local or synovial concentration of colchicine and the systemic concentration thereof, suitable for offering the best therapeutic action locally and at the same time avoiding potential systemic toxicity.

Due to the reduced side-effects obtained by the administration of the pharmaceutical composition according to the present invention, it is furthermore particularly suitable for people suffering from chronic comorbidities (Hypertension, Chronic Kidney diseases, Diabetes, Heart diseases, Immunosuppression…) fairly prevalent conditions in microcrystalline joint diseases (50% of Gout patients having at least 3 comorbidities). Indeed, the management of microcrystalline joint diseases patients having multiple comorbidities, remains a challenge for medical practitioners due to frequent and major contraindications to either Colchicine, NSAIDS or Corticosteroids. In comparison to the existing oral colchicine treatment, the present invention, in addition to avoid gastrointestinal side effects, prevents major toxicity risks for patients suffering from renal or hepatic impairments or for co-medicated patients with CYP3A4/PGP drug inhibitors, which are fairly prevalent medications.

SUMMARY

In one aspect, there is provided the use of a pharmaceutical composition under the form of a suspension comprising controlled release microparticles comprising colchicine in the manufacture of a medicament for the treatment of crystal-associated and non-crystal associated acute inflammatory arthritis, in particular a crystal-associated arthropathy or flares or acute forms of tendinitis and capsulitis by intra-articular injection into a joint of said pharmaceutical composition, wherein the microparticles have a mean particle size greater than 10 µm, wherein the time required to release 80% by weight of the colchicine in the microparticles is greater than 1 day and may reach 15 days, wherein the colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising controlled release microparticles comprising colchicine, wherein the microparticles have a mean particle size greater than 10 µm, wherein said pharmaceutical composition presents an *in vitro* dissolution profile, wherein less than 25% of colchicine is released within 60 minutes, less than 50% of colchicine is released in 12 hours, wherein the

colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

In another aspect, the present disclosure refers to a formulation under the form of a powder comprising controlled release microparticles comprising colchicine and a polymeric matrix, wherein the microparticles have a mean particle size equal or greater than 10 µm, and wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least a poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone), wherein the percentage weight ratio between the colchicine and the total weight of the microparticles ranges 0.1 to 35% by weight, in particular from 0.5 to 30% by weight, more particularly between 1 and 25% by weight, and even more particularly between 2 and 20% by weight.

In another aspect, the present disclosure refers to a pharmaceutical composition under the form of a sterile and injectable suspension suitable for an intra-articular injection, obtained by mixing a formulation under the form of a powder as defined above, with an aqueous injection vehicle, wherein the pharmaceutical composition optionally comprises an excipient selected from a group consisting of a tonicity-enhancing agent, a wetting-agent, a viscosity-enhancing agent, a density-enhancing agent or a mixture thereof, and wherein said excipient may be present in the aqueous injection vehicle or in the powder.

According to a first example, herein is provided a pharmaceutical composition under the form of a suspension comprising controlled release microparticles comprising colchicine for use in the treatment of crystal-associated and non-crystal associated acute inflammatory arthritis, in particular a crystal-associated arthropathy or flares or acute forms of tendinitis and capsulitis by intra-articular injection into a joint of said pharmaceutical composition, wherein the microparticles have a mean particle size greater than 10 µm, wherein the time required to release 80% by weight of the colchicine in the microparticles is superior to 1 day and may reach 15 days, wherein the colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

Herein is further described a pharmaceutical composition under the form of a suspension comprising controlled release microparticles comprising colchicine, suitable for intra-articular injection into a joint, for use in the treatment of a crystal and non-crystal-

associated acute inflammatory arthritis or acute forms of tendinitis and capsulitis, wherein the microparticles have a mean particle size greater than 10 μm, wherein the time required

to release 80% by weight of the colchicine in the microparticles lies between 1 day and 15 days, wherein the colchicine is present in a concentration ranging from 0.05 to 5 mg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

According to a second main example, herein is further provided a formulation under the form of a powder comprising controlled release microparticles comprising colchicine and a polymeric matrix, wherein the microparticles have a mean particle size equal or greater than 10 µm, and wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least a poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone), wherein the percentage weight ratio between the colchicine and the total weight of the microparticles ranges 0.1 to 35% by weight, in particular from 0.5 to 30% by weight, more particularly between 1 and 25% by weight, and even more particularly between 2 and 20% by weight.

Herein is further described a formulation under the form of a powder comprising controlled release microparticles comprising colchicine and a polymeric matrix, wherein the microparticles have a mean particle size equal or greater than 10 µm, and wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least a poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone), wherein the percentage weight ratio between the colchicine and total weight of the microparticles ranges from 1 to 35% by weight, in particular from 2 to 30% by weight, more particularly between 5 and 25% by weight, and even more particularly between 10 and 20% by weight.

According to a third main example, herein is further provided a pharmaceutical composition comprising controlled release microparticles comprising colchicine, wherein the microparticles have a mean particle size greater than 10 µm, wherein said pharmaceutical composition presents an *in vitro* dissolution profile, wherein less than 25% of colchicine is released within 60 minutes, less than 50% of colchicine is released in 12 hours, , wherein the colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

According to a fourth main example, herein is further provided a formulation under the form of a powder comprising controlled release microparticles comprising

colchicine and a polymeric matrix, wherein the microparticles have a mean particle size equal or greater than 10 µm, and wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least a poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone), wherein the percentage weight ratio between the colchicine and the total weight of the microparticles ranges 0.1 to 35% by weight, in particular from 0.5 to 30% by weight, more particularly between 1 and 25% by weight, and even more particularly between 2 and 20% by weight.

According to a fifth main example, herein is further provided a pharmaceutical composition under the form of a sterile and injectable suspension suitable for an intra-articular injection, obtained by mixing a formulation under the form of a powder as described above, with an aqueous injection vehicle, wherein the pharmaceutical composition optionally comprises an excipient selected from a group consisting of a tonicity-enhancing agent, a wetting-agent, a viscosity-enhancing agent, a density-enhancing agent or a mixture thereof, and wherein said excipient may be present in the aqueous injection vehicle or in the powder.

The pharmaceutical composition suitable for an intra-articular injection as described herein after is effective in treating crystal-associated and non-crystal associated acute inflammatory arthritis, in particular effective in treating non-crystal associated acute arthritis, such as Rheumatoid arthritis, Ankylosing spondylitis, Juvenile arthritis, Psoriatic arthritis, Lupus or in treating crystal-associated arthropathies attacks or flares, such as gout, chondrocalcinosis, calcifying tendinitis and Milwaukee shoulder syndrome with minimal long-term side effects.

Said pharmaceutical composition suitable for an intra-articular injection is suitable for local or synovial administration by injection into a site at or near the site of pain.

FIG1. represents the results of a *in vivo* studies demonstrating the efficacy in the treatment of pain of the suspension conform to the present disclosure as injected into ankle joint in a rat model.

DETAILED DESCRIPTION OF THE INVENTION

As apparent from the BACKGROUND paragraph above, the prescription of colchicine is nowadays delicate as only oral compositions are available and high risk of

CLAIMS

1. Use of a pharmaceutical composition under the form of a suspension comprising controlled release microparticles comprising colchicine in the manufacture of a medicament for the treatment of crystal-associated and non-crystal associated acute inflammatory arthritis, in particular a crystal-associated arthropathy or flares or acute forms of tendinitis and capsulitis by intra-articular injection into a joint of said pharmaceutical composition, wherein the microparticles have a mean particle size greater than 10 µm, wherein the time required to release 80% by weight of the colchicine in the microparticles is greater than 1 day and may reach 15 days, wherein the colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

2. The use according to claim 1, wherein the colchicine is present in a concentration ranging from 5 to 2000 µg per ml of suspension, in particular from 5 to 1500 µg per ml of suspension, in particular from 5 to 1000 µg per ml of suspension, and more particularly from 5 to 500 µg per ml of suspension.

3. The use according to claim 1 or 2, wherein the microparticles are microparticles comprising a polymeric matrix or multivesicular liposomes.

4. The use according to anyone of claims 1 to 3, wherein the microparticles are microparticles comprising colchicine and a polymeric matrix, wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone).

5. The use according to anyone of claims 1 to 4, wherein the crystal-associated and non-crystal associated acute inflammatory arthritis is selected from non-crystal associated acute arthritis, such as Rheumatoid arthritis, Ankylosing spondylitis, Juvenile arthritis, Psoriatic arthritis, Lupus and crystal-associated arthropathy attacks or flares or acute forms of tendinitis and capsulitis, and more particularly selected from gout, chondrocalcinosis, calcifying tendinitis and Milwaukee shoulder syndrome.

6. The use according to anyone of claims 1 to 5, wherein the joint is selected from the metatarsophalangeal joints, the metacarpophalangeal joints, the knee joint, the shoulder joint, the wrist joint, the elbow joint, the ankle joint, the hip joint, a vertebral joint and the midfoot joints.

7. The use according to anyone of claims 1 to 6, wherein the time required to release 80% by weight of the colchicine in the microparticles is superior to 1 day, for example 1.5 day, and may reach 10 days, is superior to 1 day, for example 1.5 day, and may reach 7 days, is superior to 1 day, for example 1.5 day, and may reach 5 days, and for example is superior to 1 day, for example 1.5 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days or 10 days, more particularly is superior to 1 day, for example 1.5 day, and may reach 7 days, or is comprised between 2 days and 15 days, between 2 days and 10 days and between 2 days and 7 days.

8. The use according to anyone of claims 1 to 7, wherein less than 50% by weight of colchicine is released at 12 hours after the administration.

9. The use according to anyone of claims 1 to 8, wherein the pharmaceutical composition is further characterized in that it is effective to maintain systemic concentration of colchicine 12 hours after the intra-articular injection lower than 5 ng/ml, particularly lower than 2 ng/ml, and more particularly lower than 1 ng/ml and to maintain synovial concentration of colchicine greater than 2 ng/ml, in particular comprised between 2 and 500 ng/ml, more particularly comprised between 2 and 250 ng/ml, more particularly comprised between 2 and 200 ng/ml, for example between 2 and 100 ng/ml, and even more particularly between 2 and 50 ng/ml.

10. The use according to anyone of claims 1 to 9, wherein the microparticles have a mean particle size lower than 100 µm, in particular lower than 80 µm, and more particularly lower than 50 µm, for example between 10 and 50 µm, between 15 and 40 µm or between 10 and 40 µm.

11. The use according to anyone of claims 1 to 10, wherein it is obtained by mixing a formulation under the form of a powder comprising controlled release microparticles comprising colchicine having a mean particle size equal or greater than 10 µm, with an aqueous injection vehicle, wherein the pharmaceutical composition optionally comprises an excipient selected from a group consisting of a tonicity-enhancing agent, a wetting-agent, a viscosity-enhancing agent, a density-enhancing agent or a mixture thereof, and wherein said excipient may be present in the aqueous injection vehicle or in the powder.

12. The use according to anyone of claims 1 to 11, wherein it has a viscosity of from 5 to 1000 mPa.s, in particular from 5 to 500 mPa.s, in particular from 5 to 100 mPa.s and more particularly from 5 to 50 mPa.s at a shear rate of 10 s^{-1}.

13. The use according to anyone of claims 1 to 12, wherein said pharmaceutical composition further comprises an immediate release dosage form containing colchicine, in particular wherein the maximal weight ratio of immediate release colchicine relative to the total amount of colchicine is 25%.

14. The use according to anyone of claims 4 to 13, wherein the polymeric matrix further comprises one or more additional polymer(s) or copolymer(s) selected from poly(lactide) distinct from poly(lactic-co-glycolic acid) copolymer, poly(glycolide) distinct from poly(lactic-co-glycolic acid) copolymer, poly(lactide-co-caprolactone), poly(ethylene glycol), poly(ethylene oxide), PLGA-b-PEO-b-PLGA, PLGA-b-PEO, polyhydroxyalkanoates, poly(hydroxybutyrate), poly(trimethylene carbonate), poly(dioxanone), poly(valerolactone), poly(alpha- hydroxy acids), poly(lactones), poly(amino acids), polyanhydrides, poly(orthoester), poly(acetals), polyurethanes, polythioesters, polyphosphoesters, poly(ester-co-amide), poly(vinyl alcohol), PVA-g-PLGA, poly (ether ester) multiblock copolymers, polyvinyl pyrrolidone, poly(methacrylate), PEO-PPO-PEO, gelatin, heparin, chondroitin sulfate; polysaccharides such as alginates, starch, chitosan and dextrans and any combinations thereof, and in particular selected from poly(lactide) distinct from poly(lactic-co-glycolic acid) copolymer and poly(caprolactone).

15. The use according to anyone of claims 4 to 14, wherein the polymeric matrix comprises poly(lactic-co-glycolic acid), copolymer poly(caprolactone) or a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone) in an amount of greater than 70% by weight, with respect to the total weight of the polymeric matrix, in particular greater than 80% by weight, and even more particularly greater than 90% by weight.

16. The use according to anyone of claims 1 to 15, wherein, the drug loading content or percentage weight ratio between the colchicine and the total weight of the microparticles ranges from 0.1% to 35%, in particular from 0.5 to 30%, even more particularly from 1 to 25%, for example from 2 to 20%.

17. The use according to anyone of claims 1 to 16, wherein the volume is adapted to the joint, and namely ranges from 2 to 5 ml for the shoulder, from 1 to 2 ml for a vertebral joint, from 0.1 to 1 ml for the midfoot joints, from 0.1 to 0.5 ml for the metatarsophalangeal joints, from 0.1 to 0.5 ml for the metacarpophalangeal joints, from 2 to 5 ml for the knee joint, from 0.5 to 1 ml for the wrist joint, from 2 to 5 ml for the elbow joint, from 1 to 3 ml for the ankle joint and from 2 to 5 ml for the hip.

18. The use according to anyone of claims 1 to 17, wherein the pharmaceutical composition is to be used in the treatment of crystal-associated and non-crystal associated acute inflammatory arthritis, in particular a crystal-associated arthropathy or flares or acute forms of tendinitis and capsulitis in a patient have renal and/or hepatic impairment of in a patient being simultaneously, separately or sequentially treated by at least one active ingredient selected from: atazanavir, clarithromycin, darunavir, ritonavir, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, cyclosporine and ranolazine.

19. A pharmaceutical composition comprising controlled release microparticles comprising colchicine, wherein the microparticles have a mean particle size greater than 10 µm, wherein said pharmaceutical composition presents an *in vitro* dissolution profile, wherein less than 25% of colchicine is released within 60 minutes, less than 50% of colchicine is released in 12 hours, wherein the colchicine is present in a concentration ranging from 2.5 to 2500 µg per ml of suspension and wherein the pharmaceutical composition has a volume ranging from 0.1 ml to 5 ml.

20. A formulation under the form of a powder comprising controlled release microparticles comprising colchicine and a polymeric matrix, wherein the microparticles have a mean particle size equal or greater than 10 µm, and wherein the polymeric matrix comprises at least a poly(lactic-co-glycolic acid) copolymer, at least a poly(caprolactone) or at least a mixture of poly(lactic-co-glycolic acid) copolymer and poly(caprolactone), wherein the percentage weight ratio between the colchicine and the total weight of the microparticles ranges 0.1 to 35% by weight, in particular from 0.5 to 30% by weight, more particularly between 1 and 25% by weight, and even more particularly between 2 and 20% by weight.

21. The formulation according to claim 20, wherein the powder further comprises an immediate release dosage form containing colchicine, in particular wherein the maximal weight ratio of immediate release colchicine relative to the total amount of colchicine is 25%.

22. A pharmaceutical composition under the form of a sterile and injectable suspension suitable for an intra-articular injection, obtained by mixing a formulation under the form of a powder according to the claim 20 or 21, with an aqueous injection vehicle,

wherein the pharmaceutical composition optionally comprises an excipient selected from a group consisting of a tonicity-enhancing agent, a wetting-agent, a viscosity-enhancing agent, a density-enhancing agent or a mixture thereof, and wherein said excipient may be present in the aqueous injection vehicle or in the powder.

23. A pharmaceutical composition according to claim 22, wherein the colchicine is present in a concentration ranging from 5 to 2000 μg per ml of suspension, in particular from 5 to 1500 μg per ml of suspension, in particular from 5 to 1000 μg per ml of suspension, and more particularly from 5 to 500 μg per ml of suspension.