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(54) **Title:** COMPOSITIONS COMPRISING AN OXISOQUINOLINE METHYLBENZAMIDE AND A POLYMER

(57) **Abstract:** A pharmaceutical depot comprising (i) N-ethyl-3-[7-{2- [ethyl(methyl)amino] ethoxy } -4-methyl- 1 -oxisoquinolin-2(1H)-yl] -4-methylbenzamide, or a pharmaceutically-acceptable salt thereof, as a pharmaceutical agent (PA) and (ii) a polymer which degrades to create an acidic microclimate, wherein the PA is released from the polymer upon polymer degradation.

COMPOSITIONS COMPRISING AN OXISOQUINOLINE METHYLBENZAMIDE AND A POLYMER

The present invention relates to a pharmaceutical depot comprising N-ethyl-3-[7-
{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-
methylbenzamide or a pharmaceutically-acceptable salt thereof, and to uses of the
5 pharmaceutical depot.

WO2006/067444 discloses quinazolinone derivatives, including N-ethyl-3-[7-{2-
[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide,
and pharmaceutically-acceptable salts thereof, and teaches that the quinazolinone
derivatives are inhibitors of the production of cytokines such as Tumour Necrosis Factor
10 (hereinafter TNF), for example TNF α , and various members of the interleukin (hereinafter
IL) family, for example IL-1, IL-6 and IL-8 (especially IL-1). In particular, and without
wishing to imply that the quinazolinone derivatives disclosed in WO2006/067444 possess
pharmacological activity only by virtue of an effect on a single biological process, it is
believed that the quinazolinone derivatives inhibit the effects of cytokines by virtue of
15 inhibition of the enzyme p38 kinase. p38 kinase (otherwise known as cytokine suppressive
binding protein, hereinafter CSBP) and reactivating kinase (hereinafter RK) is a member of
the mitogen-activated protein (hereinafter MAP) kinase family of enzymes which is known
to be activated by physiological stress such as that induced by ionising radiation, cytotoxic
agents, and toxins, for example endotoxins such as bacterial lipopolysaccharide, and by a
20 variety of agents such as the cytokines, for example TNF α and IL-1. It is known that p38
kinase phosphorylates certain intracellular proteins that are involved in the cascade of
enzymatic steps which leads to the biosynthesis and excretion of cytokines such as TNF α
and IL-1.

The quinazolinone derivatives disclosed in WO2006/067444 therefore are believed
25 to be useful in the treatment of diseases or medical conditions in which excessive
production of cytokines occurs, for example excessive production of TNF α or IL-1. Such
diseases and medical conditions include inflammatory and allergic diseases, such as
inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout).

For the treatment of diseases and medical conditions such as inflammation of the
30 joints, it would be desirable to administer the quinazolinone derivative directly to the site
(such as the joint) requiring treatment, preferably so as to achieve a controlled- and/or
sustained-release of the quinazolinone derivative at that site. Thus, there exists a need for

a formulation or composition comprising N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide, or a pharmaceutically-acceptable salt thereof, in a form suitable for such administration, for example for a pharmaceutical depot.

5 Although WO2006/067444 suggests that the quinazolinone derivatives disclosed therein may be included in a pharmaceutical composition, for example in a form suitable for oral or topical use, for administration by inhalation or insufflation, or for parenteral administration, there is no disclosure in WO2006/067444 of a pharmaceutical depot comprising a quinazolinone derivative as disclosed therein, let alone of such a
10 pharmaceutical depot comprising N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide, or a pharmaceutically-acceptable salt thereof.

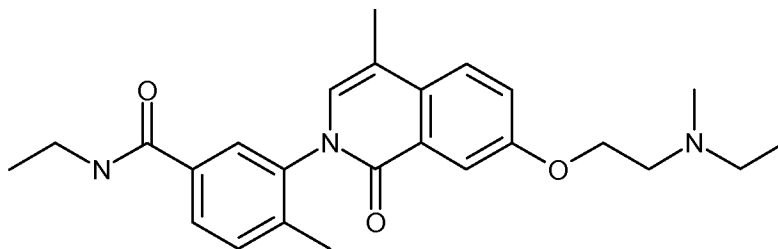
 According to the present invention, there is provided a pharmaceutical depot comprising (i) N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-
15 2(1H)-yl]-4-methylbenzamide, or a pharmaceutically-acceptable salt thereof, as a pharmaceutical agent (PA) and (ii) a polymer which degrades to create an acidic microclimate, wherein the PA is released from the polymer upon polymer degradation.

 The IUPAC name for N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide is believed to be N-ethyl-3-[7-[2-
20 [ethyl(methyl)amino]ethoxy]-4-methyl-1-oxo-2-isoquinolyl]-4-methyl-benzamide

 In the pharmaceutical depot of the present invention, the pharmaceutical agent (hereinafter the PA) is N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide, or a pharmaceutically-acceptable salt thereof. Thus, references herein to the PA include the compound N-ethyl-3-[7-{2-
25 [ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide *per se*, as well as pharmaceutically-acceptable salts thereof.

 As the skilled person would appreciate, a pharmaceutical depot is a composition that releases a PA, especially a pharmaceutically effective amount of a PA (herein N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-
30 methylbenzamide or a pharmaceutically-acceptable salt thereof) over time, so as to provide for the controlled- and/or sustained-release administration of the PA comprised therein.

N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide has the structure:



and is disclosed in Example 26 of WO2006/067444.

5 Suitable pharmaceutically-acceptable salts of N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide for including in the pharmaceutical depot of the present invention are based on reasonable medical judgement as being suitable for administration to a subject, for example a warm-blooded animal such as man, without undesirable pharmacological activities and without
10 undue toxicity. Suitable pharmaceutically-acceptable salts include acid-addition salts, for example acid addition salts with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, citric, maleic, tartaric, fumaric, hemifumaric, succinic, hemisuccinic, mandelic, methanesulfonic, dimethanesulfonic, ethane-1,2-sulfonic, benzenesulfonic, salicylic or 4-toluenesulfonic acid.

15 The N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide and pharmaceutically-acceptable salts thereof may be synthesised from suitable starting materials using standard procedures of organic chemistry, for example as discussed in WO-A-2005/042502.

The pharmaceutical depot of the present invention enables the administration of the
20 PA using a controlled- and/or sustained-release formulation so as to maintain a therapeutic level of the PA over an extended period of time. This is advantageous because it reduces the frequency of dosing and provides a convenient mode of administration of the PA, which is particularly desirable for the administration of the PA directly into the joint, i.e. by intra-articular administration. Controlled- and/or sustained-release formulations also
25 can reduce the severity and frequency of any undesirable side effects associated with a particular PA. Improvements in the convenience of administration and reduced occurrence and severity of side effects in turn enhance patient compliance.

Many compounds that represent a PA are found to be unsuitable for including in pharmaceutical depots, primarily due to factors such as instability of the compounds in the formulations required for controlled- and/or sustained-release and/or for intra-articular administration. The present inventors have surprisingly found that the PA included in the pharmaceutical depot of the present invention is hydrolytically stable in the acidic microclimate created upon the degradation of the polymer included therein and therefore that the PA is suitable for including in the pharmaceutical depot. The PA was identified as being suitable for including in a pharmaceutical depot according to a method disclosed in a co-pending patent application filed by AstraZeneca AB on the same day as the present application. The method comprises the step of performing a screening cascade on the PA, wherein the screening cascade includes the step(s) of conducting a low concentration hydrolytic stress test on the PA and/or conducting a high concentration hydrolytic stability assay on the PA.

Furthermore, the present inventors have surprisingly found that the PA included in the pharmaceutical depot of the present invention can be provided at a sustained high local concentration of the PA at a site of administration, for example at a joint, to provide for the effective controlled- and/or sustained-release of the PA. In other words, the pharmaceutical depot is effective to slowly release the PA so as to achieve a long acting effect.

Advantageously, the PA may be included in the pharmaceutical depot of the present invention without any chemical modification being required prior to its inclusion therein.

As the skilled person would appreciate, a "pharmaceutical agent" (or PA) is an agent that causes a pharmacological effect in a subject to which it is administered, for example in a warm-blooded animal such as man, for example so as to treat or prevent a disease or medical condition. As discussed above, the PA in the pharmaceutical depot of the present invention is N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide, or a pharmaceutically-acceptable salt thereof, which is believed to cause a pharmacological effect by means of the inhibition of the effects of cytokines (such as TNF, for example TNF α , and various members of the IL family, for example IL-1, IL-6 and IL-8) by virtue of inhibition of the enzyme p38 kinase.

The PA that is included in the pharmaceutical depot of the present invention is effective in the treatment of an inflammatory disease or condition, for example a condition caused by inflammation of a joint, such as osteoarthritis in which both acute and chronic synovial inflammation may occur. Osteoarthritis (also known as degenerative arthritis or degenerative joint disease) is the most common form of arthritis, with many sufferers worldwide and improved formulations for delivery of PAs for treatment of osteoarthritis are highly desirable.

As the skilled person will appreciate, the PA is present in the pharmaceutical depot of the present invention in a therapeutically effective amount. A “therapeutically effective amount” is any amount of the PA (for example as contained in the pharmaceutical depot) which, when administered to a subject suffering from a disease or medical condition against which the PA is effective, causes reduction, remission, or regression of the disease or medical condition.

The therapeutically effective amount of the PA that is included in the pharmaceutical depot will necessarily vary depending upon the nature and severity of the disorder to be treated and the particular patient treated, according to well known principles of medicine. Additionally, the therapeutically effective amount of the PA that is included in the pharmaceutical depot will necessarily vary according to the desired controlled- and/or sustained-release profile, for example depending on the period of time over which release of the PA is required and the concentration of PA desired over that time.

In addition to the PA, the pharmaceutical depot of the present invention comprises a polymer which degrades to create an acidic microclimate, for example a polymer which degrades in the presence of water to create an acidic microclimate. By this, we mean a polymer that degrades or breaks down chemically to provide an acidic pH in a small, localised area (such as a joint) to which the pharmaceutical depot is administered.

Preferably, the acidic pH is essentially uniform in the localised area and differs from the surrounding area, which may be at a physiological pH (typically of about pH 7.4). The acidic pH is typically a pH of less than about 7.4, for example a pH in the range of from about 1 to about 7, such as from about 3 to about 7; conveniently from about 1 to less than 7 or from about 3 to less than 7.

Typically, the PA is dispersed or encapsulated in the polymer, such that the PA is continually released from the polymer as the polymer degrades over time to create the

acidic microclimate. The PA that is included in the pharmaceutical depot of the present invention has been found to be hydrolytically stable in the acidic microclimate that is created by the degradation of the polymer. The release of the PA from the polymer provides for the controlled- and/or sustained-release of the PA from the pharmaceutical depot into a subject, for example a warm-blooded animal such as man, to which the pharmaceutical depot is administered. Preferably, a high local concentration (i.e. in the area to which the pharmaceutical depot is administered, such as a joint) to elicit the desired therapeutic effect and a low systemic concentration to mitigate against any undesired systemic toxicity of the PA is achieved upon polymer degradation and release of the PA. Thus, the pharmaceutical depot delivers the PA to the subject at concentrations effective for treatment of the particular disease or medical condition over a sustained period of time.

Any suitable polymer may be used in the pharmaceutical depot of the present invention, provided that the polymer degrades to create an acidic microclimate, i.e. upon administration to a subject, for example to a warm-blooded animal such as man, and is biodegradable and biocompatible.

As the skilled person would appreciate, by the term "biocompatible" we mean a material that is compatible with living tissue or a living system by not being toxic, injurious, or physiologically reactive and not causing immunological rejection.

By the term "biodegradable" we mean a material that is degraded in a biological environment.

For example, a polymer may be "biodegradable" such that the entire polymer biodegrades and does not need to be removed after use, i.e. once all of the PA has been released. Such polymers may comprise hydrolysable and enzymatically cleavable ester linkages that break down under biological conditions (for example in the presence of water and biological enzymes found in tissues of warm-blooded animals such as humans) to produce non-toxic, biocompatible and/or biodegradable products. Alternatively, a polymer may be "biodegradable" by virtue of having a finite half-life in a biological environment. For example the polymer may have a half-life of from 1 to 12 months, such as from 1 to 6 months.

Typically, the polymer includes at least one acidic functional group or at least one functional group that may react to produce an acidic functional group, i.e. which acidic functional group is a group that is capable of donating a proton to a basic functional group

such as an amine. Examples of suitable acidic functional groups include carboxylic acid groups (i.e. $-\text{CO}_2\text{H}$) and sulfonic acid groups (i.e. $-\text{S}(\text{O})_2\text{OH}$). Examples of suitable functional groups that may react to produce an acidic functional group include esters (i.e. $\text{RC}(\text{O})\text{OR}$, where R may represent alkyl or aryl), which esters may react with water to produce a corresponding carboxylic acid group and an alcohol.

Preferably, the polymer is selected so as to degrade and release the PA over a period of from about 30 to 90 days. For example, the polymer may degrade and release the PA over a period of about 30, about 60 or about 90 days. For example, the polymer may degrade and release the PA over a period of about 120, about 150 or about 180 days.

Suitable polymers include a polyester of a hydroxyfatty acid and derivatives thereof (for example polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly- β -hydroxybutyric acid, ϵ -capro-lactone ring opening polymer, lactic acid-glycolic acid copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethyleneglycol copolymer or polyglycolic acid-polyethyleneglycol copolymer), a polymer of an alkyl α -cyanoacrylate (for example poly(butyl 2-cyanoacrylate)), a polyalkylene oxalate (for example polytrimethylene oxalate or polytetramethylene oxalate), a polyortho ester, a polycarbonate (for example polyethylene carbonate or polyethylenepropylene carbonate), a polyortho-carbonate, a polyamino acid (for example poly- γ -L-alanine, poly- γ -benzyl-L-glutamic acid or poly- γ -methyl-L-glutamic acid), a hyaluronic acid ester, and the like, and one or more of these polymers can be used.

If the polymers are copolymers they may be any of random, block and graft copolymers. When the above α -hydroxycarboxylic acids, hydroxydicarboxylic acids and hydroxytricarboxylic acids have optical activity in their molecules, any one of D-isomers, L-isomers and DL-isomers may be used. Among others, α -hydroxycarboxylic acid polymer (preferably lactic acid-glycolic acid polymer), its ester, poly- α -cyanoacrylic acid esters, etc. are preferred, and lactic acid-glycolic acid copolymer (also referred to as poly(lactide-co-glycolide) or poly(lactic-co-glycolic acid), and hereinafter referred to as PLGA) are most preferred. Thus, in one aspect the polymer is PLGA. As used herein, the term PLGA includes polymers of lactic acid (also referred to as polylactide, poly(lactic acid), or PLA).

Suitable PLGA polymers may have a molar ratio of lactic acid:glycolic acid in the range of 100:0 to 50:50, conveniently in the range of 95:5 to 50:50. For example, the PLGA polymer may have a molar ratio of lactic acid:glycolic acid of 95:5 or of 50:50.

Suitable PLGA polymers may have a block length in the range of from 1 to 5, preferably of from 2 to 4.

Suitable PLGA polymers may have a weight-average molecular weight of from about 3,000 to about 50,000, preferably of about 4,000 to about 40,000, and more preferably of about 5,000 to about 30,000 Daltons. The degree of dispersion (weight-average molecular weight/number-average molecular weight, hereinafter referred to as polydispersity) may range from about 1.2 to about 4.0, preferably from about 1.3 to about 3.5.

As the skilled person would appreciate, the weight-average molecular weight, number-average molecular weight and polydispersity may be determined by any suitable method or means, for example by size exclusion chromatography (SEC) with narrow polydispersity polystyrene reference substances with peak molecular weights of 1,000,000, 130,000, 50,000, 20,000, 10,000, 5,000, 2,000, and 580 respectively. The determination may be carried out using a SEC column Mixed Bed D 5 μ m (manufactured by Polymer Laboratories Ltd., UK) and using 5% methanol in tetrahydrofuran as the mobile phase.

The PLGA may be prepared by any conventional method, or may be commercially available. For example, PLGA can be produced by ring-opening polymerisation with a suitable catalyst from cyclic lactide, glycolide, etc. (see Encyclopedic Handbook of Biomaterials and Bioengineering Part A: Materials, Volume 2, Marcel Dekker, Inc. (1995); EP-0058481B2; Effects of polymerization variables on PLGA properties: molecular weight, composition and chain structure and Dorta et al, Int. J. Pharm., 100, pp 9-14 (1993)).

It is believed that PLGA is biodegradable by means of the degradation of the entire solid polymer composition, due to the break down of hydrolysable and enzymatically cleavable ester linkages under biological conditions (for example in the presence of water and biological enzymes found in tissues of warm-blooded animals such as humans) to form lactic acid and glycolic acid. Both lactic acid and glycolic acid are water-soluble, non-toxic products of normal metabolism, which may further biodegrade to form carbon dioxide and water.

In other words, PLGA is believed to degrade by means of hydrolysis of its ester groups in the presence of water, for example in the body of a warm-blooded animal such as man, to produce lactic acid and glycolic acid and create the acidic microclimate. Lactic and glycolic acid are by-products of various metabolic pathways in the body of a warm-blooded animal such as man under normal physiological conditions and therefore are well tolerated and produce minimal systemic toxicity.

The polymer is provided in any suitable form in which the PA may be dispersed or encapsulated therein prior to the degradation of the polymer. For example, the pharmaceutical depot may comprise the polymer in the form of microparticles or nanoparticles, or in a liquid form, with the PA dispersed or encapsulated therein.

Suitable microparticles typically have an average particle size in the range of 0.1 to 1000 μm , preferably 1 to 750 μm and more preferably 10 to 500 μm .

Suitable nanoparticles typically have an average particle size in the range of 1 to 2000nm, preferably 10 to 1000nm, and more preferably 50 to 500nm.

In particular, the microparticles are substantially spherical in shape (i.e. are microspheres).

When the polymer is in the form of microparticles, the microparticles may be prepared using any appropriate method, such as by a solvent evaporation or solvent extraction method. For example, in the solvent evaporation method, the PA and the polymer may be dissolved in a suitable volatile organic solvent (for example a ketone such as acetone, a halogenated hydrocarbon such as chloroform or methylene chloride, a halogenated aromatic hydrocarbon, a cyclic ether such as dioxane, an ester such as ethyl acetate, a nitrile such as acetonitrile, or an alcohol such as ethanol) and dispersed in an aqueous phase containing a suitable emulsion stabiliser (for example polyvinyl alcohol, PVA). The organic solvent is then evaporated to provide microparticles with the PA encapsulated therein. In the solvent extraction method, the PA and polymer may be dissolved in a polar solvent (such as acetonitrile, dichloromethane, methanol, ethyl acetate or methyl formate) and then dispersed in an aqueous phase (such as a water/PVA solution). An emulsion is produced to provide microparticles with the PA encapsulated therein. Spray drying is an alternative manufacturing technique for preparing the microparticles.

In one aspect, the pharmaceutical depot may comprise the polymer (such as PLGA as described above) in the form of microparticles with the PA encapsulated therein. For example, the pharmaceutical depot may comprise a PLGA polymer having a lactide:glycolide molar ratio of 50:50 in the form of microparticles with the PA
5 encapsulated therein. Such a pharmaceutical depot may be suitable for controlled- and/or sustained-release of the PA over a period of about 30 days. Further, as an example, the pharmaceutical depot may comprise a PLGA polymer having a lactide:glycolide molar ratio of 95:5 in the form of microparticles with the PA encapsulated therein. Such a pharmaceutical depot may be suitable for controlled- and/or sustained-release of the PA
10 over a period of from about 60 to 90 days. Such a pharmaceutical depot may be suitable for controlled- and/or sustained-release of the PA over a period of up to 120, up to 150 or up to 180 days.

The pharmaceutical depot may comprise the PA and the polymer in any suitable amounts. For example, the pharmaceutical depot may comprise from 1 to 30% by weight
15 of the PA and from 70 to 99% by weight of the polymer.

For example, when the pharmaceutical depot of the present invention comprises PLGA microparticles, the PLGA may be present in an amount ranging from about 70% to about 99% by weight of the microparticles. This amount of PLGA may be used when about 1% to about 30% by weight of the PA is loaded into the microparticles. Also, this
20 amount of the polymer is calculated for the microparticles comprising the PA and the PLGA, but not other pharmaceutical excipients, for example used for suspending the microparticles before lyophilisation. The PLGA may be used in an amount of from about 88% to about 90% by weight of the microparticles, when about 10% to about 12% by weight of the PA is loaded in the microparticles. The proportion of the polymer typically
25 depends on the strength of pharmacological activity of the PA used and the rate and duration of release of the PA.

The pharmaceutical depot may further comprise a suitable pharmaceutically-acceptable diluent or carrier, which should be water miscible. Suitable diluents or carriers include, for example, suitable porosity-modifying agents (such as sodium chloride) that
30 rapidly dissolve leaving pores and/or suitable plasticisers to modify the rate of diffusion and/or reduce porosity (see, for example, Burgess, D. J., Hickey, A. J., *Drugs and the Pharmaceutical Sciences* (149) pp 305-353).

The diluent or carrier may be included in the pharmaceutical depot in any suitable amount. For example, the diluent or carrier may be included in an amount of from 0 to 50% by weight of the total composition. Preferably, the pharmaceutical depot does not contain an additional diluent or carrier.

5 The pharmaceutical depot typically is provided for local delivery at a desired site of treatment, such as at a joint.

The pharmaceutical depot may be formulated for administration by injection, such as by intra-articular injection. Thus, in particular, the pharmaceutical depot may be provided in an injectable form (i.e. as an injectable pharmaceutical depot). By “injectable”
10 we mean that the pharmaceutical depot can be drawn into a syringe and injected into a subject, for example a warm-blooded animal such as man, without causing adverse effects due to the presence of solid material in the depot. For example, the pharmaceutical depot may be injectable into a joint, such as an inflamed joint. In other words, there is provided a pharmaceutical depot for intra-articular injection. Suitable joints include knee, hip,
15 shoulder, ankle, elbow, wrist, toe, finger and spinal facet joints. The pharmaceutical depot remains in the joint after injection thereto and achieves a local delivery of the PA in a controlled and sustained manner, preferably over a period of time ranging from 30 to 90 days. Pharmaceutical depots that achieve a local delivery of the PA in a controlled and sustained manner over a period of up to 90 days are advantageous because this minimises
20 the number of local injections required to be made to a joint, which enables the depots to meet current recommendations for intra-articular therapy which advise not to exceed three to four small (about 2 ml) local injections into a joint per year due to possible adverse effects.

The pharmaceutical depot may be formulated for injection into the intra-articular
25 space of an affected joint, for example into the synovial fluid-containing portion of an affected joint, such as at an osteoarthritis site. As skilled person would appreciate the synovial fluid is contained within a central joint space defined by opposing bones of the joints. The present inventors have found that upon injection of the pharmaceutical depot into the synovial fluid, the PA is released and substantially enters the surrounding tissue
30 with only minor amounts entering the blood stream, i.e. to achieve a high local concentration of PA in the area to which the pharmaceutical depot is administered (such as a joint) and a low systemic concentration. Additionally, the pharmaceutical depot provides

an acceptable “burst” (i.e. release of PA) on the first day following administration, which is advantageous in use and is unexpected in view of the teaching of the prior art, such as in US-6,217,911, which teaches that little or no burst release is preferred. The efficient release profile provided by the pharmaceutical depot of the present invention would not have been predicted from the prior art and aids in the effectiveness of the pharmaceutical depot.

Preferably, the pharmaceutical depot provides a sustained high local concentration of the PA in an articular joint upon administration by injection thereto, such as above 100 nanomolar.

Injectable pharmaceutical depots may comprise a suspension or dispersion of the PA and polymer combination in a pharmaceutically-acceptable diluent or carrier, which should be water miscible. Suitable diluents or carriers include aqueous diluents or carriers such as an isotonic aqueous solution of a viscosity improver (such as sodium carboxymethylcellulose), a surfactant (such as polysorbate 80) and/or a tonicity adjuster (such as sodium chloride). Injectable pharmaceutical depots may comprise further active agents, such as a local anaesthetic.

The pharmaceutical depot of the present invention may be formulated for human medicine or veterinary use. For example, there may be provided a pharmaceutical depot formulated for intra-articular injection for human medicine or veterinary use.

The present invention further provides a pharmaceutical depot as defined herein for use in inhibiting the effects of cytokines, for example by virtue of the inhibition of the enzyme p38 kinase, in a subject.

According to another aspect of the present invention, there is provided the use of a pharmaceutical depot as defined herein for inhibiting the effects of cytokines, for example by virtue of the inhibition of the enzyme p38 kinase, in a subject.

According to another aspect of the present invention, there is provided the use of a pharmaceutical depot as defined herein in the manufacture of a medicament for use in inhibiting the effects of cytokines, for example by virtue of the inhibition of the enzyme p38 kinase, in a subject.

According to another aspect of the present invention, there is provided a method for inhibiting the effects of cytokines, for example by virtue of the inhibition of the enzyme

p38 kinase, in a subject in need thereof, which method comprises administering to said subject a pharmaceutical depot as defined herein.

The present invention further provides a pharmaceutical depot as defined herein for use in the prevention or treatment of an inflammatory disease, such as osteoarthritis, in a subject.

According to another aspect of the present invention, there is provided the use of a pharmaceutical depot as defined herein for the prevention or treatment of an inflammatory disease, such as osteoarthritis, in a subject.

According to another aspect of the present invention, there is provided the use of a pharmaceutical depot as defined herein in the manufacture of a medicament for use in the prevention or treatment of an inflammatory disease, such as osteoarthritis, in a subject.

According to another aspect of the present invention, there is provided a method for the prevention or treatment of an inflammatory disease, such as osteoarthritis, in a subject in need thereof, which method comprises administering to said subject a pharmaceutical depot as defined herein.

The "subject" to which the pharmaceutical depot of the invention is to be administered is an animal, especially a warm-blooded animal, such as a domestic animal or man, particularly man.

The invention will now be illustrated by the following non-limited examples.

Example 1

A pharmaceutical depot was prepared that comprised PLGA microparticles encapsulating N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide as the PA.

(i) Microparticle Preparation

60 mg of N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide and 340 mg of PLGA (molar lactide:glycolide ratio of 50:50 and a molecular weight of 19.5 KD) were dissolved in dichloromethane/Methanol 3:1 ratio (2 ml). This solution was then dispersed in an aqueous phase of 0.5% PVA w/v under high shear to form an emulsion. The high shear was created by using a static mixer with a high flow rate of aqueous phase e.g. 1000mls/min. The resulting emulsion was added to water (1250 ml) at 30°C and stirred at 500rpm (using a Heidolph RZR1 stirrer) for 1 hour. The

resulting suspension was cooled in an ice bath and the microparticles allowed to sediment for 45 minutes. Approximately 90% (by volume) of the supernatant was removed, taking care not to disturb the sedimented microparticles. Water (1 L) was added and the process repeated. Approximately 95% (by volume) of the supernatant was removed and the microparticles transferred to a glass test tube. The wash/sedimentation cycle was repeated a further 2 times and the microparticles were transferred to a freeze dry vial with the minimum volume of water. The vial was flash frozen and the microparticles were freeze-dried for 48 hours.

(ii) *In Vitro* Release Protocol

0.8 mg of microparticles containing N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide in 50:50 PLGA were suspended in PBS containing 0.1% w.v Tween 80 (20 ml). The resultant slurry was kept static at 37°C and samples were taken at 24 hours by removal of media (1 ml) followed by addition on media (1 ml) to ensure the volume of media within the experiment remained constant.

Samples were taken at regular intervals (see Figure 1) until the depot was no longer releasing N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide and analysed by HPLC. The results are shown in Table 1 below.

Table 1

Polymer lactide:glycolide molar ratio / MW (KD)	PA load (% by weight)	Encapsulation Efficiency (%)	In vitro Burst (%)	In vitro Release (%)
50:50/ 19.5	6.82	45.93	5.67	Day 14 – 83.92

The microparticles with 50:50 PLGA provided reasonable encapsulation efficiencies, producing N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide loads of about 7%. The *in vitro* release profile data is shown in Figure 1. The *in vitro* release studies show that the N-ethyl-3-[7-{2-

[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H-yl]-4-methylbenzamide in 50:50 PLGA microparticles had an acceptable burst on day one and released over 2 weeks *invitro*.

CLAIMS

1. A pharmaceutical depot comprising (i) N-ethyl-3-[7-{2-[ethyl(methyl)amino]ethoxy}-4-methyl-1-oxoisoquinolin-2(1H)-yl]-4-methylbenzamide,
5 or a pharmaceutically-acceptable salt thereof, as a pharmaceutical agent (PA) and (ii) a polymer which degrades to create an acidic microclimate, wherein the PA is released from the polymer upon polymer degradation.
2. The pharmaceutical depot according to claim 1, wherein the polymer is selected
10 from a polyester of a hydroxyfatty acid and derivatives thereof, a polymer of an alkyl α -cyanoacrylate, a polyalkylene oxalate, a polyortho ester, a polycarbonate, a polyortho-carbonate, a polyamino acid, a hyaluronic acid ester, and mixtures thereof.
3. The pharmaceutical depot according to claim 2, wherein the polymer is a lactic
15 acid-glycolic acid copolymer.
4. The pharmaceutical depot according to claim 3, wherein the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid in the range of 100:0 to 50:50.
- 20 5. The pharmaceutical depot according to claim 4, wherein the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 95:5.
6. The pharmaceutical depot according to claim 4, wherein the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.
25
7. The pharmaceutical depot according to any one of claims 1 to 6, wherein the pharmaceutical depot is formulated for controlled- and/or sustained-release of the PA over a period of from about 10 to 90 days.
- 30 8. The pharmaceutical depot according to claim 7, wherein the pharmaceutical depot is formulated for controlled- and/or sustained-release of the PA over a period of from about 14 days.

9. The pharmaceutical depot according to claim 7, wherein the pharmaceutical depot is formulated for controlled- and/or sustained-release of the PA over a period of about 60 days.

5 10. The pharmaceutical depot according to claim 7, wherein the pharmaceutical depot is formulated for controlled- and/or sustained-release of the PA over a period of about 90 days.

10 11. The pharmaceutical depot according to any one of claims 1 to 10, which is formulated for administration by injection.

12. The pharmaceutical depot according to claim 11, which is formulated for administration by intra-articular injection.

15 13. The pharmaceutical depot according to any one of claims 1 to 12, which is formulated for human medicine use.

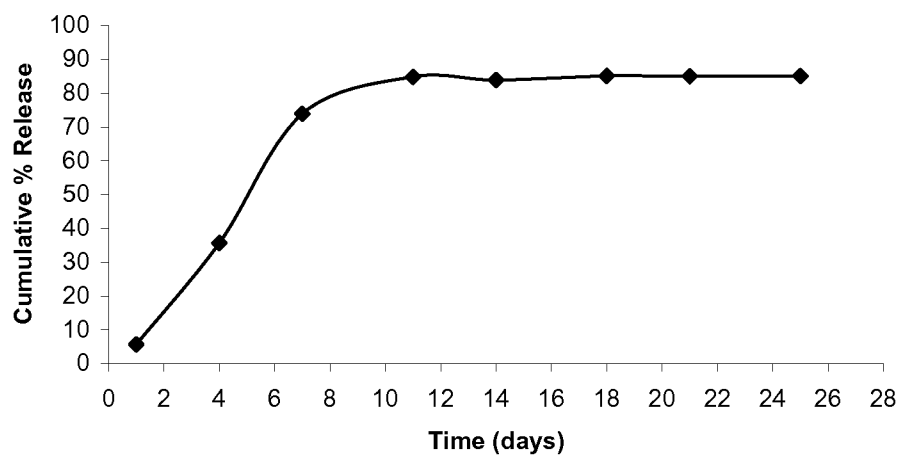
14. The pharmaceutical depot according to any one of claims 1 to 12, which is formulated for veterinary use.

20 15. The pharmaceutical depot according to any one of claims 1 to 14, for the prevention or treatment of osteoarthritis.

25 16. The use of a pharmaceutical depot according to any one of claims 1 to 14, for the prevention or treatment of osteoarthritis.

17. A pharmaceutical depot generally as herein described.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051177

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K31/506
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/149031 A1 (ASTRAZENECA AB [SE]; MARTIN BARRIE [GB]; WILLIS PAUL [GB]) 27 December 2007 (2007-12-27) examples 1 d, e, f	1-17
A	WO 2004/024694 A1 (KYORIN SEIYAKU KK [JP]; SHIGA FUTOSHI [JP]; KANDA TAKAHIRO [JP]; TAKAN) 25 March 2004 (2004-03-25) page 10 - page 10; figure Formula V	1-17
A	WO 2006/067444 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; NASH IAN ALUN [GB]; PAGE) 29 June 2006 (2006-06-29) cited in the application paragraphs [0207], [280] - paragraph [0282] sentences 17, 20 - sentence 21; claim 8	1-17

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/051177

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