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(71) Applicant *(for all designated States except US)*: **OSTEOLOGIX A/S** [DK/DK]; c/o Symbion Science Park, Fruebjergvej 3, DK-2100 København Ø (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHRISTGAU, Stephan** [DK/DK]; Ræveskovsvej 10A, DK-2820 Gentofte (DK). **HANSEN, Christian** [DK/DK]; Rungsted Strandvej 19, DK-2950 Vedbæk (DK). **NILSSON, Henrik** [SE/DK]; Cort Adelersgade 4, st.th., DK-1053 Copehagen K (DK).

(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen V (DK).

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(54) Title: COMBINATION TREATMENT WITH 5-LOX INHIBITORS

(57) Abstract: Combination treatments, wherein a 5-LOX inhibitor are administered together with a bone or cartilage beneficial compound in order to obtain a therapeutically beneficial effect in the treatment and/or prophylaxis of osteoarthritis, rheumatoid arthritis, osteoporosis or pain, and pharmaceutical compositions comprising a combination of a 5-LOX inhibitor and a bone and cartilage beneficial compound.

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Combination treatment with 5-LOX inhibitors

Field of the invention

The present invention relates to combination treatments, wherein a 5-LOX inhibitor are administered together with a bone or cartilage beneficial compound for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain, including joint pain. The invention also relates to pharmaceutical compositions comprising a 5-LOX inhibitor together with a bone and cartilage beneficial compound.

Background of the invention

Pain can present itself in many ways, and is associated with a multitude of physiological reactions and medical conditions, many of which seems to be associated with an inflammatory response and/or cytokines and signaling molecules such as prostaglandins, leukotrienes, TNF-α and substance P involved in inflammatory responses and soft tissue reactions to noxious stimuli. In management of pain it is often useful to distinguish between chronic pain and acute pain. The later form of pain can usually be associated with a stimulus causing tissue injury and release of intra-cellular and inter-cellular signaling molecules responsible for initiating the sensation of pain. The cascade of signaling molecules will involve both proinflammatory cytokines, but also various neurotransmitters and CNS related signaling molecules involved in mediating the sensory pain signal. Chronic pain can in many situations be difficult to associate with specific pathological mechanisms at the tissue level, but in many chronic conditions associated with pain, such as rheumatoid arthritis (RA) and osteoarthritis (OA), evidence of systemic elevation in inflammatory processes and inflammation related cytokines can be detected, and at least in part this can explain the pain of the patient. However, it must be pointed out that many conditions of severe chronic pain exist, which appear to be completely maladaptive and not related to any ongoing noxious stimuli, i.e. in conditions such as fibromyalgia.

A number of drugs have been developed to treat pain symptoms. These drugs are usually referred to as palliative agents. In very broad terms, most palliative drugs used in clinical practice today can be divided in two classes, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Opioids target primarily receptors in the central nervous system (CNS) responsible for the sensation of pain, whereas NSAIDs comprise a heterogeneous group of compounds with an ability to reduce inflammatory signaling molecules such as prostaglandin synthesis and cyclo-oxygenase enzymes. These

actions provides the main rationale for the widespread medical use of NSAIDs, where their anti-inflammatory as well as anti-pyretic and analgesic activities makes these drugs the treatment of choice for a wide range of inflammation related diseases as well as to relieve the aches and pain of everyday life.

Both NSAIDs and opioids are associated with significant side effects such as a development of drug dependency and abuse (opioids) and gastrointestinal (GI) and cardiovascular complications (NSAIDS). Conventional non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen, aspirin and paracetamol inhibit both isoforms of the cyclo-oxygenase (COX) enzyme, i.e. COX-1 and COX-2. Inhibition of COX-1 is thought to be principally responsible for the gastrointestinal (GI) adverse effects of NSAIDs, due to the fact that COX-1 activity serves a vital role in the cytoprotection of the stomach epithelial lining cells. As a result selective/pre-dominant COX-2 inhibitors e.g. rofecoxib, were designed to spare the stomach and block predominantly the COX-2 isoform, whilst the COX-1 isoform is largely spared. However, it must be stressed that the so-called COX-2 inhibitors are not absolutely specific for this isoform of cyclooxygenase, they mere have a preference such as e.g. a 10 fold higher affinity for the COX-2 isoform compared to the COX-1 isoform, and thus they are able to inhibit the GI-protective COX-1 enzyme to some extent and these drugs are still associated with a significantly increased risk of GI side effects.

Furthermore, there is some uncertainty regarding the cardiovascular and renal effects of the COX-2 selective inhibitors and there has been some concern that COX-2 inhibitors confer an increased thromboembolic risk. Furthermore, experiences from the now widespread clinical use of COX-2 inhibitors have revealed that this class of compounds still is associated with significant increased risk of GI toxicity although the COX-2 inhibitors appear to have a better gastric tolerability profile than conventional NSAIDs. In fact, it seems that COX inhibition, besides causing a reduction in the synthesis of vasodilatory and gastroprotective prostaglandins, leads to an up-regulation of arachidonic acid metabolism by the 5-Lipoxygenase (5-LOX) enzyme, which is a rate limiting enzyme in the pathway for formation of leukotrienes. Leukotrienes in turn can activate both pro-inflammatory and catabolic cytokines and cellular responses, contributing to inflammation as well as other undesired adverse effects such as sensation of pain.

Leukotrienes produced by 5-LOX contribute to developing and sustaining inflammation, notably by recruiting leukocytes at inflamed sites. Leutrienes also promote the development of gastrointestinal (GI) damage by reducing the production of protective mucins by the epithelial lining cells in the stomach. GI related side effects such as epigastric/abdominal pain, nausea, vomiting, diarrhea, dyspepsia, bloating, flatulence, anorexia, mucosal erosions and/or inflammation (esophagitis, gastritis, duodenitis, enteritis), gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations and GI strictures are the most troublesome side effect of NSAIDs and a significant contributor to the increased morbidity associated with long term NSAID treatments in chronic diseases such as OA and RA.

Dual COX/LOX inhibitors are therefore desirable anti-inflammatory compounds and a number of such compounds have been developed, although not yet marketed, for the treatment of for instance osteoarthritis.

[2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3,dihydro-1H-pyrrolizine-5-yl]-acetic acid, or "licofelone", also known as ML3000 (Merckle), is an example of a dual COX/5-LOX inhibitor. Data from animal studies indicate that the gastrointestinal protective properties of licofelone are closely linked to its 5-LOX inhibitory activity. Licofelone has completed clinical development for the treatment of osteoarthritis (OA) and is currently awaiting marketing authorization from regulatory authorities. Licofelone, through its inhibition of 5-LOX, decreases the production of proinflammatory leukotrienes and prostaglandins, which are involved in the pathophysiology of OA and in gastrointestinal (GI) damage induced by NSAIDs. Clinical evaluation of licofelone has shown the compound has the potential to combine good analgesic and anti-inflammatory effects with excellent GI tolerability.

Licofelone also appears to be as effective as the selective COX-2 inhibitor celecoxib in the treatment of the signs and symptoms of OA. Licofelone has a GI safety profile similar to that of celecoxib, but may offer the advantage of fewer incidences or worsening of peripheral oedema. Recent data have also shown that licofelone co-administration with low-dose aspirin does not lead to increased GI toxicity. This is in contrast to both conventional NSAIDs and COX-2 inhibitors, which in similar clinical settings have revealed much higher GI toxicity. The emerging clinical data for licofelone indicate that it is an effective and well-tolerated therapy that could offer safety advantages over current treatment options, without compromising the palliative and

anti-inflammatory efficacy, and that it could be suitable for the long-term treatment of a broad spectrum of patients with OA.

Other dual COX/5-LOX inhibitors are currently under development. A number of distinct structural families with a dual inhibiting action on both COX and 5-LOX have been described by Charlier & Michaux (Eur. J. Med. Chem. 2003, 38, 645-659) and elsewhere.

Osteoarthritis (OA) is a chronic joint disease, which is generally considered a condition accompanying aging. However, the disease process of OA is not merely a consequence of aging of the tissue as distinct genetic, environmental and psychosocial factors have been demonstrated to play a role in the initiation and progression of OA. The clinical presentation of OA varies tremendously. The disease can present a very heterogeneous clinical picture with a varying number of joints involved and marked fluctuations in disease severity and symptoms. Furthermore the progression and outcome as well as symptoms and degree of disease severity varies considerably between patients. However, one of the main findings associated with the disease and forming the basis for diagnosis of the condition is the presence of pain and functional impairment, both locally at affected joints and systemically affecting most aspects of the function in the OA patient. Accordingly the majority of therapies commonly used in the clinical management of OA such as NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) and the newer COX-2 inhibitors act predominantly through relieving symptoms with no or minimal documented effect in terms of slowing or halting the underlying cartilage degradation. A prominent feature of OA is an alteration in bone turnover, manifested locally at the affected joints as trabecular architectural deterioration and formation of osteophytes (small abnormal bone outgrowths in the affected joints). These structural alterations occur and develop on the subchondral bone in affected joints.

RA is an inflammatory condition where articular cartilage of affected joints is being degraded by an active process involving cells of the immune system as well as the tissues of the joint (i.e. the synovial membrane, the cartilage and subchondral bone). The etiology of RA is complex and a number of environmental and genetic factors have been suggested to have a role in the development of the disease. However, immune-system activation plays a major role in the disease etiology of RA, as a significant elevation in both systemic and local signaling molecules and other active components

of immune system activation can be detected in this disease. Among the characteristic hallmarks of the disease is the presence of cartilage destruction, focal bone erosions, periarticular osteoporosis and generalized bone loss resulting in increased prevalence of osteoporotic fractures. Some of the disease mechanisms responsible for focal bone loss may be similar to processes of generalized osteoporosis and associated with osteoclast activation. Generalized bone loss in patients with RA will occur as a result of the systemic and local activation of the immune-system and the presence of proinflamatory cytokines with an ability to stimulate resorption of bone. In turn these mediators accelerate bone turnover and systemic bone loss and by the inflammatory processes resulting in systemic increase of several cytokines shown to up regulate systemic bone turnover. In addition, bone loss also takes place focally as a consequence of the arthritic disease process. Another significant contributing factor to systemic bone loss in RA is the common therapeutic use of glucocorticoids which in addition to their well-documented anti-inflammatory effect also have a stimulating effect on bone resorption.

In RA the major clinical manifestation of the disease is the presence of swollen and tender joints with significant pain both systemically and localized in the affected joints. Thus, analgesic and palliative treatments remains one of the most used therapeutic interventions used in the clinical management of RA. NSAIDs and opioids remain widely used in management of rheumatological diseases. NSAIDs including COX-2 inhibitors are effective palliative agents when given in high doses and reduce the need for opioids, but they are associated with a number of deleterious side-effects, of which the well documented gastrointestinal (GI) irritation is the most serious. Traditional NSAIDs are also associated with reduced platelet function and thus an increased risk of cardiovascular events. Opioids are often used with great caution due to the fear of exposing the patient to risk of developing drug dependency.

In addition to RA and OA a multitude of other clinical situations exist, where chronic pain is a substantial symptom of the disorder. Among such conditions are Chrohn's disease, migraine, low back pain, cancer pain, neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself), psychogenic pain (pain not due to past disease or injury or any visible sign of damage inside or outside the nervous system), e.g. fibromyalgia and whiplash syndrome. In all these conditions, a very large systemic burden of NSAIDs can be required to obtain a required palliative effect. Consequently the GI side effects associated with long term

NSAID therapy becomes a significant source of morbidity and even mortality in the clinical management of these conditions.

Symptom relieving palliative therapies currently used in clinical management of OA, RA and other conditions of systemic or localized pain (i.e. NSAIDs, such as naproxen, meloxicam, ibuprofen and acetyl-salicylic acid, and COX-2 inhibitors, such as celecoxib and rofecoxib) have no effect on the underlying pathological disease mechanisms such as the tissue destruction resulting in permanent joint damage in RA and OA. As an example of the general inability of analgesic and/or palliative treatments to exert any chondroprotective effects in joint diseases, recent reviews of the literature indicate that different classes of NSAIDs may have effects on chondrocytes ranging from deleterious to beneficial with regard to preservation and promotion of cartilage matrix integrity exemplified on i.e. glycosaminoglycan synthesis (El Hajjaji H et al. J Rheumatol. 2003; 30:2444-51; Pelletier J-P et al. J Rheumatol. 1989; 16; 646-655) or markers of bone and cartilage turnover (Christgau S & Cloos P. Clin Appl Imunol Rev. 2004; 4: 277-294; Gineyts E et al, Ann Rheum. Dis. 2004; 63; 857-861). Very few, if any, therapies are available that have a convincing effect of slowing or halting the underlying cartilage degradation, which is the prime culprit causing the progressive joint destruction accompanying the disease. The newly developed COX/5-LOX inhibitors provide a significantly improved medical option for the treatment of the pain and functional impairment associated with OA, but this class of compounds is unlikely to provide much benefit with regard to decreasing or stopping the underlying tissue destruction occurring in the disease. Thus, there is an unmet therapeutic need for treatments, compounds and pharmaceutical compositions, which can act on the cells and enzyme systems mediating the cartilage degradation in OA, as well as relieving the immediate symptoms of the disease.

With the exception of glucosamine sulphate, which has shown a mild chondroprotective effect in clinical trials, no structure modifying drugs are currently marketed for use in treatment of OA or RA.

In the context of the present invention the terms 'structure modifying' or 'structure modification' refers to an ability of a pharmaceutical composition to significantly affect the turnover of bone and/or cartilage with the ability to reduce catabolism and/or increase anabolism thereby halting degradation/destruction of bone and/or cartilage and possibly enabling a improvement in previously damaged bone and/or cartilage

structures. The term 'chondro-protective' is used for medical treatments able to prevent (further) degradation of articular cartilage either by acting on cells and tissues responsible for catabolism of the tissue and/or by reducing the levels of localized and/or systemic cytokines and/or signaling molecules involved in mediating a pro-catabolic stimulus to cells and tissues involved in degradation of articular cartilage such as chondrocytes, synovial lining cells, synovial fibroblasts, subchondral osteoclasts and inflammatory cells such as macrophages and activated T-cells present in an inflammatory joint condition such as RA.

It has been speculated that bisphosphonates, selective estrogen receptor modulators (SERMs), hormone replacement therapy (HRT) and other compounds used in current medical practice for treatment and/or prophylaxis of postmenopausal osteoporosis may have a beneficial effect and a potential role as structure modifying and/or chondroprotective agents with an ability to decrease joint tissue degradation both of cartilage and subchondral bone. However, this remains to be demonstrated in clinical studies. A number of preclinical and a few clinical experiments have been conducted to assess the chondroprotective potential of agents normally regarded as purely antiresorptive such as bisphosphonates and SERMs (i.e. see Hoegh-Andersen et al. Arthritis Res. Ther. 2004; 6: 169-180, Lehman et al, Ann Rheum Dis. 2002; 61; 530 – 533 and Christgau et al, Menopause, 2004; 11; 404 – 411). However, none of these anti-resorptive treatments have been introduced in routine clinical practice and their use in connection or combination with dual COX/LOX-5 inhibitors has not been suggested before.

In the treatment of OA and RA, as well as in other disease states involving elevated inflammation and/or extracellular matrix destruction mediated by proinflammatory cytokines, there is a need for new and/or improved treatments and pharmaceutical compositions therefore, addressing the progression of disease, inflammation, pain and other manifestations of those disease states.

Description of the Invention

The present inventors have found that treatment of chronic conditions, in particular muscoskeletal diseases such as OA, RA and osteoporosis with 5-LOX inhibitors can be significantly improved by combining this medical intervention with another agent having positive effects on bone, cartilage turnover, bone strength and/or cartilage integrity.

5-LOX inhibitors are compounds that significantly inhibit 5-LOX, thereby decreasing the production of proinflammatory leukotrienes and prostaglandins, which are involved in e.g. the pathophysiology of OA and in gastrointestinal (GI) damage. Preferred compounds according to the present invention have a 5-LOX IC_{50} of less than about 1 μM, such as, e.g. less than about 0.75 μM, less than about 0.50 μM, less than about 0.40 μM, less than about 0.30 μM or less than about 0.20 μM. Furthermore, preferred compounds according to the invention inhibits 5-LOX at less than about 10 μM such as, e.g., about 5 μM or less, about 2 μM or less, about 1 μM or less, about 0.75 μM or less, about 0.5 μM or less, about 0.25 mM or less or about 0.1 μM or less

As mentioned above 5-LOX inhibitors such as, e.g., licofelone may also have an effect as inhibitors of either or both of COX-1 and COX-2, as well as 5-LOX. However, in the present context, it is the compounds ability to act as a LOX-5 inhibitor that is determinative for its applicability as a component of a composition according to the present invention. Accordingly, in the following compounds will be denoted "5-LOX" inhibitors even though they may also have an inhibitory effect on either or both of COX-1 and COX-2.

In case the 5-LOX inhibitor also inhibits either or both of COX-1 and COX-2, it preferably inhibits them at less than 10 μM. In a specific embodiment the present invention includes compounds, which selectively inhibit COX-1 over COX-2. In another embodiment the compounds selectively inhibits COX-2 over COX-1. Preferably, the compounds have a COX-2 IC_{50} of less than about 5 μM such as, e.g., about 2 μM or less, about 1 μM or less, about 0.5 μM or less, or about 0.1 μM or less. Preferably they (also) have a selectivity ratio of COX-2 inhibition over COX-1 inhibition of at least 10 such as, e.g., of at least 50, or of at least 100. Preferably, the compounds have a COX-1 IC_{50} of greater than about 1 μM such as, e.g., of greater than 20 μM.

In particular the present inventors have found that a combination of, or combined treatment with, a 5-LOX inhibitor and another "bone and cartilage beneficial compound" (abbreviated as "BCBC"), which may be defined as a compound that acts on cells involved in turnover of bone and cartilage, such as antiresorptive agents and/or pharmaceutical compounds with an ability to decrease cartilage catabolism as described herein, provides a significant therapeutic benefit compared to administration of a 5-LOX inhibitor alone and/or a BCBC alone.

Accordingly, the present invention relates to use of a combination of a 5-LOX inhibitor and a "bone and cartilage beneficial compound" ("BCBC") for the manufacture of a medicament for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain in an animal in need thereof.

In a preferred embodiment of the invention the 5-LOX inhibitor is licofelone or a pharmaceutically acceptable salt or derivative thereof.
The term "significant therapeutic benefit" includes one or more of the following beneficial effects:

i) improvement of one or more pharmacokinetic parameters of the 5-LOX inhibitor and/or BCBC compared with administration of the 5-LOX inhibitor alone or the BCBC alone in the same doses,

ii) reduction of frequency and/or magnitude of side-effects of the 5-LOX inhibitor and/or BCBC compared with administration of the 5-LOX inhibitor alone or the BCBC alone in the same doses,

iii) obtaining an additive or synergistic effect of the 5-LOX inhibitor and the BCBC compared with administration of the 5-LOX inhibitor alone or the BCBC alone in the same doses,

iv) reduction of daily dose of the 5-LOX inhibitor and/or the BCBC compared with RDD, recommended daily dose, for the 5-LOX inhibitor alone or the BCBC alone in the same doses to obtain a prophylactic and/or therapeutic effect. Some of the RDD values for the 5-LOX inhibitor and the BCBCs are given below.

In the present context, the term "pharmacokinetic parameters" includes parameters relevant for the concentration versus time curve such as, e.g., peak concentration (c_{max}), absorption (e.g. absorption rate), time to obtain peak concentration (t_{max}), distribution (e.g. distribution volume or distribution to specific tissues), metabolism (e.g. first pass metabolism), elimination (e.g. elimination rate) and excretion. In the present context, an improvement in one or more pharmacokinetic parameters means any change that lead to an improved prophylaxis and/or treatment of a subject. For instance, if a fast effect is desired for a specific active substance and the absorption rate of this active substance is very slow (which means that the effect is exerted a

relatively long time after intake of the drug), then an improvement would be to increase the absorption rate.

In a method according to the invention, the administration of the 5-LOX inhibitor and the BCBC in combination may lead to an improvement in at least one parameter selected from the group consisting of absorption rate, time to reach peak concentration (t_{max}), peak concentration (c_{max}), concentration vs. time curve, distribution volume or distribution to specific tissues, rate of metabolism, elimination rate and excretion rate.

In the present context the term "reduction in frequency of side-effects" means that harmful side-effects observed in clinical trials using treatment with combinations of the 5-LOX inhibitor and the BCBC are less frequent than if treatment was carried out using the 5-LOX inhibitor or the BCBC alone.

A "harmful side-effect" is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

In the present context, the term "reduction in magnitude of side effects" means that the measured magnitude and/or frequency of any measurable side effect is reduced.

A particular relevant side effect in the context of the present invention is a gastrointestinal (GI) side effects such as epigastric/abdominal pain, nausea, vomiting, diarrhea, dyspepsia, bloating, flatulence, anorexia, mucosal erosions and/or inflammation (esophagitis, gastritis, duodenitis, enteritis, colonitis), gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations and GI strictures.

As mentioned above, administration of the 5-LOX inhibitor and the BCBC may lead to an additive or synergistic effect. An additive effect is typically present if the effect obtained corresponds to "the sum" of effects obtained if the 5-LOX inhibitor and the BCBC were administered alone, whereas a synergistic effect is present if the effect obtained is greater than "the sum" of effects obtained if the 5-LOX inhibitor and the BCBC were administered alone. Both situations are advantageous in that it may be possible to obtain a sufficient effect using a lower amount of the 5-LOX inhibitor and/or the BCBC.

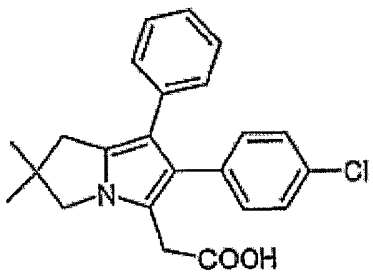
Particular desirable physiological effects where the combination treatment according to the present invention may be useful are: reduction in bone resorption, increase in bone formation, reduction in cartilage turnover, reduction in production of proinflammatory cytokines and/or in crease in bone matrix mineralization

Accordingly, in a method according to the invention, the administration of the 5-LOX inhibitor and the BCBC in combination may lead to a reduction of the daily dose of the 5-LOX inhibitor and/or the BCBC required to obtain a therapeutic or prophylactic effect, as compared with the daily doses of the 5-LOX inhibitor or the BCBC alone, which are needed to obtain the same or almost same effect.

More specifically, in a method according to the invention, the amount of the 5-LOX inhibitor and/or the BCBC administered in combination may be reduced by 10% or more, such as, e.g., 15 % or more, 20 % or more, 25 % or more, 30 % or more, 40% or more, 50% or more, 60% or more or 75% or more.

5-LOX inhibitors

Suitable 5-LOX inhibitors for use in the present invention include certain annelated pyrrole compounds (see WO 03/097041 which is hereby incorporated by reference). In a preferred embodiment of the invention the compound is licofelone known as ML-3000 or [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3,dihydro-1H-pyrrolizine-5-yl]-acetic acid and represented by the Formula I



Formula I

or pharmaceutically acceptable salts and derivatives thereof.

Other examples of suitable 5-LOX inhibitors for use in the present invention include:

- Certain di-tert-butylphenols, such as (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidence)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474) (Shionogi) (Yakugaku Zasshi. 2003 123:323-30), or such as darbufelone and pharmacologically active metabolites as well as derivatives such as dihydro-dimethyl-benzofuran and PGV-20229 (see Eur. J. Med. Chem. 2003, 38, 645-659, which is hereby incorporated by reference),- dihydro-dimethyl-benzofuran (Eur. J. Med. Chem. 2003, 38, 645-659),
- certain thiophene derived compounds such as RWJ-63556 (J. Pharmacol. Exp. Ther. 1997. 282:1094-1101),
-N-hydroxy-N-methyl-4-(2,3-bis-(4-methoxyphenyl)-thiophen-5-yl)-butanamide (S19812) (Servier) Arzneimittelforschung. 2003;53(11):774-9,
- certain methoxytetrahydropyran derivatives (Bioorg Med Chem Lett. 2002 Mar 11;12(5):779-82.),
- certain oxygenated xanthones such as 1,3,6,7-Tetrahydroxyxanthone (norathyriol) (Naunyn Schmiedebergs Arch Pharmacol. 2004, 369:507-15),
- certain pyrazole thiocarbamates (US 5,298,521),
- certain pyrazoles such as modified forms of phenidone containing compounds or the tri-flouro-benzole substituted pyrazoline derivative BW-755C (US 5,242,940), tepoxaline and derivatives as disclosed in Bioorg. Med. Chem. Lett. 1999, 9: 979-984, which is hereby incorporated by reference,
- certain di-*tert*-butylpyrimidines (US 5,356,898), and
- other 5-LOX inhibitors as disclosed in Eur. J. Med. Chem. 2003, 38, 645-659.

BCBC

As mentioned above a 5-LOX inhibitor is used in combination with a BCBC in order to obtain a beneficial therapeutic effect. In a preferred embodiment of the invention, the BCBC is selected from the group comprising bisphosphonates, strontium containing compounds, glucosamine sulphate, DMARDs and SERMs.

In a specific embodiment of the invention the BCBC is a bisphosphonate selected from the group comprising ibandronate, zoledronate, alendronate, risedronate, ethidronate chlodronate, tiludronate and pamidronate.

Examples of normal dose regimens for specific bisphosphonates include di-sodium etidronate, where 400 mg p.o. is administered daily for 14 days, followed by 500 mg Ca daily for 76 days, after which the cycle is repeated. Other examples are alendronate, where a dose of 5-10 mg p.o. is administered daily, or 70 mg p.o. once weekly;

risedronate sodium, which is administered as 35 mg p.o. once weekly; ibandronate which is administered as 2.5 mg daily or 150 mg p.o. once a month; zoledronate, which is given as an i.v. infusion one to four times per year, the annual dose being from about 1 to 4 mg; Pamidronate which is administered in a dose of 90 mg every second week; tiludronate which is given in a dose of up to 400 mg p.o. daily.

In a specific embodiment of the invention the BCBC is a SERM selected from the group comprising raloxifene, arzoxifene, droloxifene, tamoxifen, 4-hydroxy-tamoxifen, 4'-iodotamoxifen, toremifene, (deaminohydroxy)-toremifene, chlomiphene, levormeloxifene, ormeloxifene, chroman derivatives, coumarin derivatives, idoxifene, nafoxidine, TAT-59, LY-353381, CP-336156, MDL-103323, EM-800, ICI-182,ICI 183,780, ICI 164,384, ICI 183,780, ICI 164,384, diethylstilbesterol, genistein, nafoxidine, nitromifene citrate, moxesterol, diphenol hydrochrysene, erythro-MEA, allenolic acid, equilin-3-sulphate, cyclophenyl, chlorotrianisene, ethamoxytriphetol, lasofoxifene, bazedoxifene, genistein, tibolone, ospemifene, tesmilifene, droloxifene, panomifene, zindoxifene, meproxifene and faslodex

Examples of normal dose regimens for specific SERMs include raloxifene, which may be given as 50 mg - 60 mg p.o. once daily, tamoxifen, which may be administered as 20-30 (20-40) mg/day p.o., toremifene, which may be administered as 60 mg/day p.o., lasofoxifene, which may be given as 0.25-0.5 mg/day p.o., ospemifene, which may be given as 60-90 mg/day p.o., bazedoxifene, arzoxifene and levormeloxifene.

It has recently been found that some SERMs may be useful for improving sleep. It is contemplated herein, that the administration of a LOX-5 inhibitor together with a SERM may have a significant therapeutic benefit for the treatment of sleep disorders, such as, e.g., insomnia. Accordingly, the present invention relates to use of a combination of a 5-LOX inhibitor and a SERM for the manufacture of a medicament for treating and/or preventing sleep disorders, such as, e.g. insomnia.

Glucosamine sulphate used in a combination treatment with 5-LOX according to the present invention may be given in a daily dose of 500 – 3000 mg/day.

The strontium-containing compound for administration together with a 5-LOX inhibitor may be a strontium salt. Suitable strontium salts are organic strontium salts, such as, e.g. strontium malonate, strontium succinate, strontium fumarate, strontium pyrovate,

strontium carbonate, strontium oxalate, strontium salicylate, strontium ascorbate, strontium aspartate in either L and/or D-form, strontium glutamate in either L- and/or D-form, strontium pyruvate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate and strontium ranelate, strontium acetyl salicylate, strontium citrate, strontium ibuprofenate, strontium methotrexate, strontium alendronate, strontium ibandronate, strontium lactate, strontium flubiprofenate, strontium ketoprofenate, strontium phorbol 12,13-didecanoate 20-homovanillate, strontium indomethacinate, strontium carprofenate, strontium naproxenate, strontium acetyloxy-benzoate, strontium 2-Iminopiperidine, strontium salsalate and strontium sulfasalazinate and strontium threonate.
. A pharmaceutical composition according to the present invention may be manufactured with many different strontium salts comprising both inorganic and organic counter-ions to the strontium ion.

The inorganic acid for making strontium salts may be selected from the group consisting of boric acid, bromous acid, chloric acid, diphosphoric acid, disulfuric acid, dithionic acid, dithionous acid, fulminic acid, hydrazoic acid, hydrobromic acid, hydrofluoric acid, hydroiodic acid, hydrogen sulfide, hypophosphoric acid, hypophosphorous acid, iodic acid, iodous acid, metaboric acid, metaphosphoric acid, metaphosphorous acid, metasilicic acid, nitrous acid, orthophosphoric acid, orthophosphorous acid, orthosilicic acid, phosphoric acid, phosphinic acid, phosphonic acid, pyrophosphorous acid, selenic acid, sulfonic acid, thiocyanic acid and thiosulfuric acid.

The organic acid may be selected from the group consisting of C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_4(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, 2,3,5,6-tetrabromobenzoic acid, 2,3,5,6-tetrachlorobenzoic acid, 2,3,6-tribromobenzoic acid, 2,3,6-trichlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4-dihydroxybenzoic acid, 2,6-dinitrobenzoic acid, 3,4-dimethoxybenzoic acid, abietic acid, acetoacetic acid, acetonedicarboxylic acid, acetyl-salicylic acid, aconitic acid, acrylic acid, alpha-ketoglutaric acid, adipic acid, ascorbic acid, aspartic acid (L and D forms), anthranilic acid, arachidic acid, azelaic acid, behenic acid, benzenesulfonic acid, beta-hydroxybutyric acid, benzilic acid, benzoic acid, brassidic acid, carbonic acid, camphoric acid, capric acid, cholic acid, chloroacrylic acid, cinnamic acid, citrric acid, citraconic acid, crotonic acid, cyclopentane-1,2-dicarboxylic acid, cyclopentanecarboxylic acid, cystathionine,

decanoic acid, erucic acid, ethanesulfonic acid, ethylenediaminetetraacetic acid, folic acid, formic acid, fulvic acid, fumaric acid, gallic acid, glutaconic acid, gluconic acid, glutamic acid (L an D), glutaric acid, gulonic acid, heptanoic acid, hexanoic acid, humic acid, hydroxystearic acid, ibuprofenic acid, isophthalic acid, itaconic acid, lactic acid, lanthionine, lauric acid (dodecanoic acid), levulinic acid, linoleic acid (cis,cis-9,12-octadecadienoic acid), malic acid, m-chlorobenzoic acid, malic acid, maleic acid, malonic acid, melissic acid, mesaconic acid, methacrylic acid, methanesulfonic acid, monochloroacetic acid, myristic acid (tetradecanoic acid), nonanoic acid, norvaline, octanoic acid, oleic acid (cis-9-octadecenoic acid), ornithine, oxaloacetic acid, oxalic acid, palmitic acid (hexadecanoic acid), p-aminobenzoic acid, p-chlorobenzoic acid, petroselic acid, phenylacetic acid, p-hydroxybenzoic acid, pimelic acid, propiolic acid, phthalic acid, propionic acid, p-tert-butylbenzoic acid, p-toluenesulfonic acid, pyruvic acid, ranelic acid, sarcosine, salicylic acid, sebacic acid, serine, sorbic acid, stearic acid (octadecanoic acid), suberic acid, succinic acid, tartaric acid, terephthalic acid, tetrolic acid, L-threonic acid, thyronine, tricarballylic acid, trichloroacetic acid, trifluoroacetic acid, trimellitic acid, trimesic acid, tyrosine, ulmic acid, valeric acid, vanilic acid and cylohexanecarboxylic acid.

All acids, which FDA has regarded as safe for use in compositions for oral intake, may be used in the present invention.

In one embodiment of the invention, the acid may be a non-chelator of strontium. In yet a further embodiment, the acid may be a monoprotic or a diprotic acid.In another embodiment of the invention, the acid may be a bisphosphonate selected from the group consisting of ibandronate, zoledronate, alendronate, risedronate, ethidronate, chlodronate, tiludronate, minodronate, incadronate, olpadronate and pamidronate and pharmacologically active derivatives of any of the molecules.

In a specific embodiment of the invention, the strontium salt for use according to the invention is water soluble and it may have a water solubility of at least 1 g/l, such as, e.g., at least 5 g/l, at least 10 g/l, at least 20 g/l, at least 30 g/l, at least 40 g/l, at least 50 g/l, at least 60 g/l, at least 70 g/l, at least 80 g/l, at least 90 g/l or about 100 g/l measured at room temperature, i.e. a temperature of 20-25°C.

Other examples for of suitable therapeutically and/or prophylactically active substances belonging to the group of BCBCs are hormone replacement therapy (HRT) containing

estrogen in a daily dose in the range from 0.05 – 2 mg and a pharmaceutically relevant dose of a progesterone receptor agonist in a combined treatment regimen, Estriol as well as other physiological active estrogen metabolites, , Calcitonin, Dihydro-tachysterol, Vitamin D including activated vitamin D_3 (1,25-dihydroxy-cholecalciferol), Vitamin D_2 and Alphacalcidol, parathyroid hormone (PTH)and pharmaceutically active derivatives/fragments thereof, disease modifying anti rheumatic drug (DMARD), such as, e.g. Doxycycline, Chondroitin Sulfate, Methotrexate, Leflounomide (ARAVA®, Aventis), Dimethylnitrosamine, azatriopine, hydroxychloroqine, cyclosporine, minocycline, salazopyrine, penicillamine, aurothiomalate (gold salt), cyclophosphamide, and azathioprine, soluble inhibitors of RANK-ligand such as osteoprotegrin (OPG) or the monoclonal antibody AMG-162, interleukin-1 (IL-1) antagonists, Tumor necrosis factor α (TNF-α) antagonists (such as etanercept, infliximab, onercept, adalimumab, CDP 870), Glucagon like peptide-2 (GLP-2)and derivatives/fragments thereof, inhibitors/antagonists of chloride channel – 7 (CLC-7), inhibitors of cathepsin K, testosterone and selective androgen receptor modulators (SARMs),N-iminoethyl-L-lysine (see US 6,653,350), N,N-dimethyl-1-1-(4-chlorophenyl)cyclobutyl-3-methylbutyl amine hydrochloride (see US 6,232,347), 3,4-Di:alkanoyl-oxy-benzylidene di:alkanoate(s) (EP 395 441), polysulphated cyclodextrins (WO 02/05826), aggrecanase inhibitors (EP 1 081 137), selective MMP-13 inhibitors (EP 935 963), 2,3,3a,4,5,6,7,7a-octahydroindol-2-carboxylic acid (US 2003166706), (6-(5-carboxymethyl-hexyloyl)-2,2-dimethyl-hexanoic acid (see WO 04/017952), glucosamin sulphate and chondroitin sulphate (the group hereinafter referred to as "bone and cartilage beneficial compounds" (or "BCBCs")).

In accordance with a regimen, which would be used according to the invention, it is contemplated that the 5-LOX inhibitors, including compounds of Formula (I), in particular compounds of Formula (II), would be administered in combination with other medications (BCBCs) used on a regularly scheduled basis. It is also envisioned that administration in combinations could assume a number of different forms and still be within the scope of the present invention. Accordingly, the present invention relates to combinations of the 5-LOX inhibitor and the BCBC in the form of two separate compounds. By administering the compounds separately, it is possible to adjust the dosage of each compound independently of the other. Also, it is possible to administer the compounds with different time intervals. Even though the 5-LOX inhibitor and BCBC are administered sequentially, e.g. within a time interval of several hours, days or more, they are still considered to be part of the same treatment.

However, the the 5-LOX inhibitors, such as compounds of Formula (I) and in particular the compound depicted in Formula II might also be formulated with the BCBC into a convenient dosage form, such as an oral tablet, containing all of the drugs forming the combination in a single composition, but as separate compounds.

In another aspect the combination of the 5-LOX inhibitor and the BCBC may be in form of a single compound. In a specific embodiment a 5-LOX compound of e.g. Formula I and in particular Formula II is prepared as a strontium salt, i.e. a composition where the licofelone anions is precipitated from an aqueous solution as a strontium salt.

Varying half-lives for the different drugs could be accommodated by the person skilled in preparing formulations by creating controlled-release forms of said drugs with different release times so that relatively uniform dosing can be achieved.

In a further embodiment of the present invention, a 5-LOX inhibitor may be used in combination with another pharmaceutical agent used for palliative and/or analgesic and/or anti-inflammatory interventions in a patient suffering from an arthritic disease such as RA or OA. In a specific embodiment of the invention such a compound is a corticosteroid. The details and particulars described above and below relating the combination of 5-LOX and a BCBC apply *mutatis mutandis* to a combination of 5-LOX and a corticosteroid.

The present inventors have also found that the beneficial actions of 5-LOX inhibitors and a BCBC are well suited for combination therapies with palliative and/or anti-inflammatory agents commonly used in the medical treatment of patients suffering from arthritis diseases such as RA and OA, as the potential GI protective propensity of the 5-LOX inhibitors enables a reduction in side-effects and/or dose of the palliative and/or anti-inflammatory agent. Accordingly, the invention also relates to a pharmaceutical composition as described above further comprising another palliative and/or analgesic and/or anti-inflammatory agent selected from the group comprising NSAID, COX-2 inhibitors and corticosteroids.

In a specific embodiment the other palliative and/or analgesic and/or anti-inflammatory agent is a glucocorticoid selected from the group consisting of prednisone, dexamethasone, betamethasone and hydrocortisone.

Methods

As mentioned above, the combination of compounds as described herein may be used for the manufacture of medicaments for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain

Accordingly, the present invention relates to a method for the treatment and/or prophylaxis of osteoarthritis, rheumatoid arthritis, osteoporosis or pain in an animal including a mammal in need thereof, the method comprising administering to the animal a 5-LOX inhibitor and a second active substance selected from the group consisting of i) BCBC and ii) corticosteroids as described herein.

The administration of the 5-LOX and the second active substance selected from the group consisting of i) BCBC and ii) corticosteroids may take place simultaneously or sequentially. Even though the 5-LOX inhibitor and the second active substance are administered sequentially, e.g. within a time interval of several hours, days or more, they are still considered to be part of the same treatment.

The animal may be a human or a domestic animal such as a dog (*canis familiaris*), cat (*felix domesticus*), cow (*bos Taurus*), horse (*equus caballus*), donkey or pig (*sus scrofa*).

In a specific embodiment the 5-LOX inhibitor is licofelone and the daily dose of licofelone is from about 100 to about 1000 mg/day such as, e.g., from about 200 to about 500 mg/day.

In another embodiment of the present invention, the BCBC is a strontium containing compound corresponding to 100 – 3000 mg elemental strontium/day is administered to a subject in need thereof. In a specific embodiment a dose of 200 – 1000 mg/day of elemental strontium is given to the subject in need of therapeutic intervention as described in the invention.

In another embodiment the LOX inhibitor is administered in combination with acetyl salicylic acid (ASA), where the daily dose of ASA is in a range of from about 1 to about 3000 mg/day such as, e.g. from 75 – 320 mg/day, such as 75 mg once daily, 81 mg once daily, 160 mg once daily, 300 mg once daily or 160 mg twice daily

Formulations and dosages forms

The present invention relates to a pharmaceutical composition wherein the 5-LOX and i) the BCBC compound or ii) the corticosteroids are contained in a single composition.

The invention also relates to a pharmaceutical composition wherein the 5-LOX and a second active substance selected from the group consisting of i) BCBC and ii) corticosteroids are contained in a kit comprising a first and a second container, the first container comprising the 5-LOX compound and the second container comprising the second active substance.

The package for the single composition or the kit comprises a carton and a container or containersAssociated with said carton or container(s) is printed instructional and informational material, which may be attached to said carton or to said container(s) enclosed in said carton, or displayed as an integral part of said carton or container(s), said instructional and informational material giving instruction for substantially simultaneous or sequential administration of the 5-LOX and the second active substance.. In a preferred embodiment said package comprising carton and container(s) as described above will conform to all regulatory requirements relating to the sale and use of drugs for the treatment of animals, including especially said instructional and informational material.

It is also contemplated that in accordance with the present invention there will further be provided a package of the type described immediately above, comprising a suitable container as described; enclosed in said container an oral dosage form of a 5-LOX compound, such as the compound of Formula (I) together with a BCBC; and associated with said container printed instructional and informational material as above-described.

When the 5-LOX compounds, such as the one of Formula (I) and BCBCs are to be used as active ingredients in the methods and compositions of the present invention, they can be incorporated into standard pharmaceutical dosage forms. Thus, the present invention also relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an amount therapeutically effective of a 5-LOX compound, such as a compound of Formula (I), and a BCBC as above-defined. For example, they are useful when administered in systemic or local, topical, oral or

parenteral applications and for this purpose are combined with the usual pharmaceutical excipients, diluents and adjuvants, e.g., organic and inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols, etc. These pharmaceutical preparations can be employed in a solid form, e.g., as tablets, capsules, and especially in combination with or for admixture with a palatable food item suitable for mammals; or they can be administered in liquid form, e.g., as solutions and elixirs.

Pharmaceutical excipients and adjuvants which can be added include preservatives, antioxidants, antimicrobial agents and other stabilizers; wetting, emulsifying, and suspending agents, and anticaking compounds; fragrance and coloring additives; compositions for improving compressibility, or to create a delayed-, sustained-, or controlled-release of the active ingredient; and various salts to change the osmotic pressure of the pharmaceutical preparation or to act as buffers. Particular dosage forms, which have been used with success, include a 5% mixed-micelle solution of 5-LOX (e.g. Formula I) for intravenous injection, a 3% palatable paste, and oral tablets. Preferred peroral dosage forms for systemic administration are solids, e.g., palatable oral compositions such as fast dissolving palatable wafers, tablets, capsules, caplets, etc., and liquids, e.g., solutions, suspensions, emulsions, etc. Pharmaceutical compositions of special types suitable for oral administration to mammals may be used, and include, but are not limited to such items as an oral paste to be delivered to the back of the tongue of the mammal being treated, a granular form to be delivered through incorporation in the mammal's food, and a chewable form wherein the active ingredient is consumed along with the palatable chew, or a chewable form which may deliver the active ingredient by leaching from the body of the chew which is not consumed, during mastication by the mammal being treated.

However, in a preferred embodiment of the invention the pharmaceutical composition is in the form of a tablet. The tablet may be coated with a coating that enables release of at least part of the 5-LOX and/or the second active substance selected from the group consisting of i) BCBC and ii) corticosteroids, in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the 5-LOX and/or the second active substance contained in the tablet.

The tablet may have a shape that makes it easy and convenient for a patient to swallow, e.g. it may be rounded or have a rod-like shape without any sharp edges.

In a further embodiment the tablet may be designed to be divided into two or more parts.

A medicated feed used as the dosage form could be prepared in accordance with well known principles in the art of formulation, in which the drugs used in the combination were simply present together in a mixture in the feed composition. Such feed composition may be for use in a mammal, such as a dog, cat, pig, horse, cow, goat, donkey, sheep, opossum or rodent or it may be used for other animals such as chickens, parrots, turtles or lizards.

Other administration forms lying within the scope of the present invention comprise parenteral administrations such as intravenous infusion, intra muscular, intra-articular or subcutaneous injections, topical administrations in the form of e.g. creams and lotions, trans-bronchial administration in the form of e.g. a nasal spray an rectal administrations in the forms of e.g. a suppository. As described above, the present invention also contemplates co-administration in which the combination of drugs is achieved by the simultaneous administration of the drugs to be given in combination. Such co-administration could even be by means of different dosage forms and routes of administration. The present invention further contemplates the use of such combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of the drugs involved were maintained in the mammal in need thereof, even though the individual drugs making up the combination were not being administered to said mammal simultaneously. All such combinations would be within the skill of the art to devise and administer. The therapeutically effective amount of a 5-LOX compound, such as a compound of Formula (I), and a BCBC may be administered systemically to said mammal, wherein said systemic administration comprises: (1) injection or infusion into suitable body tissues or body cavities of a pharmaceutical composition containing said compounds in suitable liquid form such as aqueous solutions, emulsions or suspensions for intraarterial, intra- or transdermal (including subcutaneous), or intraspinal especially intrathecal, intra-articular and most commonly intramuscular or intravenous delivery thereof; or for serving as a depot for delivery thereof; (2) instillation into suitable body tissues or cavities of a pharmaceutical composition containing said compounds in suitable solid form, e.g., comprising a matrix

of bio-compatible and bio-erodible materials in which particles of a solid 5-LOX inhibitor and are dispersed, or in which, possibly, globules or isolated cells of a liquid 5-LOX inhibitor and BCBC compounds are entrapped, for serving as a solid implant composition for delayed-, sustained-, and/or controlled-release delivery thereof; or (3) ingestion or administration of a pharmaceutical composition containing said compound in suitable solid or liquid form for transdermal delivery thereof, for instance a transdermal patch or a subepidermal (subcuticular) implant, for peroral delivery thereof.

Said therapeutically effective amount of a 5-LOX inhibitor, such as e.g., a compound of Formula (I), and a BCBC may also be administered locally to said mammal in need thereof, wherein said local administration comprises: (1) injection or infusion into a local site of gastric acid-related condition of a pharmaceutical composition containing said compounds in suitable liquid form for delivery thereof, including components which provide delayed-release, controlled-release, and/or sustained-release of said compound into said local site; or for serving as a depot for delivery thereof wherein said composition provides storage of said compound and thereafter delayed-, sustained-, and/or controlled-release thereof; or (2) instillation of a pharmaceutical composition containing said compound in suitable solid form for serving as a solid implant for delivery thereof, said composition optionally providing delayed-, sustained-, and/or controlled-release of said compound to said local site.

Injections may also be made of pharmaceutical compositions containing 5-LOX inhibitors and the BCBCs where the pharmaceutical composition is in delayed-release, controlled-release, or sustained-release form. These formulations of recognized composition may be a solids, semi-solids, gels or other liquid/solid combinations in which an erodible matrix or series of coatings is used to provide a continuous release of the compounds at a predetermined rate or at variable rates if desired. The terms "extended-release" and "long-acting" as well as others are used to describe these formulations and it is understood that the explicit reference to time refers to the pharmacokinetic properties of the pharmaceutical preparation and in particular to the time from administration of the drug until c_{max} is obtained and until plasma levels of the pharmaceutically active component id decreased below a certain level. All of these employ various combinations of bio-erodible polymers, e.g., various cellulosic polymers, and natural materials, e.g., corn starch and magnesium stearate, to obtain slow and/or uniform dispensing of the compounds contained within the matrix.

The therapeutically effective amount for treating or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain, of 5-LOX inhibitors, such as the compound of Formula (I), and BCBCs is administered to a mammal being treated in an amount expressed as milligrams per kilogram of body weight of said mammal, per day: "mg/kg/day". The expression "per day" as used herein should not be interpreted as necessarily requiring that any particular dosage form be administered on a daily basis to the mammal being treated. The expression "per day" is merely an indication of the smallest convenient but arbitrary segment of time which is being used as part of the overall unit for measuring the dose of gastroprotective and/or analgesic and/or structure modifying compound being administered. The dose, i.e., the therapeutically effective amount of a 5-LOX inhibitor, such as a compound of Formula (I) for treating or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain will usually range from about 0.1 mg/kg/day to about 20.0 mg/kg/day, preferably from about 0.1 mg/kg/day to about 12.0 mg/kg/day, more preferably from about 0.5 mg/kg/day to about 10.0 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 8.0 mg/kg/day. Typical dosage forms and amounts for licofelone (ML3000) would include oral administration of ML3000 at a dose rate of 1 - 50.0 mg/kg/day of body weight, and in a typical clinical setting 200 mg b.i.d.

A dosage form described herein may also be formulated so as to provide controlled-, sustained-, and/or delayed release of the active ingredient(s) from said dosage form.

A useful controlled release dosage form of the 5-LOX inhibitor licofelone (Formula I) in accordance with the present invention is one, which maintains a plasma level greater than 100 ng/mL for most of the day after a single oral dose at 5 mg/kg. Preferred oral controlled release dosage forms of licofelone (ML3000) in accordance with the present invention are ones which maintain a plasma ML3000 concentration greater than 100 ng/mL for a period of time greater than that for which an immediate release dosage form of ML3000 maintains a comparable plasma level, when said immediate release dosage form and controlled release dosage form are administered at the same dose.

Immediate release licofelone (ML3000) dosage forms containing doses of 2.5 and 5 mg/kg maintain a plasma ML3000 concentration above 100 and 200 ng/mL for 8 hours, respectively.

A number of other factors will influence the required dose for optimal treatment of the individual patient, such as body weight, the level and clinical presentation of pain. The skilled physician will know to take these conditions into account when administering the medical treatment according to the present invention to a patient in need thereof.

It is necessary for the skilled professional carrying out the present invention, not only to determine the preferred route of administration and the corresponding dosage form and amount, but said skilled professional must also determine the dosing regimen, i.e., the frequency of dosing. In general terms it is most likely that the choice will be between once-a-day dosing and twice-a-day (b.i.d.) dosing, and that the former will provide more rapid and profound therapy, while the latter will provide less profound but more sustained therapy.

However, this generalization does not take into account such important variables as the specific type of disease involved, the specific therapeutic agent involved and its pharmacokinetics, and the specific patient (mammal) involved. For an approved product in the marketplace, much of this information is already provided by the results of clinical studies carried out to obtain such approval. In other cases, such information may be obtained in a straightforward manner in accordance with the teachings and guidelines contained in the instant specification taken in light of the knowledge and skill of the artisan. The results, which are obtained, can also be correlated with data from corresponding evaluations of an approved product in the same assays.

Other aspects of the invention

Other aspects of the invention appear from the appended claims. The details and particulars described above and relating to a pharmaceutical composition according to the invention apply *mutatis mutandis* to the other aspects of the invention.

The invention will be further illustrated in light of the following examples. However, the examples only tend to illustrate the invention and not to limit its scope in any way.

Examples

Example 1

Licofelone and raloxifene composition

Tablet formulation

Ingredient	Amount (mg)
Raloxifene	30 mg
Licofelone (ML3000)(formula II)	200 mg
Lactose	80 mg
Corn starch (for mixing)	15 mg
Corn starch (for paste)	15 mg
Magnesium Stearate (1%)	10 mg
Total	350 mg.

Raloxifene and liclofelone, lactose and corn starch (for mixing) are blended to uniformity. The cornstarch for paste is suspended in 200 ml of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders (wet granulation). The wet granules are passed through a number 8 hand screen and dried at 80°C. After drying, the granules are lubricated with 1 % magnesium stearate and pressed into a tablet. Such tablets can be administered to a human female subject in need thereof, such as an OA or RA patient, from one to two times daily.

Example 2

Licofelone and alendronate composition

Tablet formulation

Ingredient	Amount (mg)
Alendronate	10 mg
Licofelone (ML3000)(formula II)	200 mg
Lactose	100 mg
Corn starch (for mixing)	15 mg
Corn starch (for paste)	15 mg
Magnesium Stearate (1%)	10 mg
Total	350 mg.

Alendronate and liclofelone lactose and cornstarch (for mixing) is blended to uniformity. The cornstarch for paste is suspended in 200 ml of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders (wet granulation). The wet granules are passed through a number 8 hand screen and dried at 80°C. After drying, the granules are lubricated with 1 % magnesium stearate and pressed into a tablet. Such tablets can be administered to a human subject in need thereof, such as an OA or RA patient, from one to two times daily.

Example 3

Manufacture of strontium licofenate

In a glass-beaker of volume 200 mL, 0.1 mole of the sodium salt of licofelone (formula II) was dissolved in a small volume of water at room temperature. The final volume was 50 mL. In another beaker 0.05 mole $SrCl_2$ ($SrCl_2$ hexahydrate, Sigma-Aldrich 43,966-5) was dissolved in 100 mL of water. This latter solution was slowly decanted into the first solution of the dissolved sodium salt, which resulted in formation of a fine-grained white precipitate. The solution was filtered and allowed to rest at room temperature (22-24°C) for several days until significant amounts of crystallized precipitate of strontium licofenate appeared in the filtrate, and could be dried for used in a pharmaceutical composition according to the present invention.

Example 4

In vitro assessment of dual 5-LOX/COX inhibitors

In order to elucidate potential anti-inflammatory activities and in particular the ability of a compound or mixture of compounds to inhibit of the synthesis of Leukotriene B_4 (LTB_4) and Prostaglandin (PGE_2) by 5-lipoxygenase (5-LOX) and cyclo-oxygenase 1 and 2 (COX 1 and 2) the following in vitro experiment is devised.

Human HL-60 cells, differentiated for 6–8 days with DMSO (1.2% v/v) are used for the 5-LOX assay. The COX activity assays are carried out with purified enzymes, COX 1 (obtained from ram seminal vesicles), COX 2 (obtained from sheep placenta) and with human THP-1 cells, differentiated for 24 h with PMA (50 nM).

The production leukotrienes (LTB_4) and prostaglandins (PGE_2) in the 5-LOX and COX assays are determined by enzyme linked immunoassays obtained from R&D systems and performed basically as described by the manufacturer.

The ability of th3e tested compounds or mixture of compounds to display distinct inhibitory effects on the production of LTB_4 by 5-LOX (IC_{50} values are determined according to determination of the leukotriene and prostaglandin synthesis by the quantitative immunoassays) and on the synthesis of PGE_2 by COX 1 (IC_{50} are determined) and COX 2 enzymes (IC_{50} are determined) forms the basis for classification of the compound. A 5-LOX inhibiting activity is considered to be significant when the IC_{50} is below 10 mM, preferably below 1 mM. The compound or mixture of compounds is said to have a COX-2 specific method of action when the IC_{50} for COX-1 is at least 10 fold lower than the IC_{50} for COX 1.

Example 4

Treatment of OA patients with licofelone and alendronate

The aim of this experiment is to evaluate the combined effects of ML3000 (formula II) and the bisphosphonate alendronate given to patients with a clinical diagnosis of mild to moderate OA. The patients are selected to comprise OA patients with a clinical diagnosis of OA at either the hip and/or knee joints with a well defined clinical presentation of the disease. Pain and function of the patients are evaluated with a standardized scoring system (WOMAC score) at the initiation of the study and after 2, 4 and 6 weeks. The presence of gastric irritations, including ulcers is determined by upper endoscopic examinations performed at baseline and at study termination. The response in the treated patients is compared to the response in a similar placebo treated group.

Study protocol and patients

Briefly described the study cohort consists of patients above 50 years of age (mean about 59 years) with OA of the medial femoro-tibial compartment and/or the hip diagnosed according to the clinical and radiological criteria of the American College of Rheumatology. The patients are recruited at a department of orthopaedic surgery. The severity of their disease corresponds to grade 2 or 3 on the Kellgreen and Lawrence scoring scale, with average disease duration of about years. They are divided in two groups equally sized treated with either 25 mg ML3000 (liclofelone, formula II) and 10 mg alendronate (Fosamax) daily or placebo for six weeks. Urine samples are obtained at baseline and after 12 month as second morning void samples without dietary restrictions.

The primary outcome measures in the trial are disease symptoms as assessed by the Western Ontario and McMasters University osteoarthritis index (WOMAC, VA 3.0 version) performed bi-weekly. As a secondary outcome measures the presence of upper GI damage, as well as biomarkers of bone and cartilage turnover are measured. For the later purpose, urine samples are obtained at baseline and after 2 and 6 weeks and measured for the presence of cartilage degradation products using the CartiLaps assay specific for C-telopeptide fragments of articular cartilage derived collagen type II, and the urine CrossLaps ELISA (CTX-I) specific for osteoclast generated degradation products of bone matrix type I collagen.

CTX-II measurements

Urinary levels of collagen type II C-telopeptide fragments are measured by the CartiLaps ELISA assay. The assay uses a highly specific monoclonal antibody MAbF46 specific for a 6-amino acid epitope (EKGPDP) derived from the collagen type II C-telopeptide. The assay is performed essentially as described by the manufacturer (Nordic Bioscience, Herlev, Denmark). All samples are measured in duplicates. All samples from one individual are measured in the same ELISA plate and two control samples are included on each ELISA plate. Average intra- and inter- assay CV is determined. Three genuine control samples are included on each microtitre plate and if measurements deviate more than ±20% from the predetermined values the plate is re-measured.

The concentration of the CTX-II ELISA (ng/l) is standardized to the total urine creatinine (mmol/l): concentration/creatinine = ng/mmol. Creatinine concentration is measured using a Cobas MIRA analyzed according to the manufactures instructions (Roche Diagnostics, Basel, Switzerland).

Claims

1. Use of a combination of a 5-LOX inhibitor and a "bone and cartilage beneficial compound" ("BCBC") for the manufacture of a medicament for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain, including joint pain in an animal in need thereof.

2. Use according to claim 1, wherein the 5-LOX inhibitor is licofelone or a pharmaceutically acceptable salt or derivative thereof.

3. Use according to claim 1 or 2, wherein the BCBC is selected from the group consisting of bisphosphonates, strontium containing compounds, glucosamine, DMARDs and SERMs.

4. Use according to claim 3, wherein the BCBC is a bisphosphonate selected from the group consisting of ibandronate, zoledronate, alendronate, risedronate, ethidronate chlodronate, tiludronate and pamidronate.

5. Use according to claim 3, wherein the strontium containing compound is an organic strontium salt.

6. Use according to claim 5, wherein the strontium salt is selected from the group consisting of strontium malonate, strontium succinate, strontium fumarate, strontium pyrovate, strontium carbonate, strontium oxalate, strontium salicylate, strontium ascorbate, strontium aspartate in either L and/or D-form, strontium glutamate in either L- and/or D-form, strontium pyruvate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate and strontium ranelate, strontium acetyl salicylate, strontium citrate, strontium ibuprofenate, strontium methotrexate, strontium alendronate, strontium ibandronate, strontium lactate, strontium flubiprofenate, strontium ketoprofenate, strontium phorbol 12,13-didecanoate 20-homovanillate, strontium indomethacinate, strontium carprofenate, strontium naproxenate, strontium acetyloxy-benzoate, strontium 2-Iminopiperidine, strontium salsalate and strontium sulfasalazinate and strontium threonate.

7. Use according to claim 3, wherein the BCBC is a selective estrogen receptor modulator (SERM) selected from the group consisting of raloxifene, arzoxifene,

droloxifene, tamoxifen, 4-hydroxy-tamoxifen, 4'-iodotamoxifen, toremifene, (deaminohydroxy)-toremifene, chlomiphene, levormeloxifene, ormeloxifene, chroman derivatives, coumarin derivatives, idoxifene, nafoxidine, TAT-59, LY-353381, CP-336156, MDL-103323, EM-800, ICI-182,ICI 183,780, ICI 164,384, ICI 183,780, ICI 164,384, diethylstilbesterol, genistein, nafoxidine, nitromifene citrate, moxesterol, diphenol hydrochrysene, erythro-MEA, allenolic acid, equilin-3-sulphate, cyclophenyl, chlorotrianisene, ethamoxytriphetol, lasofoxifene, bazedoxifene, genistein, tibolone, ospemifene, tesmilifene, droloxifene, panomifene, zindoxifene, meproxifene and faslodex.

8. Use according to claim 1 or 2, wherein the BCBC is selected from the group comprising hormone replacement therapy (HRT), Estriolas well as other physiological active estrogen metabolites, Calcitonin, Dihydro-tachysterol, Vitamin D including activated vitamin D_3 (1,25-dihydroxy-cholecalciferol), Vitamin D_2 and Alphacalcidol, parathyroid hormone (PTH) and pharmaceutically active derivatives/fragments thereof, disease modifying anti rheumatic drug (DMARD), osteoprotegrin (OPG) as well as other antagonists/inhibitors of RANK-ligand (such as AMG 162), interleukin-1 (IL-1) antagonists, Tumor necrosis factor α (TNF-α) antagonists (such as etanercept, infliximab, onercept, adalimumab, CDP 870), Glucagon like peptide – 2 (GLP-2) and derivatives/fragments thereof, inhibitors/antagonists of chloride channel – 7 (CLC-7), inhibitors of cathepsin K, testosterone and selective androgen receptor modulators (SARMs), N-iminoethyl-L-lysine, N,N-dimethyl-1-1-(4-chlorophenyl)cyclobutyl-3-methylbutyl amine hydrochloride, 3,4-Di:alkanoyl-oxy-benzylidene di:alkanoate(s), polysulphated cyclodextrins, aggrecanase inhibitors, selective MMP-13 inhibitors, 2,3,3a,4,5,6,7,7a-octahydroindol-2-carboxylic acid, (6-(5-carboxymethyl-hexyloyl)-2,2-dimethyl-hexanoic acid, glucosamin sulphate and chondroitin sulphate.

9. Use according to claim 1 or 2, wherein the BCBC is glucosamine sulphate

10. Use according to any of the preceding claims, wherein the combination of the 5-LOX inhibitor and the BCBC is in the form of two separate compounds.

11. Use according to any of claims 1-9, wherein the combination of the 5-LOX inhibitor and the BCBC is in form of a single compound.

12. Use according to claim 11, wherein the single compound is a strontium licofelone salt.

13. Use according to any of the preceding claims, wherein the combination further comprises a palliative and/or analgesic and/or anti-inflammatory agent selected from the group comprising NSAID, COX-2 inhibitors and corticosteroids.

14. Use according to claim 13, wherein the palliative and/or analgesic and/or anti-inflammatory agent is a glucocorticoid selected from the group consisting of prednisone, dexamethasone, betamethasone and hydrocortisone.

15. Use of a combination of a 5-LOX inhibitor and a corticosteroid for the manufacture of a medicament for treating and/or preventing osteoarthritis, rheumatoid arthritis, osteoporosis or pain in an animal in need thereof.

16. A pharmaceutical composition comprising a combination of a 5-LOX inhibitor and a BCBC as defined in any of claims 1-14 together with one or more pharmaceutically acceptable excipients.

17. A pharmaceutical composition according to claim 16, wherein the 5-LOX and the BCBC compound are contained in a single composition.

18. A pharmaceutical composition according to claim 16, wherein the 5-LOX and the BCBC are contained in a kit comprising a first and a second container, the first container comprising the 5-LOX compound and the second container comprising the BCBC.

19. A pharmaceutical composition according to any of claims 16-18, comprising instructions for substantially simultaneous or sequential administration of the 5-LOX and the BCBC.

20. A pharmaceutical composition according to any of claims 16-19 in the form of a tablet.

21. A pharmaceutical composition according to claim 20, wherein the tablet is coated with a coating that enables release of at least part of the 5-LOX and/or the second

active substance selected from the group consisting of BCBC in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the 5-LOX and/or the second active substance contained in the tablet.

22. A pharmaceutical composition according to claim 20 or 21, wherein the tablet has a shape that makes it easy and convenient for a patient to swallow.

23. A pharmaceutical composition according to any of claims 20-22, wherein the tablet has a rounded or a rod-like shape without any sharp edges.

24. A pharmaceutical composition according to any of claims 20-23, wherein the tablet is designed to be divided into two or more parts.

25. A method for the treatment and/or prophylaxis of osteoarthritis, rheumatoid arthritis, osteoporosis or pain in an animal including a mammal in need thereof, the method comprising administering to the animal a combination of a 5-LOX inhibitor and a BCBC.

26. A method according to claim 25, wherein the combination of the 5-LOX inhibitor and the BCBC is as defined in any of claims 1-24.

27. A method for the treatment and/or prophylaxis of osteoarthritis, rheumatoid arthritis, osteoporosis or pain in an animal including a mammal in need thereof, the method comprising administering to the animal a combination of a 5-LOX inhibitor and a corticosteroid.

28. A method according to any of claims 25-27, wherein the animal is a human.

29. A method according to any of claims 25-27, wherein the animal is a domestic animal such as a dog (*canis familiaris*), cat (*felix domesticus*), cow (*bos Taurus*), horse (*equus caballus*), donkey or pig (*sus scrofa*).

30. A method according to any of claims 25-29, wherein the 5-LOX inhibitor is licofelone and the daily dose of licofelone is from about 100 to about 1000 mg/day such as, e.g., from about 200 to about 500 mg/day.

31. A method according to any of claims 25-30, wherein administration of the 5-LOX and the BCBC or corticosteroid takes place simultaneously or sequentially.