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(54) Benævnelse: TAPENTADOL TIL SMERTEBEHANDLING AF ARTROSE

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OH ET AL.: "(226) Tapentadol immediate release is associated with improved gastrointestinal tolerability compared with oxycodone immediate release over 90 days in patients with lower back or osteoarthritis pain" JOURNAL OF PAIN, SAUNDERS, PHILADELPHIA, PA, US, Bd. 9, Nr. 4, 30. März 2008 (2008-03-30), Seite 32, XP022571437 ISSN: 1526-5900


Fortsættes ...
The invention relates to the use of tapentadol for treating pain due to osteoarthritis.

Arthrosis (osteoarthritis, arthrosis deformans) is the most widespread human joint disease. It is a dynamic, but slow progressing, degenerative disease of the cartilage and other articular tissue, particularly in the elderly, with intermittent inflammatory episodes. It may be distinguished from other rheumatic diseases by the absence of inflammatory parameters, restricted mobility, short-term articular stiffness and its radiological features.

Arthrosis or joint wear and tear is joint damage that starts with the degradation of the articular cartilage. In severe cases, it ultimately results in transformation processes in the adjacent bone and the surface of the joint is destroyed. Therefore, the consequences of the disease are pain and stiffness of the joint with restricted movement. The joints can become deformed and ultimately completely ossified. Arthrosis generally progresses slowly. As a result, the layer of cartilage firstly becomes thicker and the chondrocytes become more metabolically active. Changes to the subchondral trabecula result in reduced pressure relief by the spongy bone. The reparation tissue is subjected to more stress and as the duration of the disease advances, the equilibrium alters with respect to destruction. X-rays reveal a narrowing of the articular space and osteophytes form at the edges. D Höfler et al, AVP Therapieempfehlungen der Arzneimittelkommission der Deutschen Ärzteschaft, Arzneiverordnung in der Praxis,"Degenerative Gelenkerkrankungen", 2nd Edition 2001; and H Bröll et al, CliniCum, Special Edition September 2001, Konsensus-Statement,"Arthrose - Diagnostik % Therapie", for example, may be referred to in full for further details.

All joints can be affected by arthrotic changes in principle. However, those most commonly affected are the knee joints (gonarthrosis) and hip joints (coxarthrosis) which have to bear a great amount of weight. The disease also frequently occurs in the small vertebral joints (spondylarthrosis) and in the finger joints. ICD-10 defines arthrosis of the hips and knees as primary cartilage diseases associated with painful restrictions of movement (pain following periods of inactivity, weight-bearing pain) or difficulty in walking. Inflammation, such as synovitis, can become established, but does not have to.

Cardinal and early symptoms of arthrosis are pain (early triad: pain following periods of inactivity, fatigue-induced pain, weight-bearing pain; late triad: constant pain, night pain, muscular pain). These are accompanied by restrictions in movement, sensitivity to changes in
the weather and crepitation. The causes of pain with arthrosis are primarily the result of irritation in the periarticular tendon and ligament attachments, secondary inflammation, distension of the joint capsule, reactive effusion, increased pressure in the subchondral bone and microfractures.

In early stages pain only occurs on weight-bearing and subsides again after a few minutes if movement is continued, e.g. upon walking further. When accompanied by inflammation, the typical symptoms of activated arthrosis are exhibited: the joint is painful, feels warm and is swollen. Mobility is restricted. The inflammation often subsides even without treatment. This explains the generally episodic course of arthrosis: phases of more severe pain and restricted movement alternate with phases of less pain and good mobility. The more advanced the signs of wear and tear, the more rapidly one pain phase succeeds another. Ultimately, the pain is constant.

There are numerous drug-based and non-drug based treatments available which may be used individually or in combination:

- general measures, e.g. swimming, cycling, targeted gymnastics, use of walking aids, diet etc.;
- physical therapies, e.g. heat packs, electrotherapy and kinesiotherapy etc.;
- pharmacotherapy;
- orthopaedic techniques, e.g. bandages, orthoses etc; and
- operative therapy, e.g. transplantation of autologous cartilage cells, artificial joint replacement etc.

The European League Against Rheumatism (EULAR) recommends that the Lequesne Index, i.e. an overall evaluation by the doctor and the patient's assessment of the pain, be used to assess the success of a specific therapy. In addition to an assessment of swelling, reddening and resistance to pressure of the joint, the FDA recommends that the pain and function be assessed by means of the Western-Ontario-McMaster-Universities-Osteoarthritis-Index (WOMAC) and the Lequesne Index. For drugs used for the symptomatic treatment of arthrosis, the Osteoarthritis Research Society recommends the scales for the WOMAC pain score as the main target criterion and the WOMAC mobility restriction score or Lequesne Index as the secondary target criterion plus an overall assessment by the doctor and patients.
The pharmacotherapeutic spectrum of the groups of active substances available to treat arthrosis includes

- non-opioid analgesics, e.g. paracetamol;
- nonsteroidal anti-inflammatory drugs (NSAIDs), e.g. acemecatin, acetylsalicylic acid, aceclofenac, diclofenac, ibuprofen, ketoprofen, mefenamic acid, tiaprofenic acid, indometacin, lonazolac, naproxen, proglumetacin, meloxicam, piroxicam, rofecoxib, celecoxib;
- opioid analgesics, e.g. dihydrocodeine, tramadol, tilidine-naloxone, morphine, buprenorphine, oxycodone, fentanyl and hydromorphone;
- percutaneously administered antiphlogistics and hyperaemic agents;
- glucocorticosteroid crystal suspensions for intraarticular injections; and
- other active substances for oral or intraarticular injections, e.g. glucosamine, ademetionine, oxaceprol, hyaluronic acid etc.


Opioid analgesics are not part of the routine repertoire of drug treatment for arthrosis, but are unavoidable in certain situations. However, conventional opioid analgesics sometimes have significant side effects, in particular constipation, nausea, vomiting, headache, sedation, fatigue, respiratory depression, allergies and sometimes a drop in blood pressure. These side effects complicate the long-term therapy of chronic pain conditions in the case of arthrosis. Therefore, treatment with conventional opioid analgesics is generally indicated only after all other therapeutic options have been exhausted, for example in the case of patients who cannot undergo an operation, but are suffering extreme pain at rest which fails to respond to other substances with an analgesic action.
There is a requirement for alternative pharmacotherapeutic methods for arthrosis characterised by effective pain control and a reduced side-effects profile.

Therefore, it was the object of the invention to find compounds that are effective in pain control in the case of arthrosis and have advantages over conventional analgesics.

This object is achieved by the subject matter of the claims.

The invention relates to the use of tapentadol to produce a medicine for treating pain due to osteoarthritis.

It was surprisingly found that tapentadol, preferably as a prolonged release (PR) formulation (synonym for extended release (ER) formulation), i.e. a formulation with extended release within the meaning of the European Pharmacopoeia, combines excellent efficacy for the treatment of pain due to osteoarthritis with a reduced side effect spectrum. Extended release is usually understood to mean modified release which differs from the release of conventional pharmaceutical forms administered via the same route. The modification of the release is usually achieved by a special design of the pharmaceutical form or a special production method.

Figure 1 shows a schematic representation of the titration scheme adhered to during the investigation of the efficacy of tapentadol for treating pain due to osteoarthritis.

Figure 2 shows a schematic representation of the efficacy of tapentadol (100 mg and 200 mg) compared to a placebo and oxycodone.

Figure 3 shows a mathematical evaluation of the distribution of the serum concentration within a patient population following the administration of different doses of tapentadol.

Figure 4 shows a mathematical evaluation of the connection between the serum concentration of tapentadol and its effect with respect to pain alleviation in a patient population on the basis of data from various clinical studies.
Tapentadol, i.e. \(\text{(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol}\), is a
synthetic, centrally acting analgesic which is effective in the treatment of moderate to severe,
acute or chronic pain.

Tapentadol exhibits a dual mechanism of action, on the one hand as a \(\mu\)-opioid receptor
agonist and on the other as a noradrenaline transporter inhibitor. In humans, the affinity of
tapentadol to the recombinantly produced \(\mu\)-opioid receptor is 18-times less than that of
morphine. However, clinical studies have shown the pain-alleviating action of tapentadol to
be only two to three times less than that of morphine. The only slightly reduced analgesic
efficacy with at the same time an 18-times reduced affinity to the recombinant \(\mu\)-opioid
receptor indicates that the noradrenaline transporter inhibiting property of tapentadol also
contributes to its analgesic efficacy. Consequently, it is to be assumed that tapentadol has a
similar analgesic efficacy to that of pure \(\mu\)-opioid receptor agonists, but has fewer of the side
effects associated with the \(\mu\)-opioid receptor. The compound can be used in the form of its
free base or as a salt or solvate. The production of the free base is known, for example, from

For the purposes of the description "tapentadol" means \(\text{(-)-(1R,2R)-3-(3-dimethylamino-1-}
\text{ethyl-2-methyl-propyl)-phenol}\) and the pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts include salts of inorganic acids such as e.g.
hydrogen chloride, hydrogen bromide and sulphuric acid and salts of organic acids such as
methanesulphonic acid, fumaric acid, maleic acid, acetic acid, oxalic acid, succinic acid,
malic acid, tartaric acid, mandelic acid, lactic acid, citric acid, glutaminic acid, acetylsalicylic
acid, nicotinic acid, aminobenzoic acid, \(\alpha\)-lipoic acid, hippuric acid and aspartic acid. The
preferred salt is hydrochloride.

In a preferred embodiment, the medication is a solid dosage form. Preferably, the medication
is formulated for oral administration. However, other administration forms are also possible,
for example buccal, sublingual, transmucosal, rectal, intralumbar, intraperitoneal, transdermal,
intravenous, intramuscular, intragluteal, intracutaneous and subcutaneous.

Depending upon the formulation, the medication preferably contains suitable additives and/or
excipients. Suitable additives and/or excipients for the purpose of the invention are all
substances for obtaining galenic formulations known to the person skilled in the art from the prior art. The selection of these excipients and the amounts to use depend upon how the medication is to be administered, i.e. orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or topically.

The preparations suitable for oral administration are those in the form of tablets, chewable tablets, coated tablets, capsules, granules, drops, juices or syrups; those suitable for parenteral, topical and inhalative administration are solutions, suspensions, easily reconstituted dry preparations and sprays. A further possibility are suppositories for use in the rectum. Use in a depot in dissolved form, a carrier foil or a plaster, possibly with the addition of means to encourage skin penetration, are examples of suitable percutaneous administration forms.

Examples of excipients and additives for oral administration forms are disintegrants, lubricants, binders, fillers, mould release agents, optionally solvents, flavourings, sugar, in particular carriers, diluents, colorants, antioxidants, etc.

For suppositories, it is possible to use, inter alia, waxes or fatty acid esters and for parenteral means of application, carriers, preservatives, suspension aids, etc.

Excipients can be, for example: water, ethanol, 2-propanol, glycerin, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, sucrose, dextrose, molasses, starch, modified starch, gelatin, sorbitol, inositol, mannitol, microcrystalline cellulose, methyl cellulose, carboxymethylcellulose, cellulose acetate, shellac, cetyl alcohol, polyvinylpyrrolidone, paraffins, waxes, natural and synthetic rubbers, acacia gum, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulphate, edible oils, sesame oil, coconut oil, peanut oil, soya bean oil, lecithin, sodium lactate, polyoxyethylene and propylene fatty acid ester, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulphate, zinc sulphate, calcium sulphate, potash, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talc, kaolin, pectin, crospovidone, agar and bentonite.
The production of this medication and pharmaceutical compositions is performed with the aid of means, devices, methods and processes which are well known in the prior art of pharmaceutical formulation, such as those described for example in "Remington’s Pharmaceutical Sciences", ed AR Gennaro, 17th edition, Mack Publishing Company, Easton, Pa. (1985), in particular in Part 8, Chapters 76 to 93.

Thus, for a solid formulation such as a tablet, for example, the active substance of the medication can be granulated with a pharmaceutical carrier, e.g. conventional tablet ingredients, such as cornstarch, lactose, sucrose, sorbitol, talc, magnesium stearate, dicalcium phosphate or pharmaceutically acceptable rubbers, and pharmaceutical diluents such as water, for example, to form a solid composition containing the active substance in a homogeneous distribution. Here, a homogeneous distribution should be understood to mean that the active substance is distributed uniformly throughout the entire composition so that this can be easily divided into equally effective single dose forms, such as tablets, capsules, coated tablets. The solid composition is then divided into single-dose forms. The tablets or pills can also be coated or compounded in some other way in order to produce a dosage form with delayed release. Suitable coating means are, inter alia, polymeric acids and mixtures of polymeric acids with materials such as e.g. shellac, cetyl alcohol and/or cellulose acetate.

The amounts of tapentadol to be administered to patients vary depending upon the weight of the patient, the method of administration and the severity of the disease. In a preferred embodiment the medication contains tapentadol in an amount of 10 to 300 mg, more preferred 20 to 290 mg, even more preferred 30 to 280 mg, most preferred 40 to 260 mg, as an equivalent dose based on the free base.

Delayed release of tapentadol is possible from formulations for oral, rectal or percutaneous administration. Preferably, the medication is formulated for once-daily administration, for twice-daily administration (bid) or for thrice-daily administration, with twice-daily administration (bid) being particularly preferred.

The delayed release of tapentadol can, for example, be achieved by retardation by means of a matrix, a coating or release systems with an osmotic action (see e.g. US-A-2005-58706).
In a preferred embodiment the mean serum concentration of tapentadol following twice-daily administration of the medication over a period of at least three days, more preferred at least four days and in particular at least five days, is on average at least 5.0 ng/ml, at least 10 ng/ml, at least 15 ng/ml or at least 20 ng/ml, more preferred at least 25 ng/ml or at least 30 ng/ml, even more preferred at least 35 ng/ml or at least 40 ng/ml, most preferred at least 45 ng/ml or at least 50 ng/ml and in particular at least 55 ng/ml or at least 60 ng/ml. This means that tapentadol is administered twice daily over a period of at least three days, and then the serum concentration is measured preferably 2 h after the last administration. The authoritative numerical value is then obtained as the mean value for all the patients investigated.

In a preferred embodiment the mean serum concentration of tapentadol in at most 50% of the patient population, which preferably comprises at least 100 patients, more preferred in at most 40%, even more preferred in at most 30%, most preferred in at most 20% and in particular in at most 10% of the patient population, following twice-daily administration over a period of at least three days, more preferred at least four days and in particular at least five days, is on average less than 5.0 ng/ml, preferably less than 7.5 ng/ml, even more preferred less than 10 ng/ml, most preferred less than 15 ng/ml and in particular less than 20 ng/ml.

In a preferred embodiment the mean serum concentration of tapentadol in at most 50% of the patient population, comprising preferably at least 100 patients, more preferred in at most 40%, even more preferred in at most 30%, most preferred in at most 20% and in particular in at most 10% of the patient population, following twice-daily administration over a period of at least three days, more preferred at least four days and in particular at least five days, is on average more than 300 ng/ml, more preferred more than 275 ng/ml, even more preferred more than 250 ng/ml, most preferred more than 225 ng/ml and in particular more than 200 ng/ml.

Preferably, the mean serum concentration of tapentadol in at least 50% or 55% of the patient population, which preferably comprises at least 100 patients, more preferred in at least 60% or 65%, even more preferred in at least 70% or 75%, most preferred in at least 80% or 85% and in particular in at least 90% or 95% of the patient population, following twice-daily administration over a period of at least three days, more preferred at least four days and in particular at least five days, lies on average in the range of from 1.0 ng/ml to 500 ng/ml, more preferred in the range of from 2.0 ng/ml to 450 ng/ml, even more preferred in the range of
from 3.0 ng/ml to 400 ng/ml, most preferred in the range of from 4.0 ng/ml to 350 ng/ml and in particular in the range of from 5.0 ng/ml to 300 ng/ml.

In a preferred embodiment the percentage standard deviation (coefficient of variation) of the mean serum concentration of tapentadol, preferably in a patient population of 100 patients, following twice-daily administration of the medication over a period of at least three days, more preferred at least four days and in particular at least five days, is at most ± 90%, more preferred at most ± 70%, even more preferred at most ± 50%, at most ± 45% or at most ± 40%, most preferred at most ± 35%, at most ± 30% or at most ± 25% and in particular at most ± 20%, at most ± 15% or at most ± 10%.

Preferably, the serum concentrations are average values produced from measurements on a patient population of preferably at least 10, more preferred at least 25, even more preferred at least 50, even more preferred at least 75, most preferred at least 100 and in particular at least 250 patients. A person skilled in the art knows how to determine the serum concentrations of tapentadol. In this context reference is made, for example, to TM Tschentke et al, Drugs of the Future, 2006, 31(12), 1053.

In a preferred embodiment

- the medication is formulated for oral administration;
- the medication is a solid and/or pressed and/or film-coated dosage form; and/or
- the medication tapentadol has delayed release from a matrix; and/or
- contains the medication tapentadol in a amount of 0.001 to 99.999 % by weight, more preferred 0.1 to 99.9 % by weight, even more preferred 1.0 to 99.0 % by weight, even more preferred 2.5 to 80 % by weight, most preferred 5.0 to 50 % by weight and in particular 7.5 to 40 % by weight, based on the total weight of the medication; and/or
- the medication contains a pharmaceutically acceptable carrier and/or pharmaceutically acceptable excipients; and/or
- the medication has a total mass in the range of from 25 to 2 000 mg, more preferred 50 to 1,800 mg, even more preferred 60 to 1 600 mg, even more preferred 70 to 1 400 mg, most preferred 80 to 1 200 mg and in particular 100 to 1 000 mg, and/or
- the medication is selected from the group consisting of tablets, capsules, pellets and granules.
The medication can be provided as a simple tablet and as a coated tablet (e.g. as a film-coated tablet or sugar-coated tablet). The tablets are usually round and biconvex, but oblong shapes are also possible. Granules, spheroids, pellets or microcapsules, which are used to fill sachets or capsules or pressed into disintegrating tablets, are also possible.

Medications containing at least 0.001 to 99.999 % tapentadol, in particular low active doses, are preferred in order to avoid side effects. The medication contains preferably 0.01 % by weight to 99.99 % by weight tapentadol, more preferred 0.1 to 90 % by weight, even more preferred 0.5 to 80 % by weight, most preferred 1.0 to 50 % by weight and in particular 5.0 to 20 % by weight. To avoid side effects, it may be advantageous to increase the amount of tapentadol to be administered gradually (titration) at the start of the treatment to allow the body to slowly become accustomed to the active substance. Preferably, tapentadol is first administered in a dose which is below the analgesically active dose.

It is particularly preferred that the medication has an oral pharmaceutical form, which is formulated for twice-daily administration and contains tapentadol in an amount of 20 to 260 mg as an equivalent dose based on the free base.

In a preferred embodiment the medication is an oral administration form with the immediate release of tapentadol.

According to the invention tapentadol is used for treating pain due to osteoarthritis. The arthrosis is preferably selected from the group consisting of gonarthrosis, coxarthrosis and spondylarthrosis.

Preferably, the painful arthrosis is an arthrosis as defined by ICD-10 (International Statistical Classification of Diseases and Related Health Problems, WHO edition, preferably 2007 version). Preferably, the arthrosis is selected from polyarthrosis [M15], coxarthrosis [M16], gonarthrosis [M17], arthrosis of the first carpometacarpal joint [M18], other arthrosis [M19] and spondylarthrosis [M47]. The references in brackets refer to the ICD-10 nomenclature.

If the arthrosis is polyarthrosis [M15], this is preferably selected from the group consisting of primary generalised (osteo)arthrosis [M15.0], Heberden's nodes (with arthropathy) [M15.1], Bouchard's nodes (with arthropathy) [M15.2], secondary multiple arthrosis (post-traumatic
polyarthrosis) [M15.3], erosive (osteo)arthrosis [M15.4], other polyarthrosis [M15.8] and unspecified polyarthrosis (generalised (osteo)arthrosis not otherwise specified) [M15.9].

If the arthrosis is coxarthrosis [M16], this is preferably selected from the group consisting of bilateral primary coxarthrosis [M16.0], other primary coxarthrosis (unilateral or not otherwise specified) [M16.1], bilateral coxarthrosis resulting from dysplasia [M16.2], other dysplastic coxarthrosis (unilateral or not otherwise specified) [M16.3], bilateral post-traumatic coxarthrosis [M16.4], other post-traumatic coxarthrosis [M16.5] (unilateral or not otherwise specified), other bilateral secondary coxarthrosis [M16.6], other secondary coxarthrosis (unilateral or not otherwise specified) [M16.7] and unspecified coxarthrosis [M16.9].

If the arthrosis is gonarthrosis [M17], this is preferably selected from the group consisting of bilateral primary gonarthrosis [M17.0], other primary gonarthrosis (unilateral or not otherwise specified) [M17.1], bilateral post-traumatic gonarthrosis [M17.2], other post-traumatic gonarthrosis [M17.3] (unilateral or not otherwise specified), other bilateral secondary gonarthrosis [M17.4], other secondary gonarthrosis (unilateral or not otherwise specified) [M17.5] and unspecified gonarthrosis [M17.9].

If the arthrosis is arthrosis of the first carpometacarpal joint [M18], this is preferably selected from the group consisting of bilateral primary arthrosis of the first carpometacarpal joint [M18.0], other primary arthrosis of the first carpometacarpal joint (unilateral or not otherwise specified) [M18.1], bilateral post-traumatic arthrosis of the first carpometacarpal joint [M18.2], other post-traumatic arthrosis of the first carpometacarpal joint [M18.3] (unilateral or not otherwise specified), other bilateral secondary arthrosis of the first carpometacarpal joint [M18.4], other secondary arthrosis of the first carpometacarpal joint (unilateral or not otherwise specified) [M18.5] and unspecified arthrosis of the first carpometacarpal joint [M18.9].

If the arthrosis is other arthrosis [M19], this is preferably selected from the group consisting of primary arthrosis of other joints (primary arthrosis not otherwise specified) [M19.0], post-traumatic arthrosis of other joints (post-traumatic arthrosis not otherwise specified) [M19.1], other secondary arthrosis (secondary arthrosis not otherwise specified) [M19.2], other specified arthrosis [M19.8] and unspecified arthrosis [M19.9].
The pain is preferably moderate to strong. In a preferred embodiment the pain is selected from the group consisting of pain following periods of inactivity, weight-bearing pain, fatigue-induced pain, periarticular pain on pressure, radiating pain (e.g. knee pain in the case of coxarthrosis), pain at rest after spending a long time in the same position, constant pain, spontaneous pain, pain on movement, night pain, muscular pain, pain at the end of the range of movement, osseous pain as spontaneous pain and pain at rest.

Even if the medications according to the invention only exhibit few side effects, it may be advantageous, to avoid certain types of dependency, for example, to also use morphine antagonists, in particular naloxyne, naltrexone and/or levallorphan, in addition to tapentadol.

The invention furthermore relates to a method for treating pain due to osteoarthritis, in which tapentadol is administered to a patient in a pharmaceutically acceptable amount.

The following examples serve as further explanation of the invention but should not be construed as restrictive.

**Example 1:**

**Objective:**

The efficacy and tolerability of tapentadol with prolonged release (*prolonged release (PR)) and oxycodone HCl with controlled release (*controlled release (CR)) were compared with a placebo in patients with moderate to severe pain due to osteoarthritis of the knee.

**Methods (*randomised, placebo-controlled double-blind study):**

Patients (N = 670) were randomly selected and treated twice daily over 28 days either with tapentadol PR 100 mg, with tapentadol PR 200 mg, with oxycodone HCl CR 20 mg or with a placebo. The dose was titrated at the start of the treatment. The primary efficacy endpoint was the average perception of pain during the preceding 24 hours at the time of the last medical examination (*final visit*) based on a visual analog 100-mm scale (VAS, 0 mm = no pain, 100 mm = most severe pain imaginable)).
The study consisted of a 14-day, double-blind titration phase (3 days -> 11 days) followed by a 14-day double-blind maintenance phase (at the highest dose of the titration scheme in each case; see Figure 1):

- tapentadol PR 100 mg: 25 mg (bid) -> 50 mg (bid) -> 100 mg (bid);
- tapentadol PR 200 mg: 100 mg (bid) -> 150 mg (bid) -> 200 mg (bid);
- oxycodone HCl CR 20 mg: 10 mg (bid) -> 10 mg (bid) -> 20 mg (bid).

Results:

The difference in the adjusted mean square error (± standard error) in mean pain intensity compared to the placebo was significant for tapentadol PR 200 mg (-8.4 mm [±3.30]; P = 0.021). The differences in the adjusted mean square errors (± standard error) in mean pain intensity compared to the placebo was: for tapentadol PR 100 mg -5.9 mm (±3.34; P = 0.142) and for oxycodone HCl CR 20 mg -5.4 mm (±3.22; P = 0.091), i.e. tapentadol PR 100 and oxycodone HCl CR 20 mg exhibited similar behaviour (see Figure 2).

In all the groups, gastrointestinal disorders (included nausea, constipation and vomiting) and disorders of the nervous system (including tiredness and dizziness) were the most common side effects:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Placebo</th>
<th>Tapentadol PR 100 mg</th>
<th>Tapentadol PR 200 mg</th>
<th>Oxycodone HCl CR 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>23%</td>
<td>30%</td>
<td>49%</td>
<td>56%</td>
</tr>
<tr>
<td>Constipation</td>
<td>5%</td>
<td>7%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>15%</td>
<td>24%</td>
<td>34%</td>
<td>43%</td>
</tr>
</tbody>
</table>

A mathematical evaluation of the distribution of serum concentration within a patient population following the administration of different doses of tapentadol is depicted in Figure 3.

The clinical data confirm that tapentadol PR 200 mg is effective for 4 weeks in the treatment of moderate to severe chronic pain due to osteoarthritis. With respect to gastrointestinal side
effects and side effects associated with the central nervous system, the clinical data indicate that tapentadol is better tolerated than oxycodone HCl.

A mathematical evaluation of the connection between serum concentration of tapentadol and efficacy with respect to the alleviation of pain in a patient population based on data from various clinical studies is shown in Figure 4.

Examples 2 to 4:

Objective:

The efficacy and tolerability of tapentadol with immediate release (immediate release (IR)) and oxycodone HCl with immediate release (immediate release (IR)) were compared with a placebo in patients with moderate to severe pain due to osteoarthritis of the knee or hip.

Example 2:

Methods (randomised double-blind study, 90-day phase III, actively controlled flexible dosage)

Patients (N = 878) were randomly given tapentadol IR (50 or 100 mg every 4 to 6 hours as required; up to 600 mg/day) or oxycodone HCl IR (10 or 15 mg every 4 to 6 hours as required; up to 90 mg/day) in a ratio of 4:1. The pain intensity during the 24 hours prior to each visit was recorded on the basis of an 11-point evaluation scale (0 = no pain, 10 = most severe pain possible) from the first day of the medication to the last day. The tolerance was assessed from the first day of the medication to the second day after the last medication of the study.

Results:

Overall, 679 patients in the tapentadol IR group and 170 patients in the oxycodone HCl IR group were included in the efficacy and safety analysis. The pain intensities were similar between both groups over the time period. The average baseline pain intensity amounted to 7.0 for the tapentadol IR group and 7.2 for the oxycodone HCl IR group. These values
decreased towards the end of the double-blind period to 4.9 and 5.2 respectively for the tapentadol IR group and for the oxycodone HCl IR group. The most frequently occurring side effects were nausea, vomiting, dizziness, constipation, headache and fatigue. The patients in the tapentadol IR group exhibited a significantly (P < 0.001 for all measurements) lower instance of nausea (18%), vomiting (17%) and constipation (13%) compared to the oxycodone HCl IR group (nausea 29%; vomiting 30%; constipation 27%), whereas the instance of fatigue, dizziness and headache was similar in both groups.

Severe side effects were reported in 0.7% of the patients in the tapentadol IR group and in 1.8% of the patients in the oxycodone HCl IR group. However, these were not attributed to the active substance used.

Example 3:

Methods (randomised double-blind study, phase III)

878 patients were randomly given tapentadol IR (50 or 100 mg; maximum 600 mg/day) or oxycodone HCl IR (active control; 10 or 15 mg; maximum 90 mg/day) every 4 to 6 hours as required over 90 days. The treatment groups were compared with the aid of the Cochran-Mantel-Haenszel test.

Results:

The analysis covered 679 patients in the tapentadol IR group and 170 patients in the oxycodone HCl IR group. Patients with opioid experience (i.e. patients who had taken an opioid at least 5 days a week 30 days prior to the study) amounted to 49.0% in the tapentadol IR group and 48.2% in the oxycodone HCl IR group. The average point number for the pain decreased from the baseline to the end of the study from 7.0 to 4.9 for tapentadol IR and from 4.2 to 5.2 for oxycodone HCl IR. The most frequently occurring side effects were nausea, vomiting, dizziness, constipation, headache and fatigue. Significantly fewer (P < 0.001) gastrointestinal side effects (nausea 18%; vomiting 17%; constipation 13%) occurred in the tapentadol IR group than in the oxycodone HCl IR group (nausea 29%; vomiting 30%; constipation 27%), whereas the instance of headache, dizziness and fatigue was comparable in
both groups. In general, patients who were not accustomed to opioids had more side effects, but this tendency was less pronounced for tapentadol IR than for oxycodone HCl IR.

In the case of patients without opioid experience, vomiting occurred in 18% of the cases in the tapentadol IR group and in 39% of the cases in the oxycodone HCl IR group, whereas nausea was reported in 22% of the cases in the tapentadol IR group and in 35% of the cases in the oxycodone HCl IR group. In patients with opioid experience vomiting was reported in 16% of the cases in the tapentadol IR group and in 21% of the cases in the oxycodone HCl IR group, whereas nausea occurred in 14% of the cases in the tapentadol IR group and in 23% of the cases in the oxycodone HCl IR group. Opioid experience did not lead to a decrease in the instance of constipation in either of the two groups (tapentadol IR: opioid experience 12%; no opioid experience 14%) (oxycodone HCl IR: opioid experience 27%; no opioid experience 27%).

Example 4:

Methods (randomised, placebo-controlled double-blind study, actively controlled, phase III)

674 patients were randomly administered placebo, tapentadol IR 50 or 75 mg, oxycodone HCl IR 10 mg every 4 to 6 hours during waking hours. The end points of the study comprised the sum of pain intensity difference (SPID) over 5 days (primary end point), assessment of tolerance and analysis of age and gender in order to examine potential differences between the sub-groups of the population.

Results:

666 randomly allocated patients were included in the safety analysis; 659 patients were included in the efficacy analysis. Tapentadol IR 50 and 75 mg exhibited a significant improvement in pain alleviation on the basis of a 5-day SPID point assessment (P < 0.001) compared to the placebo. The oxycodone HCl IR 10 mg group also exhibited significant improvements with respect to the 5-day SPID point assessment (P < 0.001) compared to the placebo group, which confirms the sensitivity of the assay. On the basis of previously specified criteria for the 5-day SPID tapentadol IR 50 and 75 mg was at least as effective as oxycodone HCl IR 10 mg. 5-day SPID point values were similar between patients < 65 and ≥ 65 years in all groups of the active treatment as well as between the male and female sub-
groups. Joint side effects included gastrointestinal side effects and side effects of the central nervous system. Overall, the instance of gastrointestinal side effects for tapentadol IR 50 and 75 mg showed a dose dependency (29% or 40% respectively) that was lower than in the case of oxycodone HCl IR 10 mg (69%). This trend could also be observed within the sub-groups. Patients of < 65 and ≥ 65 years reported fewer gastrointestinal side effects with tapentadol IR 50 mg (25% or 36% respectively) than with 75 mg (42% or 38% respectively) and both were less than with oxycodone HCl IR 10 mg (66% or 74% respectively). In the male and female sub-groups gastrointestinal side effects were reported in 21% or 39% of cases respectively with tapentadol IR 50 mg and in 28% or 54% of cases respectively with tapentadol IR 75 mg compared to 58% or 81% respectively for oxycodone HCl IR 10 mg.

Conclusions:

The clinical data prove that tapentadol IR is effective in the treatment of moderate to severe chronic pain due to osteoarthritis. With respect to gastrointestinal side effects the clinical data indicate an improved tolerance of tapentadol compared to oxycodone HCl.
1

P A T E N T K R A V

1. Anvendelse af tapentadol til fremstilling af et lægemiddel til behandling af smerter
ved artrose.

2. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
lægemidlet er en fast læggemiddelform.

3. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
lægemidlet er formuleret til oral indgivelse.

4. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
lægemidlet er formuleret til indgivelse to gange dagligt.

5. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
lægemidlet indeholder tapentadol i en mængde fra 10 til 300 mg.

6. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
lægemidlet
   - indeholder et farmaceutisk acceptabelt bærestof; og/eller
   - har en samlet vægt i intervallet fra 25 til 2.000 mg; og/eller
   - valgt fra gruppen bestående af tabletter, kapsler, pellets og granulater.

7. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
artrosen er valgt fra gruppen bestående af gonartrose, coxartrose og spondylartrose.

8. Anvendelse ifølge et hvilket som helst af de foregående krav, kendetegnet ved at
smerten er moderat stærk.

9. Anvendelse ifølge et hvilket som helst af foregående krav, kendetegnet ved at
smerten er valgt fra gruppen bestående af smerter forårsaget af aktivitet efter længere
tids inaktivitet, belastningssmerter, træthedssmerter, periartikulære tryksmerter, strålende
smerter, smerter efter en længere periode i den samme stilling, vedvarende smerter, be-
vægelsessmerter, nattesmerter, muskelsmerter, kroniske smerter og knoglesmerter såsom
spontane smerter og smerter under afslapning.
Figure 1

Treatment

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<th>Visit 4</th>
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<th>Visit 6</th>
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14-day titration
14-day maintenance
Figure 2

Tapentadol PR 100 mg
Tapentadol PR 200 mg
Oxycodone HCl CR 20 mg
Figure 4

Pain relief VAS (mm)

Serum concentration of tapentadol [ng/ml]