 diabetes controlled by hygiene and dietary measures or by drugs (HbA1c ≤ 11%) for at least the previous three months;
- diabetic neuropathy for at least six months;
- patient-assessed pain intensity ≥ 5/10 on inclusion;
- analgesic treatment for at least the previous three months (if opioids, equivalent oral morphine dose ≤ 160 mg/day) and dissatisfied with their treatment.

Among the non-inclusion criteria:
- history of epilepsy, mild to moderate brain injury, stroke, transient ischaemic accident, brain tumour in past year; history of severe brain injury in the previous 15 years;
- history of cancer in the past two years, except for successfully treated basal cell carcinoma.

Administered treatments
Treatment comprised a three-week titration phase, followed by a 12-week maintenance phase after randomisation into two groups.
During the titration phase, patients received tapentadol SR at the rate of 50 mg twice daily for the first three days, then 100 mg twice daily (the requisite minimum dose for the maintenance phase), then if necessary an additional 50 mg twice daily every three days (maximum dose of 500 mg/day). At the end of titration, patients who had a reduction in pain intensity of at least one point were divided into two groups for the double-blind maintenance phase:
- tapentadol SR groups, continuing treatment at the optimum dosage determined at the end of titration,
- placebo group with weaning off tapentadol SR in the first three days.
Paracetamol at the maximum dose of 2 g/day was permitted during the titration phase (except for the final four days). Tapentadol IR was permitted during the maintenance phase (two doses of 25 mg for the first four days, then one daily dose).

**Endpoints**
The primary efficacy endpoint was the change in the patient-assessed pain intensity according to an 11-point numeric scale between the start and end of the maintenance phase (week 12).
Among the secondary endpoints:
- percentage of responders in the twelfth week: reduction in pain intensity ≥ 30% and ≥ 50% between the start of the titration phase and the end of the maintenance phase,
- use of additional doses of tapentadol SR during the maintenance phase (in study 56),
- change in the scores in the quality of life questionnaires (EQ5D and SF-36).

**Statistical analysis**
In study 56, the number of subjects needed was estimated at 150 per group (placebo or tapentadol SR) assuming a mean difference of 1 point in the pain intensity at the end of the maintenance phase, with a standard deviation of 2.6, an alpha error risk of 5%, and a power of 90%. Assuming these same parameters with a standard deviation of 3 points, the number of subjects needed in study 36 was fixed at 190 per group.
The difference between the two groups was assessed by covariance analysis (ANCOVA), adjusted for the treatment, the site, the dose at the end of the titration phase, and the mean pain intensity at the start of the maintenance phase.

**Results**

**Treatment exposure**
In all, treatment discontinuations related to (Table 3):
- in the titration phase, between 22 and 34% of patients in the tapentadol SR and placebo groups, respectively, and these were mainly adverse event-related
- in the maintenance phase, between 29 and 31% of patients, more frequently on account of adverse events (between 8 and 15%) in the tapentadol SR compared with the placebo group.
During the maintenance phase, the mean daily doses of tapentadol SR were 418.6 mg in study 36 and 371.9 mg in study 56, and the median doses were 463.5 mg and 397.8 mg, respectively.
Table 3. Analysis populations and treatment discontinuations

<table>
<thead>
<tr>
<th>Patients included in titration phase (n)</th>
<th>Study KF5503/36</th>
<th>Study KF5503/56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients completing the titration phase, n (%)</td>
<td>Tapentadol SR n = 591</td>
<td>Tapentadol SR n = 459</td>
</tr>
<tr>
<td>Early treatment discontinuations in the maintenance phase, n (%)</td>
<td>198 (33.7)</td>
<td>101 (22.0)</td>
</tr>
<tr>
<td>- adverse events, n (%)</td>
<td>102 (17.3)</td>
<td>69 (15.0)</td>
</tr>
<tr>
<td>Treatment duration, mean (standard deviation)</td>
<td>19.3 (± 5.9)</td>
<td>19.8 (± 5.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients randomised for the maintenance phase (ITT*)</th>
<th>Study KF5503/36</th>
<th>Study KF5503/56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients completing the maintenance phase (per protocol), n (%)</td>
<td>Tapentadol SR n = 196</td>
<td>Placebo n = 193</td>
</tr>
<tr>
<td>Early treatment discontinuations in the maintenance phase, n (%)</td>
<td>59 (30.6)</td>
<td>134 (69.4)</td>
</tr>
<tr>
<td>- adverse events, n (%)</td>
<td>15 (7.8)</td>
<td>59 (30.1)</td>
</tr>
<tr>
<td>- lack of efficacy, n (%)</td>
<td>27 (14.0)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>Treatment duration, mean (standard deviation)</td>
<td>66.9 (± 30.1)</td>
<td>137 (± 28.5)</td>
</tr>
</tbody>
</table>

*Intention-to-treat population

Characteristics of the patients

The characteristics of the patients (age, sex, history of opioid use) at the start of the titration phase were similar to those at the start of the maintenance phase as well as being similar between the treatment groups (Table 4).

Table 4. Characteristics of the patients

<table>
<thead>
<tr>
<th>Per protocol population</th>
<th>Study KF5503/36 n = 389</th>
<th>Study KF5503/56 n = 318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patients, mean (standard deviation)</td>
<td>60.2 (± 10.6)</td>
<td>58.7 (± 10)</td>
</tr>
<tr>
<td>Patients aged under 65 years, n (%)</td>
<td>256 (65.8)</td>
<td>231 (72.6)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>154 (39.6)</td>
<td>131 (41.2)</td>
</tr>
<tr>
<td>Opioid-naïve patients, n (%)</td>
<td>255 (65.6)</td>
<td>218 (68.6)</td>
</tr>
<tr>
<td>Pain on inclusion:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Intensity score/10, mean (standard deviation)</td>
<td>7.4</td>
<td>7.3</td>
</tr>
<tr>
<td>- Severe pain, n (%)</td>
<td>(309) 79.4</td>
<td>277 (87.1)</td>
</tr>
<tr>
<td>Pain at start of maintenance phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Intensity score/10, mean (standard deviation)</td>
<td>3.5 (± 1.9)</td>
<td>3.6 (± 2.0)</td>
</tr>
<tr>
<td>- Severe pain, n (%)</td>
<td>46 (11.8)</td>
<td>47 (14.8)</td>
</tr>
</tbody>
</table>

19 Severe pain: pain score ≥ 6/10 on the 11-point numeric pain scale.
Efficacy with respect to the primary endpoint
Between the start and end of the maintenance phase, the mean reduction in pain intensity was greater in the tapentadol SR groups than in the placebo group (Table 5).

Table 5. Change in the pain score between the start and end of the maintenance phase (ITT analysis)

<table>
<thead>
<tr>
<th>Mean pain intensity (score / 10)</th>
<th>Placebo</th>
<th>Tapentadol SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study KF5503/36</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On inclusion, mean (standard deviation)</td>
<td>n = 192</td>
<td>n = 193</td>
</tr>
<tr>
<td>Mean difference (maintenance – inclusion), mean (standard deviation)</td>
<td>1.3 (2.4)</td>
<td>-0.1 (1.7)</td>
</tr>
<tr>
<td>Mean difference versus placebo* (SD) [95% CI]</td>
<td>-</td>
<td>-1.3 (0.2) [-1.7; -0.92]**</td>
</tr>
<tr>
<td><strong>Study KF5503/56</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On inclusion, mean (standard deviation)</td>
<td>n = 152</td>
<td>n = 165</td>
</tr>
<tr>
<td>Mean difference (maintenance – inclusion) (SD)</td>
<td>1.3 (2.2)</td>
<td>0.3 (2.0)</td>
</tr>
<tr>
<td>Mean difference versus placebo* (SD) [95% CI] / p-value</td>
<td>-</td>
<td>-1.0 (0.2) [-1.4; -0.5]**</td>
</tr>
</tbody>
</table>

*ANCOVA adjusted to the baseline value. Results are expressed as least-squares means (LS means). 
**p < 0.05

Efficacy with respect to the secondary endpoints
The percentage of responders was different between the two treatment groups with:
- at least a 30% improvement in the pain intensity for 54% (study 36) to 55% (study 56) of patients in the tapentadol SR groups, and for 42 to 45% of patients in the placebo group, respectively.
- at least a 50% improvement in the pain intensity was recorded for 38 to 40% of patients in the tapentadol SR groups and for 28 to 29% of patients in the placebo group.

The percentage of patients using additional analgesia during the maintenance phase was 73.7% in the placebo group versus 64.5% in the tapentadol SR groups (p = 0.07). In terms of quality of life, the change in the scores between the beginning and end of the maintenance phase compared with placebo can be considered to be of little clinical relevance.

8.1.3 Efficacy in non-cancer-related rheumatic pain

Three double-blind, randomised, controlled, phase III studies carried out from 2007 to 2008 evaluated the efficacy of tapentadol SR versus placebo in the treatment of non-cancer-related rheumatic pain linked to gonarthritis in the case of studies KF5503/11 and KF5503/12, and to chronic lumbar pain in the case of study KF5503/23.

Methods

The methods in the three studies are described in Table 6.

Table 6. Methods used in the phase III studies of non-cancer-related rheumatic pain

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Inclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the efficacy and safety of a 15-week treatment with PALEXIA LP (Tapentadol SR) in comparison with placebo in patients with moderate to severe, chronic pain due to gonarthritis (studies 11 and 12) or chronic lumbar pain (study 23).</td>
<td></td>
</tr>
<tr>
<td><strong>Main patient selection criteria</strong></td>
<td>men and non-pregnant and non-lactating women, aged 40 years or over;</td>
</tr>
<tr>
<td>- suffering for at least 3 months from:</td>
<td>- gonarthritis with functional capacity of grade I to III and knee pain (studies 11 and 12)</td>
</tr>
<tr>
<td></td>
<td>- chronic non-cancer-related lumbar pain (study 23)</td>
</tr>
<tr>
<td>- patient-assessed pain intensity ≥ 5/10.</td>
<td>- taking analgesics for at least 3 months and dissatisfied with their treatment; patients pretreated with opioids had to be exposed to an equivalent oral morphine dose ≤ 160 mg/day.</td>
</tr>
</tbody>
</table>
Non-inclusion, in particular:
- history of epilepsy; mild to moderate brain injury in the last year; stroke; transient ischaemic accident; brain tumour; history of severe brain injury in the previous 15 years;
- history of cancer in the past two years, except for successfully treated basal cell carcinoma during those 2 years.

### Treatment duration and methods
- Treatment included:
  - a 3-week titration phase:
    - Tapentadol SR groups: 50 mg (starting dose, twice daily) for the first 3 days, then 100 mg twice daily for the following 4 days (minimum dose required for the maintenance phase) then, if necessary, with increments every 3 days: 150-200-250 mg twice daily (maximum dose of 500 mg/day);
    - Oxycodone SR groups: 10 mg (starting dose, twice daily) for the first 3 days, then 20 mg twice daily for the following 4 days (minimum dose required for the maintenance phase) then, if necessary, with increments every 3 days, 30-40-50 mg increase twice daily (maximum dose of 100 mg/day);
    - Placebo group.
- 12-week maintenance phase: to enter this phase, patients should not have taken paracetamol and been on a stable dose of study treatment for 3 days. In the maintenance phase, only limited use (≤ 3 days) of paracetamol (≤ 1 g/day) other than for the chronic pain that led the patient to be included in the study was permissible.

Paracetamol at the maximum dose of 1 g/day was the alternative treatment allowed in the titration phase.

### Primary endpoint
Change in pain intensity, assessed by the patient on an 11-point numeric scale, between the mean over the 12-week maintenance period and the baseline value.

### Relevant secondary endpoints
- Change in mean pain intensity between the final week of the maintenance period and the baseline value (primary efficacy endpoint required by the FDA).
- Percentage of responders in the twelfth week

### Statistical analysis
Assuming a clinically-relevant mean difference in pain intensity between the groups of 0.7 points and a standard deviation of 2.7, the number of subjects needed per group was estimated at 314. The inter-group difference (active treatment versus placebo) was assessed by covariance analysis, adjusted for the treatment, the centres, and the baseline pain scores.

### Results

#### Treatment exposure
In the three studies, the mean treatment durations were longer in the placebo and tapentadol SR groups (between 102 and 105 days) than in the oxycodone SR groups (from 26 to 62 days), linked with a higher percentage of treatment discontinuations due to safety issues in the oxycodone SR groups during the titration phase (Table 7).

#### Table 7. Duration of exposure to the treatment and mean dose administered

<table>
<thead>
<tr>
<th>Studies</th>
<th>Placebo</th>
<th>Tapentadol SR</th>
<th>Oxycodone SR</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KF5503/11</strong></td>
<td><strong>n = 337</strong></td>
<td><strong>n = 344</strong></td>
<td><strong>n = 342</strong></td>
<td><strong>n = 1023</strong></td>
</tr>
<tr>
<td>Premature discontinuations: titration phase</td>
<td>83 (24.6%)</td>
<td>80 (23.3%)</td>
<td>169 (49.4%)</td>
<td>332 (32.5%)</td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td>47 (13.9%)</td>
<td>67 (19.5%)</td>
<td>52 (15.2%)</td>
</tr>
<tr>
<td>Daily dose (mg/day): titration phase</td>
<td>244.6</td>
<td>40.9</td>
<td>357.9</td>
<td>70.7</td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KF5503/12</strong></td>
<td><strong>n = 337</strong></td>
<td><strong>n = 319</strong></td>
<td><strong>n = 331</strong></td>
<td><strong>n = 987</strong></td>
</tr>
<tr>
<td>Premature discontinuations: titration phase</td>
<td>58 (17.2%)</td>
<td>77 (24.1%)</td>
<td>148 (44.7%)</td>
<td>283 (28.7%)</td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td>58 (17.2%)</td>
<td>56 (17.6%)</td>
<td>62 (18.7%)</td>
</tr>
<tr>
<td>Daily dose (mg/day): titration phase</td>
<td>221.4</td>
<td>37.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td>315.2</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td><strong>KF5503/23</strong></td>
<td><strong>n = 319</strong></td>
<td><strong>n = 318</strong></td>
<td><strong>n = 328</strong></td>
<td><strong>n = 965</strong></td>
</tr>
<tr>
<td>Premature discontinuations: titration phase</td>
<td>108 (33.9%)</td>
<td>83 (26.1%)</td>
<td>129 (39.3%)</td>
<td>320 (33.2%)</td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td>50 (15.7%)</td>
<td>63 (19.8%)</td>
<td>57 (17.4%)</td>
</tr>
<tr>
<td>Daily dose (mg/day): titration phase</td>
<td>250.9</td>
<td>44.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>maintenance phase</td>
<td>381.8</td>
<td>71.4</td>
<td></td>
</tr>
</tbody>
</table>
Characteristics of the patients
Included patients were aged at least 40 years (mean age around 50 to 60 years, depending on the study) and more than half of them were women. The mean pain intensity on inclusion was 7/10, with over 80% of subjects classed as "severe" (baseline pain intensity ≥ 6). In the gonarthrosis studies (studies 11 and 12), the majority (> 67%) of patients had not taken opioids in the three months prior to the inclusion visit; in contrast, in the chronic lumbar pain study (study 23), more than half (around 55%) of subjects had taken them.

Efficacy with respect to the primary endpoint
A difference in the variation of the mean pain intensity between inclusion and the maintenance period was found that favoured the active treatments (tapentadol SR, oxycodone SR) versus placebo in studies 11 and 23 (gonarthrosis and chronic lumbar pain, respectively), but not in study 12 (cf Table 8).

Table 8. Change in pain intensity, assessed by the patient, between the mean over the 12-week maintenance period and the baseline value

<table>
<thead>
<tr>
<th>Mean pain intensity (score / 10)</th>
<th>Placebo</th>
<th>Tapentadol SR</th>
<th>Oxycodone SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study KF5503/11</td>
<td>n = 337</td>
<td>n = 344</td>
<td>n = 342</td>
</tr>
<tr>
<td>On inclusion (SD)</td>
<td>7.2 (1.3)</td>
<td>7.4 (1.3)</td>
<td>7.2 (1.3)</td>
</tr>
<tr>
<td>Mean difference (maintenance – inclusion) (SD)</td>
<td>-2.2 (2.4)</td>
<td>-2.9 (2.3)</td>
<td>-2.5 (2.3)</td>
</tr>
<tr>
<td>Mean difference versus placebo* (SD) [95% CI]</td>
<td>-0.7 (0.2)</td>
<td>[-1.0; -0.3], p &lt; 0.001</td>
<td>-0.3 (0.2)</td>
</tr>
<tr>
<td>Study KF5503/12</td>
<td>n = 337</td>
<td>n = 319</td>
<td>n = 331</td>
</tr>
<tr>
<td>On inclusion (SD)</td>
<td>7.3 (1.1)</td>
<td>7.3 (1.1)</td>
<td>7.3 (1.1)</td>
</tr>
<tr>
<td>Mean difference (maintenance – inclusion) (SD)</td>
<td>-2.2 (2.1)</td>
<td>-2.5 (2.2)</td>
<td>-2.1 (2.2)</td>
</tr>
<tr>
<td>Mean difference versus placebo* (SD), [95% CI] / p-value</td>
<td>-0.2 (0.2)</td>
<td>[-0.5; 0.1]</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>Study KF5503/23</td>
<td>n = 319</td>
<td>n = 318</td>
<td>n = 328</td>
</tr>
<tr>
<td>On inclusion (SD)</td>
<td>7.6 (1.3)</td>
<td>7.5 (1.3)</td>
<td>7.5 (1.2)</td>
</tr>
<tr>
<td>Mean difference (maintenance – inclusion) (SD)</td>
<td>-2.1 (2.2)</td>
<td>-2.8 (2.5)</td>
<td>-2.9 (2.4)</td>
</tr>
<tr>
<td>Mean difference versus placebo* (SD), [95% CI] / p-value</td>
<td>-0.7 (0.2)</td>
<td>[-1.1; -0.3], p &lt; 0.05</td>
<td>-0.8 (0.2)</td>
</tr>
</tbody>
</table>

*ANCOVA adjusted to the baseline value. Results are expressed as least-squares means (LS means).

Efficacy with respect to the secondary endpoints
A difference in the change in mean pain intensity between inclusion and the final week of maintenance, which was the primary efficacy endpoint in the United States, was found in favour of tapentadol SR versus placebo in study 11 and the two active treatments (tapentadol SR and morphine SR) in study 23, but not in study 12 (Table 9).

Table 9. Results for the change in mean pain intensity between inclusion and the final week of maintenance in studies 11 and 23.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Placebo</th>
<th>Tapentadol SR</th>
<th>Oxycodone SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF5503/11</td>
<td>n = 337</td>
<td>n = 344</td>
<td>n = 342</td>
</tr>
<tr>
<td>Difference vs placebo for week 12* (SD) [95% CI], p vs placebo</td>
<td>-0.7 (0.2)</td>
<td>[-1.0; -0.3], p &lt; 0.001</td>
<td>-0.3 (0.2)</td>
</tr>
<tr>
<td>Percentage of responders (week 12):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Improvement ≥ 30% in the pain score, n (%)</td>
<td>121 (35.9)</td>
<td>148 (43.0)</td>
<td>85 (24.9)**</td>
</tr>
<tr>
<td>- Improvement ≥ 50% in the pain score, n (%)</td>
<td>82 (24.3)</td>
<td>110 (32.0)**</td>
<td>59 (17.3)**</td>
</tr>
<tr>
<td>Study KF5503/12</td>
<td>n = 319</td>
<td>n = 318</td>
<td>n = 328</td>
</tr>
<tr>
<td>Difference versus placebo* (SD), [95% CI], p vs placebo</td>
<td>-0.3 (0.2)</td>
<td>[-0.6; 0.1]; p = 0.15</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>Percentage of responders (week 12):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Improvement ≥ 30% in the pain score, n (%)</td>
<td>138 (40.9)</td>
<td>131 (41.1)</td>
<td>86 (26.0)**</td>
</tr>
<tr>
<td>- Improvement ≥ 50% in the pain score, n (%)</td>
<td>91 (27.0)</td>
<td>99 (31.0)</td>
<td>73 (22.1)</td>
</tr>
<tr>
<td>Study KF5503/23</td>
<td>n = 319</td>
<td>n = 318</td>
<td>n = 328</td>
</tr>
</tbody>
</table>

HAS – Medical, Economic and Public Health Assessment Division
### 8.1.4 Real-life data

The company provided data from a non-comparative, non-interventional, prospective, post-inclusion study, carried out in Germany between 2010 and 2011.

**Methods**

The primary objective of this study was to describe the safety and efficacy profile of PALEXIA LP in real life over a period of three months in patients with intense chronic pain not previously treated with PALEXIA.

The calculation of the number of patients needed was not performed and there were many endpoints, including the percentage of patients:

- having reached the expected mean pain at the end of the study,
- having at least a 50% reduction in pain in comparison with inclusion.

**Results**

In all, 3222 patients (recruited by their doctor) received at least one dose of tapentadol SR, 3134 of whom were included in the per-protocol analysis. The median age was 69 years, and 82% of the patients were suffering from pain of the lower spine, and in 9% of cases the pain was cancer-related. In the majority of patients the pain was of a mixed type, both nociceptive and neuropathic (84%). About 42% of patients had already been treated with step III analgesics. The reasons for prescribing were mainly an inadequate analgesic effect (91%), unsatisfactory quality of life (70%), and a safety problem (32%). The median daily dose at the end of the study was 200 mg and the titration phase lasted more than one week for 42% of patients. The mean treatment duration was 87.2 days (± 29.6), and the percentage of discontinuations was 20.3%, mainly due to dissatisfaction with the analgesic effect (7.5%) and adverse events (5.4%).

**Efficacy**

The mean pain intensity was 7/10 on inclusion and 3/10 at the time of the final visit (p < 0.01). Assuming an expected pain intensity of 2.8/10, 63% of patients had reached this threshold by the time of the final visit. The reduction in pain intensity was at least 50% for 69% of patients.

This study, carried out in a large sample population, provides additional information in terms of the real-life use of PALEXIA LP. It does not however permit an evaluation of the efficacy of PALEXIA LP in comparison with existing strong opioids, and these results are of a descriptive nature. Moreover, they are scarcely applicable to patients with cancer pain.
08.2 Safety/Adverse effects

8.2.1 Clinical study data

8.2.1.1 Safety data in cancer pain

**Study KF5503/15**
In study KF5503/15, 338 patients with cancer pain received at least one dose of tapentadol SR during the titration phase (versus morphine SR (n = 158)), then 106 during the maintenance phase (versus placebo (n = 112) and versus morphine SR (n = 109)).

During the titration phase, fewer patients had adverse events in the tapentadol SR groups (50.0%) than in the morphine SR groups (63.9%), with mainly: constipation (14.2% vs 17.7%), nausea (12.4% vs 24.1%), vomiting (5.3% vs 15.8%), dry mouth (1.2% vs 6.3%), vertigo (5.0% vs 6.3%), drowsiness (4.1% vs 6.3%) and asthenia (3% vs 5.1%). The percentage of patients with serious adverse events was 7.4% (n = 25) in the tapentadol SR groups and 3.8% (n = 6) in the morphine SR groups.

During the maintenance phase, the percentage of patients with adverse events was overall similar in the three treatment groups, with 56.3% in the placebo group, 62.3% in the tapentadol SR groups, and 62.4% in the morphine SR groups (Table 10).

Most of the adverse events were of mild to moderate intensity. The percentage of patients with serious adverse events was 8.9% in the placebo group (n = 10), 11.3% in the tapentadol SR groups (n = 12), and 5.5% in the morphine SR groups (n = 6).

Overall, early discontinuations due to the onset of an adverse event were infrequent, both during the titration phase (8.6% of subjects in the tapentadol SR groups and 7% of subjects in the morphine SR groups) and during the maintenance phase (4.7% of patients in the tapentadol SR groups versus 4.5% in the placebo group, and 6.4% in the morphine SR groups).

### Table 10. Incidence of AEs occurring in at least 5% of patients in each treatment group during the maintenance period

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 112)</th>
<th>Tapentadol SR (n = 106)</th>
<th>Morphine SR (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea</strong></td>
<td>17 (15.2)</td>
<td>16 (15.1)</td>
<td>11 (10.1)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>13 (11.6)</td>
<td>12 (11.3)</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>3 (2.7)</td>
<td>8 (7.5)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td><strong>Asthenia</strong></td>
<td>6 (5.4)</td>
<td>4 (3.8)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td><strong>Malignant tumours</strong></td>
<td>4 (3.6)</td>
<td>9 (8.5)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td><strong>Drowsiness</strong></td>
<td>2 (1.8)</td>
<td>3 (2.8)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td><strong>Decreased appetite</strong></td>
<td>6 (5.4)</td>
<td>8 (7.5)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td><strong>Hyperhidrosis</strong></td>
<td>1 (0.9)</td>
<td>4 (3.8)</td>
<td>7 (6.4)</td>
</tr>
</tbody>
</table>

**Study JNS04ER-KAJ-C02**
In all, 168 of the 343 patients with cancer pain randomised into the study received at least one dose of tapentadol SR. The percentage of patients with adverse events was similar in both groups (87.5% in the tapentadol SR groups versus 90.1 in the oxycodone SR groups), the most common being: constipation (30.4% versus 37.2%), nausea (28.6% versus 35.5%), vomiting (25% versus 23.8%), diarrhoea (6.5% versus 11%), fever (6.5% versus 8.1%), general malaise (3.6% versus 7%), drowsiness (17.3% versus 20.9%), decreased appetite (13.7% versus 14%), delirium (6% versus 3.5%), insomnia (5.4% versus 6.4%) and anaemia (2.4% versus 7%). Most of these adverse events were of mild to moderate intensity. Serious adverse events were found in 46% of patients on tapentadol SR and 40% on oxycodone SR, without any significant difference, and their “disease progression” was 21 to 24%, respectively. The percentage treatment discontinuations due to adverse events was 13 and 17%, respectively.
8.2.1.2 Safety data in chronic diabetic neuropathy pain

**Study KF5503/36**

In study KF5503/36, a total of 588 patients with diabetic neuropathy received at least one dose of tapentadol SR during the open titration phase and 389 during the maintenance period, double-blind versus placebo.

During the titration phase, 70.9% of patients reported at least one adverse event, principally nausea (21.4%), vertigo (15.8%), drowsiness (15.1%), constipation (10.7%), vomiting (8.0%), headache (7.8%), asthenia (7.0%), and pruritus (6.6%). The majority of these events were of mild to moderate intensity (89.4%), and 20.1% of subjects discontinued treatment due to the onset of an adverse event. Eight patients presented a serious adverse event.

During the maintenance phase, the percentage of adverse events was higher in the tapentadol SR groups than in the placebo group (70.9% versus 51.8%). The adverse events are summarised in Table 10. Most of these adverse events were of mild to moderate intensity (84%) and almost half were treatment-related (47% in the tapentadol SR groups). There were 11.2% versus 5.7% treatment discontinuations due to the onset of adverse events. The incidence of serious adverse events was 5.1% (n = 10), including one case of suicidal ideation in the tapentadol SR groups, versus 1.6% (n = 3) in the placebo group.

**Study KF5503/56**

In study KF5503/56, a total of 459 patients with diabetic neuropathy received at least one dose of tapentadol SR during the open titration phase and 318 during the maintenance period, double-blind versus placebo.

The safety profile was similar to that observed in study KF5503/36, with 76% of patients having reported at least one adverse event during the titration phase and a larger percentage of patients with adverse events in the tapentadol SR groups than in the placebo group (79.5% versus 61.2%). Eleven patients (2.4%) presented a serious adverse event in the titration phase and 17 in the maintenance phase, including eight (4.8%) with suicidal ideation in the tapentadol SR groups and nine (5.9%) in the placebo group.

The adverse events are summarised in Table 11.

Table 11. Incidence of AEs occurring in at least 5% of patients in each treatment group during the maintenance period

<table>
<thead>
<tr>
<th></th>
<th>Study KF5503/36</th>
<th>Study KF5503/56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 193</td>
<td>Tapentadol SR n = 196</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (6.2)</td>
<td>27 (13.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (4.1)</td>
<td>16 (8.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.0)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (1.0)</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (1.0)</td>
<td>15 (7.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (5.2)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>7 (3.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (4.1)</td>
<td>18 (9.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (3.6)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Agitation</td>
<td>8 (4.1)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14 (7.3)</td>
<td>13 (6.6)</td>
</tr>
</tbody>
</table>

* <5%
8.2.1.3 Safety data in non-cancer-related rheumatic pain

Pooled analysis of studies KF5503/11, KF5503/12, and KF5503/23

During the course of phase III clinical studies conducted in non-cancer-related rheumatic pain (gonarthrosis and chronic lumbar pain), a total of 2974 patients (placebo: n = 993, tapentadol SR: n = 980 and oxycodone SR: n = 1001) were evaluable for safety. The most commonly reported adverse events (incidence ≥ 5%) are presented in Table 12. The percentage of patients suffering from constipation, nausea, or vomiting was significantly smaller in the tapentadol SR groups than in the oxycodone SR groups (p < 0.01). The majority of these adverse events were of mild to moderate intensity. Treatment discontinuations due to adverse events totalled about 18% in the tapentadol SR groups versus 6% in the placebo group, and 39% in the oxycodone SR groups. These discontinuations occurred essentially during the 3-week titration phase. During the 12-week maintenance phase, treatment discontinuations due to adverse events were less common (< 12%) and similar in the different active treatment groups.

Table 12. Incidence of adverse events occurring in at least 5% of patients in each treatment group, safety population (pooled data for studies KF5503/11, KF5503/12, and KF5503/23)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 993</th>
<th>Tapentadol SR n = 980</th>
<th>Oxycodone SR n = 1001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>264 (26.6%)</td>
<td>420 (42.9%)</td>
<td>657 (65.6%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>73 (7.4%)</td>
<td>203 (20.7%)</td>
<td>362 (36.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>69 (6.9%)</td>
<td>166 (16.9%)</td>
<td>330 (33.0%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>29 (2.9%)</td>
<td>80 (8.2%)</td>
<td>210 (21.0%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>22 (2.2%)</td>
<td>67 (6.8%)</td>
<td>40 (4.0%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>223 (22.5%)</td>
<td>394 (40.2%)</td>
<td>463 (46.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>63 (6.3%)</td>
<td>169 (17.2%)</td>
<td>210 (21.0%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>131 (13.2%)</td>
<td>146 (14.9%)</td>
<td>132 (13.2%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>105 (10.6%)</td>
<td>174 (17.8%)</td>
<td>198 (19.8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>39 (3.9%)</td>
<td>83 (8.5%)</td>
<td>92 (9.2%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>50 (5.0%)</td>
<td>132 (13.5%)</td>
<td>237 (23.7%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>9 (0.9%)</td>
<td>52 (5.3%)</td>
<td>60 (6.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 (1.6%)</td>
<td>51 (5.2%)</td>
<td>134 (13.4%)</td>
</tr>
</tbody>
</table>

Comparative study of tapentadol SR versus oxycodone SR (study KF5503/24)

This was an open-label, randomised (4:1) controlled phase III study versus oxycodone SR, whose aim was to evaluate the safety profile of tapentadol SR (100 mg to 250 mg twice daily) under prolonged exposure of up to 1 year, in patients suffering with pain (score > 4 on the 11-point pain scale) for the previous 3 months caused by chronic lumbar pain, gonarthrosis, or coxarthrosis. The safety analysis population included 894 subjects in the tapentadol SR groups versus 223 in the oxycodone SR groups. The percentage of patients completing the study was 46.2% (413/894) in the tapentadol SR groups versus 35% (78/223) in the oxycodone SR groups, the primary reason for treatment discontinuation being the onset of an adverse event.

The most commonly reported adverse events in each treatment group (tapentadol SR versus oxycodone SR) were:
- gastrointestinal disorders: constipation (22.6% vs 38.6%; p < 0.01), nausea (18.1% vs 33.2%; p < 0.01), vomiting (7% vs 13.5%),

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- nervous system disorders: drowsiness (14.9% vs 11.2%), vertigo (14.8% vs 19.3%), headache (13.3% vs 7.6%),
- asthenia (9.7% vs 10.3%)
- pruritus (5.4% vs 10.3%).

The majority of these adverse events were of mild to moderate intensity. The incidence of treatment discontinuations due to adverse events was 22.1% in the tapentadol SR groups versus 36.8% in the oxycodone SR groups; the adverse events concerned were the following: nausea (3.4% vs 12.1%), vomiting (2.6% vs 6.7%), constipation (1.6% vs 7.2%), vertigo (3% vs 6.7%) and drowsiness (3.4% vs 4%).

The incidence of serious adverse events was similar in both groups (5.5% versus 4.0%).

**Study KF5503/18**

This was an extension study of open-label, non-comparative, development studies KF5503/11, /23, /24, and /19, whose main objective was to evaluate the long-term safety profile of tapentadol SR (titration phase of up to four weeks, followed by 48 weeks of maintenance) in patients with moderate to severe, chronic pain after completing the studies cited above. In all, 1152 patients received at least one dose of tapentadol SR and the median treatment duration was 339 days, with a treatment discontinuation percentage of 39.5%, for the most part due to adverse events (13%). The safety profile was similar to the phase III studies, with 78.6% (n = 907) of patients having had an adverse event, 7.3% (n = 84) of whom had a serious adverse event, including four patients with suicidal ideation or behaviour, one of which was a case of committed suicide.

8.2.2 Summary of safety according to the SPC

“The adverse effects of the drug reported by patients in the placebo-controlled trials were predominantly of mild to moderate severity. The most frequent adverse effects (≥ 10%) were in the gastrointestinal system (nausea, constipation) and central nervous system (dizziness, headache, and somnolence).”

The adverse events identified, according to their frequency, were the following:

- 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;
- Uncommon (≥ 1/1000, < 1/100): Hypersensitivity to the active substance, weight decreased, confusional state, agitation, perception disturbances, abnormal dreams, euphoric mood, depressed level of consciousness, memory impairment, mental impairment, syncope, sedation, balance disorder, dysarthria, hypoesthesia, paraesthesia, visual disturbance, heart rate increased or decreased, palpitations, blood pressure decreased, abdominal discomfort, urticaria, dysuria, pollakiuria, sexual dysfunction, withdrawal syndrome, feeling abnormal, irritability;
- Rare (≥ 1/10,000, < 1/1000): drug dependence, thinking abnormal, convulsion, presyncope, coordination abnormal, respiratory depression, impaired gastric emptying, feeling drunk, feeling of relaxation.

“Clinical trials performed with PALEXIA LP with patient exposure up to 1 year have shown little evidence of withdrawal symptoms upon abrupt discontinuations and these were generally classified as mild, when they occurred. Nevertheless, physicians should be vigilant for symptoms of withdrawal (see section 4.2 of the SPC) and treat patients accordingly should they occur.

The risk of suicidal ideation and attempted suicide is known to be higher in patients suffering from chronic pain. In addition, substances with a pronounced influence on the monoaminergic system have been associated with an increased risk of suicidality in patients suffering from depression, especially at the beginning of treatment. Data from clinical trials and post-marketing reports do not provide evidence for an increased risk with tapentadol”.

8.2.3 Assessment of the warning signs of suicidal ideation or behaviour by the
On 6 February 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency issued a report on the adverse events relating to suicidal ideation and behaviour encountered during the course of the clinical development of tapentadol SR.

After reviewing individual cases, the latter concluded that there was no evidence for a causal connection between tapentadol SR and suicide risk. It does state, however, that given its noradrenaline reuptake inhibitory action, tapentadol SR does have a slight effect on serotonin levels, which does not exclude the possibility that it is associated with a suicide risk similar to that observed with antidepressants. Monitoring for the risk of suicidal ideation should form part of the risk management plan.

8.2.4 Potential for abuse and dependency

According to the ANSM’s [French National Agency for Medicines and Health Products Safety] National Commission on Narcotics and Psychotropic Substances, 21

“Based on the data from experimental tests evaluating abuse and dependency in animals and from clinical studies in human subjects, tapentadol is an opioid agonist with a potential for abuse and dependency, as well as for misuse for psychoactive purposes, which could be increased owing to its weak emetic action.

The ready water-solubility of tapentadol hydrochloride powder increases the risk of the oral tablets being used parenterally, thereby increasing the risk of abuse and poisoning. Taking account of these points, it is listed as a narcotic.

Please refer to the SPC for the contraindications, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, especially on account of its both opioid and adrenergic activity.

08.3 Summary & discussion

8.3.1 Chronic cancer pain

The request for inclusion of PALEXIA LP for severe chronic cancer pain is based on data from two multicentre, randomised, controlled, phase III studies in patients with moderate to severe, chronic cancer pain. Treatment comprised a titration phase followed by a maintenance phase.

In study KF5503/15, 496 patients with a mean age of 60 years, mostly already treated with opioids and with a pain score of at least 5/10, were randomised 2:1 into two groups for a two-week titration phase: tapentadol SR (n = 338) and morphine SR (n = 158). About 17% of patients in each group did not complete the titration phase, primarily on account of adverse events (7%). At the end of this phase, patients in the tapentadol SR groups with a pain score of less than 5/10 and who had received a maximum of two daily doses of morphine IR on the last three days, were again randomised into two groups, tapentadol SR (n = 106) and placebo (n = 112), to proceed with the four-week maintenance phase, as did also patients in the stabilised morphine SR groups (n = 109), resulting in three treatment groups.

The mean pain intensity at the start of the titration phase was 6.3, and about 40% of patients had a pain score $\geq$ 7/10. At the start of the maintenance phase, the mean pain intensity score was only 3/10.

The efficacy of tapentadol SR (100 mg to 250 mg twice daily) was compared with the placebo during the maintenance phase, based on the percentage of treatment responders at the end of the maintenance phase (pain score < 5/10 and a maximum of two daily doses of morphine IR throughout the entire 28-day maintenance phase). This percentage was higher in the tapentadol SR group (62%) than in the placebo group (50%) (OR = 2; 95% CI: [1.1; 3.7]; p = 0.02), but this criterion does not constitute one of the recommended endpoints in pain clinical trials. This comparison does present limitations, given the low pain intensity score at the start of the maintenance phase and the preselection of patients who are already responders for the maintenance phase (since some of the non-responder patients had been excluded previously during the titration phase), leading to the treatment response being overestimated. The percentage of responders was 69% in the morphine SR group (40 to 100 mg twice daily).

This study does not give the results of a direct comparison between tapentadol SR and morphine SR over the entire study. Indeed, it was only planned to have such a comparison for the titration phase through a non-inferiority analysis. This was demonstrated with an inter-group difference in favour of morphine SR of -7.0 (95%CI: [-15.5; -1.4]; p = 0.01), assuming a lower limit close to the non-inferiority limit fixed at 20% which was itself broadly defined.

It should be pointed out that during the maintenance phase, the median daily doses were 300 mg of tapentadol SR as against 118 mg of morphine SR and that the use of morphine IR did not differ significantly between the tapentadol SR groups and the other two groups, going from 60 to 72% of patients. No difference was found in the variation in the mean weekly pain score between the tapentadol SR groups and the placebo group.

Study KAJ-C02 included 343 patients in Japan and Korea with a mean age of 65 years, with a minimum pain score of 4/10, and randomised into two groups: tapentadol SR (n = 171) and oxycodone SR (n = 172). The mean treatment duration was 28 days, with a median titration duration of 7 days (not determined previously). The percentage of treatment discontinuations was 28% in the oxycodone SR groups and 33% in the tapentadol SR groups; mainly related to disease progression (9 et 7%, respectively) and to adverse events (8 and 7%). The mean pain intensity was 5.4/10 on inclusion and only 21.5% of patients had severe pain. Efficacy was compared between tapentadol SR and oxycodone SR, based on the change in pain intensity between inclusion and the final three days of the study (primary efficacy endpoint) by means of a non-inferiority analysis (1 point pain margin). It should be pointed out that the median daily doses

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were 83 mg of tapentadol SR and 16.7 mg of oxycodone SR in the final three days. The 
non-inferiority of tapentadol SR was demonstrated with an intergroup difference of 
-0.1 (95% CI [-0.5;0.4]), compared with small doses of oxycodone SR, equivalent to a step 
2 treatment.

Overall, the duration of these studies is too short (maintenance or total duration of 28 days) to be 
able to assess the long-term efficacy of tapentadol SR in chronic pain. Study KF5503/15 does not 
allow a comparison to be made of the efficacy of tapentadol SR versus morphine SR or placebo 
over the totality of the treatment, and study KAJ-C02, which showed the non-inferiority of 
tapentadol SR in comparison with oxycodone SR presents problems as regards the transferability 
of the results in terms, among other things, of daily doses and pain intensity.

8.3.2 Chronic non-cancer neuropathic pain

The efficacy data for tapentadol SR in severe, chronic non-cancer neuropathic pain are based on 
two phase III studies, KF5503/36 and KF5503/56 which, respectively, included 591 and 
459 patients with diabetic peripheral neuropathy and suffering from moderate to severe pain. 
These patients had a mean age of 60 years, and 66 to 68% of them were opioid-naïve. Patients 
who, at the end of the three-week titration phase, showed a reduction of at least 1 point on the pain 
scale were included in the maintenance phase after randomisation into two groups: tapentadol SR 
versus placebo, double-blind, for 12 weeks.
Pain intensity was about 7.3/10 on inclusion and 3.5/10 at the start of the maintenance phase. The 
efficacy of tapentadol SR (100 mg to 250 mg twice daily) was compared with placebo over the 
maintenance phase by looking at the change in the pain intensity score between the start and end 
of the maintenance phase. The mean intergroup difference in this change was significantly in 
favour of tapentadol SR with -1.3/10 (95% CI [-1.7;-0.9]) in study 36 and with -1.0/10 (95% CI 
[-1.4;-0.5]) in study 56 versus placebo.
The analysis was performed on the ITT population, with estimation of the least squares taking the 
percentage of discontinuations into account (between 22 and 30% during the titration phase and 
between 29 and 31% during the maintenance phase), due primarily to adverse events.

From a methodological point of view, comparison of the efficacy of tapentadol SR versus placebo 
after part of the non-responders had been excluded during the course of the titration phase leads 
to an overestimation of the treatment response during the maintenance phase and does not allow 
a comparison to be made of the efficacy in treatment-naïve patients. Besides, strong opioids are 
recommended for this type of pain after first-line treatments have failed (tricyclic antidepressants or 
certain antiepileptics); and yet, the status of included patients with regard to this criterion is not 
known.
The superiority of tapentadol SR, demonstrated in this study by the method of least squares, 
appears to be low.

8.3.3 Chronic non-cancer-related and non-neuropathic pain

The efficacy data for tapentadol SR in severe, chronic non-cancer-related non-neuropathic pain 
are based on three phase III studies conducted in patients with moderate to severe, chronic 
rheumatic pain due to gonarthrosis in studies KF5503/11 (n = 1023) and KF5503/12 (n = 987) to 
chronic lumbar pain in study KF5503/23 (n = 965). Patients were randomised into three groups: 
tapentadol SR (100 mg to 250 mg twice daily), placebo, and oxycodone SR (20 to 50 mg twice 
daily).
The mean age of the patients varied between 50 and 60 years, and more than 80% had severe 
pain. The mean pain intensity on inclusion was between 7.2 and 7.5/10. Over 67% of the subjects 
in the studies on gonarthrosis and 45% of those in the study on chronic lumbar pain had not taken 
any opioids in the three months prior to inclusion.
The efficacy of tapentadol SR was compared to placebo with reference to the change in pain 
intensity between inclusion and the mean value over the 12-week maintenance phase (after a 
three-week titration phase). The placebo was also compared with oxycodone SR by way of a
sensitivity analysis. The change in pain intensity was -2 to -3/10 during the course of the study, and the superiority of tapentadol SR or oxycodone SR was demonstrated in studies KF5503/11 (gonarthrosis) and KF5503/23 (chronic lumbar pain), with a mean difference in change of -0.7 between tapentadol SR and placebo and -0.3 between oxycodone SR and placebo, but not in study KF5503/12 (gonarthrosis).

In conclusion, two out of three studies demonstrated the superiority of tapentadol SR with respect to placebo.

8.3.4 Safety data

The main adverse effects reported most frequently (> 10% of subjects) with tapentadol SR in the clinical studies are similar to those of the other opioid analgesics, in particular gastrointestinal disorders (nausea, constipation) and neurological disorders (vertigo, headache, drowsiness). These adverse effects were predominantly of mild to moderate intensity. Overall, the safety profile was similar to that of morphine SR or oxycodone SR, but with a lower incidence of gastrointestinal adverse effects (nausea and constipation) especially during the titration period.

A warning sign of suicidal ideation was the subject of an EMA assessment, which concluded that there was no proven causal link with tapentadol SR, while being unable to rule out the possibility of a link between its noradrenaline reuptake inhibitory action and a slight effect on serotonin levels (similar risk to that of antidepressants).

In addition, tapentadol does have a potential for abuse and dependency and is listed as a narcotic.

08.4 Planned studies

A risk management plan (RMP) is envisaged to monitor certain aspects relating to safety of use. The risks under consideration (version of 10 July 2013) are:
- Significant risks: abuse, diversion of use and dependency, convulsions;
- Potential risks: overdose, off-label use in children, medication errors, accidental exposure, diversion of use, serotonin syndrome if used with serotonergic medicinal products, suicidal ideas and behaviours;
- Important missing information: use in children.

The proposed risk management measures include, in addition to routine pharmacovigilance and risk minimisation in the SPC, setting up an observational study of use in France (current protocol).

Within the framework of use in children, the planned study KF5503/66 will evaluate the efficacy and safety of tapentadol SR versus morphine SR in patients aged from 6 years to 18 years with chronic pain requiring opioid treatment. The other clinical trials in children and young adults relate to the treatment of acute postoperative pain.
ROLE IN THE THERAPEUTIC STRATEGY

Treatment of chronic severe cancer pain

The management strategy with chronic severe cancer pain depends on the type of pain.

In cases of chronic severe cancer pain identified as nociceptive, the WHO recommends using morphine as first-line treatment in adults. The ANAES [National Health Accreditation and Assessment Agency] recommends starting with immediate-release, or possibly extended-release, oral morphine sulphate. In cases of insufficient efficacy, additional analgesia with a fast-acting morphine-based product is recommended (interdose). In cases where treatment with oral morphine has failed, the patient must be re-assessed with a view to finding a neurogenic mechanism of action or a significant emotional or cognitive factor.

More recently, the Interregional Reference Frameworks working with cancer care support groups recommend using pure opioid agonists for the management of severe, chronic cancer pain: morphine, oxycodone, and hydromorphone. Fentanyl may be used in the treatment of paroxysmal attacks in patients already receiving basic morphine treatment.

In cases of uncontrollable adverse events, it is recommended to consider opioid rotation, or else change the route of administration.

In neuropathic-type cancer pain, morphine is recommended as a third-line treatment, in the event of a contraindication or the failure of one of the first-line classes of therapy used as monotherapy or in combination (tricyclics, lidocaine, gabapentine).

Tapentadol SR is a step 3 oral opioid analgesic. The clinical studies provided, with their bias and methodological limitations, demonstrated its superiority in comparison with placebo and non-inferiority in comparison with oxycodone SR when this comparator was used in low doses, equivalent to doses of step 2 analgesics (< 20 mg oxycodone per day). Its safety profile is similar to that of strong opioid analgesics, with a potential for abuse and dependency (inclusion in the list of narcotics). On account of its noradrenergic activity, tapentadol SR could be associated with a risk of suicidal ideation and behaviour, although the EMA has not been able to prove any causal connection.

Moreover, the gradual increase in the doses of tapentadol SR is more limited than that of pure opioid agonists (maximum daily dose of 500 mg for tapentadol) and in particular morphine, whose lack of a ceiling effect (high doses up to 2 g daily in adults) and the availability of slow release forms, are useful for the treatment of intractable chronic cancer pain, and in cases of hyperalgesia progression affecting terminally ill patients.

It should be pointed out that the system of opioid rotation needs to be adapted to these proprietary medicinal products.

The Transparency Committee therefore considers that, in light of their limitations in terms of dosage, PALEXIA LP proprietary medicinal products constitute an alternative to the available step 3 oral opioid analgesics (morphine, oxycodone, and hydromorphone) in severe, chronic cancer pain, but have no place in the treatment of intractable cancer pain.

23 Fédération Nationale des Centres de Lutte Contre le Cancer : Standards, Options et Recommandations 2002 pour les traitements antalgiques médicamenteux des douleurs cancéreuses par excès de nociception chez l’adulte, mise à jour.
Treatment of chronic severe non-cancer pain
The use of opioids is limited in chronic non-cancer pain. Their use is controversial in chronic nociceptive pain, and the risk/benefit ratio of such treatment needs to be very carefully assessed.\footnote{AFSSAPS Update – 2010/2011}
In the case of neuropathic pain, they are indicated as third-line treatment, after tricyclic antidepressants or antiepileptics used as monotherapy or in combination have failed or are contraindicated.\footnote{Martinez V et al. Société française d’étude et traitement de la douleur. Les douleurs neuropathiques chroniques: diagnostic, évaluation et traitement en médecine ambulatoire. Recommandations pour la pratique clinique de la Société française d’étude et de traitement de la douleur. Douleurs 2010; 11: 3-21.}
In these types of pain, tapentadol SR has shown itself, in studies that can occasionally be methodologically skewed, to be barely clinically superior to placebo.

Taking into account the almost irrelevant clinical efficacy, the Transparency Committee considers that PALEXIA LP proprietary medicinal products have no role in the treatment of severe, chronic non-cancer pain in adults, which can only be adequately treated with opioid analgesics.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual Benefit

- Severe, chronic pain in adults (whether cancer-related or not) is an ailment entailing a very marked deterioration in quality of life.
- These proprietary medicinal products are intended as symptomatic treatment for severe, chronic pain in adults that can only be adequately treated with opioid analgesics.
- In light of the available data, the efficacy/adverse effects ratio for these medicinal products is low in cancer pain and has not been established in models of chronic non-cancer pain (rheumatic pain, diabetic neuropathy pain).
- There are treatment alternatives, including other opioid analgesics.
- PALEXIA LP proprietary medicinal products are an alternative to available step 3 oral opioid analgesics (morphine, oxycodone, and hydromorphone) in severe, chronic cancer pain, given their limitations in terms of dosage; these proprietary medicinal products have no place in the treatment of chronic intractable cancer pain, nor of severe, chronic non-cancer pain.

Public health benefit

Given its frequency and its psychosocial consequences (fatigue, anxiety, depression), severe, chronic pain in adults represents a moderate to considerable public health burden.

Improved management of intense chronic pain is a public health need which is an established priority (Law on patient rights and healthcare system quality of 4 March 2002,\(^{27}\) Public Health Act,\(^{28}\) priorities of the GTND (National Technical Group for the Definition of Objectives),\(^{29}\) Plan for the improvement of pain management\(^{30}\)).

In light of the available data, obtained from clinical trials presenting many methodological limitations, the impact of PALEXIA LP on patient morbidity is difficult to quantify (the clinical relevance of the results obtained in the trials is debatable). PALEXIA LP is not expected to have any impact on the quality of life of patients, especially in the case of cancer pain. Moreover, a possible negative impact cannot be excluded owing to the adverse effects of strong opioids (risk of abuse and dependency) and the noradrenergic activity of tapentadol.

The transferability to current practice of the presented data is restricted in the case of cancer pain owing to the use of low doses of oxycodone at step 2 analgesic levels and to the comparison versus placebo in patients who already are responders; it is not guaranteed in non-cancer pain due to the unique comparison with placebo in patients who sometimes already are responders.

Consequently, PALEXIA LP offers a partial response to an identified public health need. In all, apart from severe, chronic cancer pain in relation to which a small public health benefit is expected, PALEXIA LP is not expected to offer any public health impact in severe, chronic pain in adults.

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\(^{27}\) Law on patient rights and healthcare system quality of 4 March 2002 recognising relief from pain as everyone’s basic human right.


Taking account of these points, the Transparency Committee considers that the actual benefit of PALEXIA LP is:

- low in the treatment of severe, chronic cancer pain in adults that can only be adequately treated with opioid analgesics, with the exception of intractable cancer pain.
- insufficient in the treatment of severe, chronic non-cancer pain in adults that can only be adequately treated with opioid analgesics.

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication “severe, chronic cancer pain in adults, which can be adequately managed only with opioid analgesics”, with the exception of intractable cancer pain, and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 15%

The Transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication “severe, chronic non-cancer pain in adults that can be adequately managed only with opioid analgesics” and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

Severe, chronic cancer pain
Taking account of the comparison between PALEXIA LP proprietary medicinal products and placebo or low doses of oxycodone SR, the Transparency Committee considers that PALEXIA LP proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of severe, chronic cancer pain in adults, compared with other available opioids.

On account of its noradrenergic activity, tapentadol SR could be associated with a risk of suicidal ideation and behaviour, although the EMA has not been able to prove any causal connection.

Severe, chronic non-cancer pain
Not applicable.
010.3 Target population

The target population of PALEXIA LP is represented by adult patients suffering from severe, chronic cancer pain that can only be treated with strong opioids. According to an INVS [Sanitary Surveillance Institute] estimation\(^3\) (based on 2005 data), the number of new cancer cases in 2010 was estimated at 203,000 in men and 154,500 in women, making a total of 357,500 cases.

From the results of a European survey on use (European survey on cancer pain – EPIC)\(^3\) carried out in 2007, including 642 French patients with cancer, 43% of these patients had severe pain at some point during their illness.

The target population is therefore estimated at 153,725 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging**
  Appropriate for the prescribing conditions.

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