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(54) Title: LIDOCAINE OR ARTICAIN FOR TREATING COVID-19, AUTOIMMUNE DISEASE OR CYTOKINE STORM RESPONSE

(57) Abstract: The present invention relates to a high dose/ low volume formulation of lidocaine, or a salt thereof, or articaine, or a salt thereof, for use in the treatment of COVID-19 or an autoimmune disease or a condition in which an immune response caused by a disease or infection causes a cytokine storm. More particularly it relates to the treatment of long-covid and addresses the challenge of getting an effective dose of lidocaine or articaine into the plasma, to treat the systemic inflammation, without causing toxicity.

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LIDOCAINE OR ARTICAIN FOR TREATING COVID-19, AUTOIMMUNE DISEASE OR CYTOKINE STORM RESPONSE

INTRODUCTION

[0001] The present invention relates to a composition and method for treating an
5 autoimmune disease or a condition in which an immune response caused by a disease or
infection needs treating. Such an immune response is one causing hyper-inflammation,
such as, but not limited to a cytokine storm, giving rise to Acute Respiration Distress
Syndrome (ARDS) or Cytokine Storm Syndrome (CSS) as can occur in SARS-CoV-2
disease (COVID-19). It further relates to the treatment of systemic inflammation (including
10 hyperinflammation) and the symptoms thereof post infection, such as occurs in Long-
covid.

BACKGROUND

[0002] The COVID-19 pandemic has meant many groups have been urgently looking at
the repurposing of approved drugs that might address the symptoms of COVID-19 and the
15 longer term effects resulting from infection.

[0003] Acute respiratory distress syndrome (ARDS) is the main cause of morbidity and
mortality in Coronavirus disease 19 (Covid-19) for which, as of now, there is no effective
treatment besides respiratory support and the use of high dose dexamethasone.

[0004] Many drugs, for example chloroquine and ivermectin, have been studied on
20 hospitalized patients with severe manifestations of SARS-CoV-2 infection, but none have
shown to be successful.

[0005] ARDS is caused, and sustained, by an uncontrolled inflammatory activation
characterized by a massive release of cytokines (cytokine storm), diffuse lung edema,
inflammatory cell infiltration and disseminated coagulation. Macrophage and T lymphocyte
25 dysfunction plays a central role in this syndrome.

[0006] In several experimental *in vitro* and *in vivo* models, many of these
pathophysiological changes are triggered by stimulation of the P2X7 receptor.

[0007] In this regards, viral pathogens in the respiratory tract cause cellular stress and a
subsequent innate immune response. This causes massive exocytosis of ATP, resulting in
30 high extracellular ATP concentrations. Initially, this stimulates the purinergic P2Y2 and
P2X4 receptors, resulting in a short period of surfactant exocytosis, but as ATP levels
continue to rise, the P2X4 and P2Y2 receptors become insensitive, and the normal release
of surfactant is prevented. When the extracellular levels of ATP start to exceed the lower
threshold for the activation of the P2X7 extracellular ATP receptors (P2X7Rs) located on

the cell surface of the innate immune cells, it causes a pro-inflammatory response of the innate immunity, followed by a massive release of inflammatory mediators and a subsequent cytokine storm. The resulting vascular leakage and pulmonary edema induce the disaggregation and inactivation of pulmonary surfactant, a key element in the pathogenesis of ARDS that ends in alveolar collapse and reduced gas exchange.

[0008] Applicant hypothesized that this P2X7 receptor might be an ideal candidate to target in Covid-19-associated ARDS and Long-covid. Unfortunately, most of the known P2X7 receptor blockers become toxic when given to a patient at dose levels required for effective treatment.

[0009] They hypothesised that auto immune diseases might also be treated by the same approach – namely, blocking of the P2X7 receptor, using lidocaine or very similar drugs, such as, articaine at an effective dose. Articaine contains a thioprene ring rather than a benzene ring, which has the benefit of enhanced lipid solubility and thus increased diffusion making it more potent (x 1.5) and less toxic (0.6).

[0010] Prior art identified includes the following:

[0011] Trials, vol 22, no 1, 2021 Muller Marie et al “impact of intravenous lidocaine on clinical outcomes of patients with ARDS during COVID-19 pandemic (LidoCovid): A structured summary of a study protocol for a randomised control trial” p. 131;

[0012] Bone Marrow Transplantation, vol 28, no 1, Voltarelli J C et al., “Beneficial effect of intravenous lidocaine in cutaneous chronic graft-versus-host disease secondary to donor lymphocyte infusion”, p. 97-99;

[0013] LUNG, vol 182, no 1, 2004 Huang T K et al, “Surfactant lavage with Lidocaine improves pulmonary function in piglets after HCl-induced acute lung injury”, p15-25;

[0014] RU 2742505;

[0015] CN 111150738;

[0016] CN 103142643; and

[0017] CN 104127397.

[0018] A first object of the invention was to identify a drug or drugs for use in treating an autoimmune disease or a condition in which an immune response caused by a disease or infection needs treating.

[0019] A second and further object was to formulate such a drug for such use.

[0020] A third and further object was to deliver such drugs in a manner, and at a dose, which facilitated effective treatment.

BRIEF SUMMARY OF THE DISCLOSURE

[0021] In accordance with a first aspect of the present invention there is provided lidocaine or a salt thereof or articaine or a salt thereof for use in the treatment of an autoimmune disease or a condition in which an immune response caused by a disease or infection causes hyperinflammation.

[0022] In one embodiment it causes a cytokine storm.

[0023] The autoimmune disease may be any of those listed below:

- Achalasia
- Addison's disease
- Adult Still's disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome
- Autoimmune angioedema
- Autoimmune dysautonomia
- Autoimmune encephalomyelitis
- Autoimmune hepatitis
- Autoimmune inner ear disease (AIED)
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune urticaria
- Axonal & neuronal neuropathy (AMAN)
- Baló disease
- Behcet's disease
- Benign mucosal pemphigoid
- Bullous pemphigoid
- Castleman disease (CD)
- Celiac disease
- Chagas disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA)
- Cicatricial pemphigoid
- Cogan's syndrome
- Cold agglutinin disease
- Congenital heart block
- Cocksackie myocarditis
- CREST syndrome
- Crohn's disease
- Dermatitis herpetiformis
- Dermatomyositis
- Devic's disease (neuromyelitis optica)

- Discoid lupus
- Dressler's syndrome
- Endometriosis
- Eosinophilic esophagitis (EoE)
- 5 • Eosinophilic fasciitis
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Evans syndrome
- Fibromyalgia
- 10 • Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Giant cell myocarditis
- Glomerulonephritis
- Goodpasture's syndrome
- 15 • Granulomatosis with Polyangiitis
- Graves' disease
- Guillain-Barre syndrome
- Hashimoto's thyroiditis
- Hemolytic anemia
- 20 • Henoch-Schonlein purpura (HSP)
- Herpes gestationis or pemphigoid gestationis (PG)
- Hidradenitis Suppurativa (HS) (Acne Inversa)
- Hypogammaglobulinemia
- IgA Nephropathy
- 25 • IgG4-related sclerosing disease
- Immune thrombocytopenic purpura (ITP)
- Inclusion body myositis (IBM)
- Interstitial cystitis (IC)
- Juvenile arthritis
- 30 • Juvenile diabetes (Type 1 diabetes)
- Juvenile myositis (JM)
- Kawasaki disease
- Lambert-Eaton syndrome
- Leukocytoclastic vasculitis
- 35 • Lichen planus
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease (LAD)
- Lupus
- 40 • Lyme disease chronic
- Meniere's disease
- Microscopic polyangiitis (MPA)
- Mixed connective tissue disease (MCTD)
- Mooren's ulcer
- 45 • Mucha-Habermann disease
- Multifocal Motor Neuropathy (MMN) or MMNCB
- Multiple sclerosis
- Myasthenia gravis
- Myelin Oligodendrocyte Glycoprotein Antibody Disorder
- 50 • Myositis
- Narcolepsy
- Neonatal Lupus
- Neuromyelitis optica
- Neutropenia
- 55 • Ocular cicatricial pemphigoid

- Optic neuritis
- Palindromic rheumatism (PR)
- PANDAS
- Paraneoplastic cerebellar degeneration (PCD)
- 5 • Paroxysmal nocturnal hemoglobinuria (PNH)
- Parry Romberg syndrome
- Pars planitis (peripheral uveitis)
- Parsonage-Turner syndrome
- Pemphigus
- 10 • Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia (PA)
- POEMS syndrome
- Polyarteritis nodosa
- 15 • Polyglandular syndromes type I, II, III
- Polymyalgia rheumatica
- Polymyositis
- Postmyocardial infarction syndrome
- Postpericardiotomy syndrome
- 20 • Primary Biliary Cholangitis
- Primary sclerosing cholangitis
- Progesterone dermatitis
- Psoriasis
- Psoriatic arthritis
- 25 • Pure red cell aplasia (PRCA)
- Pyoderma gangrenosum
- Raynaud's phenomenon
- Reactive Arthritis
- Reflex sympathetic dystrophy
- 30 • Relapsing polychondritis
- Restless legs syndrome (RLS)
- Retroperitoneal fibrosis
- Rheumatic fever
- Rheumatoid arthritis
- 35 • Sarcoidosis
- Schmidt syndrome
- Scleritis
- Scleroderma
- Sjögren's syndrome
- 40 • Sperm & testicular autoimmunity
- Stiff person syndrome (SPS)
- Subacute bacterial endocarditis (SBE)
- Susac's syndrome
- Sympathetic ophthalmia (SO)
- 45 • Takayasu's arteritis
- Temporal arteritis/Giant cell arteritis
- Thrombocytopenic purpura (TTP)
- Thyroid eye disease (TED)
- Tolosa-Hunt syndrome (THS)
- 50 • Transverse myelitis
- Type 1 diabetes
- Ulcerative colitis (UC)
- Undifferentiated connective tissue disease (UCTD)
- Uveitis
- 55 • Vasculitis

- Vitiligo
- Vogt-Koyanagi-Harada Disease

5 **[0024]** Of these inflammatory diseases, those in which Cytokine Storm Syndrome presents, are particular targets for treatment.

[0025] Particularly favoured diseases for treatment are: ARDS, covid-19 and Long-covid.

[0026] Lidocaine, also known as lignocaine is sold under the brand name Xylocaine®. It is a local anaesthetic of the amino amide type.

10 **[0027]** As an approved medicine it is used intravenously, subcutaneously, topically and orally.

[0028] However, in these forms it is not particularly suited to targeting the lymphatic system and treating hyperinflammation by blocking the P2X7 receptors, thus stopping the “cytokine storm” which can be the cause of life-threatening ARDS in SARS-COV-2 disease (COVID-19) and other autoimmune diseases.

15 **[0029]** A related drug, Articaine is available in Europe with or without adrenaline. The epinephrine-free (adrenaline-free) version is sold under the brand name Ultracain D (4%). The version with epinephrine (adrenaline) is available in Europe under the brand name Supracain 4% with an epinephrine concentration of 1:200,000

20 **[0030]** Thus, in accordance with a second aspect of the present invention there is provided a pharmaceutical formulation comprising lidocaine or a salt thereof or articaine or a salt thereof which is formulated to facilitate uptake by the lymphatic system by the incorporation of one or more suitable excipients.

[0031] Furthermore, it is preferably packaged in a delivery form, and with instructions, for oromucosal or sublingual administration.

25 **[0032]** The delivery form is preferably a unit dose in a volume of less than or equal to 1ml, and more preferably still less than or equal to 0.5ml which contains a high concentration of lidocaine or a salt thereof or articaine or a salt thereof as compared to currently approved dosage forms of these drugs.

30 **[0033]** Thus, a unit dose of lidocaine contains from 60-100mg and a unit dose of articaine contains from 40-100mg.

[0034] Preferably, though not essentially, the Lidocaine or Articaine, or a salt thereof is dissolved in one or more lipophilic excipients although it is possible to achieve uptake using polar solvents.

35 **[0035]** The use of long chain fatty acids and/ or surface modifiers such as polyethylene glycol (PEG) and/ or surfactants are preferred.

[0036] Favoured delivery systems include, but are not limited to, nanoparticles, microspheres, liposomes, emulsifying drug delivery systems (EDDS) and variants thereof e.g. self-emulsifying drug delivery systems (SEDDS), self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS).

5 **[0037]** The simplest forms are drugs in oils such as medium chain triglycerides.

[0038] Thus, suitable formulations may include functional excipients, such as lipophilic and polar solvents, co-solvents, viscosity modifiers, surfactants, sweeteners and flavourants.

[0039] To make it palatable the formulation includes a sweetener, e.g. saccharin and a flavourant, e.g. a banana flavour.

10 **[0040]** To facilitate their solubility in a low volume unit dose, (less than or equal to 1ml and more preferably still less than or equal to 0.5ml) a polar solvent is also used. A preferred polar solvent is ethanol.

[0041] Additionally, one or more co-solvents are used. Suitable co-solvents include polyethylene glycol (Macrogol 400) and propylene glycol (E 1520).

15 **[0042]** A problem with using, particularly, Lidocaine is its' known toxicity. Indeed, a benefit of Articaine is it is less toxic and more potent than Lidocaine.

[0043] Local anesthetics, such as lidocaine, can cause methemoglobinemia. This can occur when administering the lidocaine at high doses, typically more than 4-5mg/kg bodyweight for local anesthesia or plasma levels > 5mg/L.

20 **[0044]** By administering the lidocaine or articaine oromucosally or sublingually, absorption mainly take place by the lymphatic system, and not the venous system. This avoids toxic plasma levels and hepatic first pass elimination, resulting in low plasma levels of lidocaine or articaine, thereby avoiding methemoglobinemia.

[0045] Finding an effective dose without causing toxicity for either drug was essential.

25 **[0046]** To achieve an IC50 for blocking the P2X7receptor, a plasma concentration of 0.3mM (66.07 ug/ml) is required. By contrast, the maximum tolerable plasma concentration of lidocaine in human is 0.02 mM (4.7 ug/ml), above this level lidocaine will become toxic. This leads to the conclusion that an inhibitory effect on the P2X7 receptor of at least 50% cannot be reached by administering lidocaine using the traditional intravenous route. This
30 is also true, to a lesser extent, for articaine.

[0047] To solve this problem, Applicant formulated lidocaine (with the same rationale applying to articaine) in a high dose/ low volume unit dose solution for oromucosal or sublingual administration. The sublingual mucosa is known for its high permeability (20 times more absorption speed compered to human skin) and additionally, the floor of the

mouth and oral cavity has a high concentration of lymph nodes, with makes it perfect for targeting the lymphatic system and immune system.

5 [0048] An effective adult unit dose of lidocaine, delivered oromucosally or sublingually, was found to be between 60-100mg, delivered 4-6 times a day. The objective was to provide an effective dose of lidocaine in the plasma of <4.7 µg/ml.

[0049] Given the increased potency of articaine, an equivalent dose would be 40-67mg, delivered 4-6 times a day. With its' reduced toxicity, equivalent dosing to lidocaine (60-100mg) 2-4 times a day might also be achieved.

10 [0050] To prove the suitability of such a delivery method a lidocaine formulation was modified from the Astra Zeneca Xylocaine 10% spray formulation by increasing the concentration of lidocaine from 10 to 25%.

[0051] Rather than deliver a spray, the formulation was delivered from small, single unit dose, sealed vials (0.4ml vol) for delivery as drops.

15 [0052] The key was to deliver a unit dose of from 60 -100mg lidocaine in a volume of equal or less than 0.5ml.

[0053] For articaine an equivalent unit dose was 40 – 67mg articaine in a volume of equal or less than 0.5ml. However, due to its' lower toxicity a dose of up to 100mg could be administered in this volume.

20 [0054] The lidocaine formulation, which is significantly more concentrated than current formulations, comprises greater than 10% by volume of lidocaine, and more preferably greater than 20%, and typically 25%. This has the advantage that it avoids a feeling of fullness in the mouth and accompanied hypersalivation, which is poorly tolerated, and which occurs with standard IV formulations (at a concentration of 10%).

25 [0055] The articaine formulation is also more concentrated than current formulations, comprises greater than 4% by volume of lidocaine, and more preferably greater than 8%, and typically 10% or more. It too can be provided in a unit dose form.

30 [0056] In accordance with a third aspect of the present invention there is provided a method of treating a subject suffering from COVID-19 or an autoimmune disease or a condition in which an immune response caused by the disease or an infection causes a cytokine storm, comprising administering to the subject an effective dose of lidocaine, or a salt thereof, or articaine, or a salt thereof, targeted to the lymphatic system, in a suitable high dose/ low volume unit dosage form.

[0057] By high dose/ low volume unit dosage form is meant the relative concentration of the lidocaine, or a salt thereof, or articaine, or a salt thereof is significantly higher than the

existing dosage form (10% for lidocaine or a salt thereof, and 4% for articaine or a salt thereof) with a unit dose volume of 1ml or less, more preferably 0.5ml or less.

[0058] Preferably the lidocaine, or a salt thereof, or articaine, or a salt thereof, is administered oromucosally or sublingually.

5 [0059] Preferably the unit dose comprises from 60-100mg of lidocaine or a salt thereof, or 40 – 100mg articaine, or a salt thereof.

[0060] Preferably the unit dose has a volume of equal or less than 0.5ml.

[0061] The treatment may be, the treatment of COVID-19, Acute respiratory distress syndrome (ARDS). Long-covid or of an autoimmune disease, particularly but not limited to:
10 scleroderma; dermatomyositis; parkinson; and psoriasis.

[0062] Most preferably the treatment is for the treatment of long-covid, or the symptoms thereof including: fatigue, moderate to severe breathlessness, pain, insomnia, dyspnoea, dizziness, cramps and or palpitations.

[0063] The primary aim of the treatment is to reduce systemic hyperinflammation. This
15 could be determined by measuring biomarkers, such as, for example, interleukin-6, ferritin, leukocytes, neutrophils, lymphocytes, platelets, C-Reactive Protein, procalcitonin, lactate dehydrogenase, aspartate aminotransferase, creatinine, and D-dimer.

[0064] Different aspects and embodiments of the invention are further described hereinafter with reference to the detailed description.

20

DETAILED DESCRIPTION

[0065] The trial formulation is illustrated in Example 1:

Example 1a

25 **Formulation**

[0066] **Active**

- lidocaine: 100mg

[0067] **Excipients:**

- Lipophilic solvent -levomenthol
- 30 • Polar solvent - ethanol 96% 241 mg / ml,
- Co-solvent - polyethylene glycol (Macrogol 400),

- Co-solvent - propylene glycol (E 1520)
 - Sweetener - Saccharin (E 954),
 - Flavor - banana flavor.
 - Diluent - water, purified)
- 5 • Total 0.4ml

[0068] The formulation of the invention was used “off-label” to treat a number of patients to determine its effect as set out in Example 2.

[0069] Example 1b

10 As example 1a except the active was articaine.

Example 2

Patient trial data

15 [0070] In the Netherlands, 22 patients were treated with the formulation of Example 1a as follows:

20 [0071] 10 patients had COVID-19 symptoms (and were positive and were seen by their general practitioner). All 10 patients presented with early signs of respiratory distress; tachypnoea (more than 30 breaths per minute), high fever and dry cough and a decreased SpO₂ < 90. Because they responded well to lidocaine sublingually, they were able to avoid hospitalization for COVID-19);

[0072] 6 patients had post-COVID respiratory complaints. They were experiencing long-term complaints, ranging from coughing, fatigue and shortness of breath to anxiety and physical limitations.

[0073] 6 patients suffered with various autoimmune diseases as follows:

- 25 • 1 patient had rheumatoid arthritis.
- 1 patient had scleroderma;
 - 1 patient had dermatomyositis;
 - 1 patient had morbus Parkinson;
 - 2 patients had psoriasis.

[0074] All patients were given the formulation as described in Example 1a above, up to 6 times a day, for up to 2 weeks.

[0075] Out of a total of 22 patients, 8 responded to this treatment within hours, and recovered, without problems, within days.

5 [0076] The 10 patients with COVID-19, and 6 with post-COVID respiratory complaints had fully recovered within two weeks.

[0077] 5 of the 6 patients with the identified autoimmune diseases experienced significant improvement after 2 weeks of treatment and all had no side effects.

10 [0078] Only 1 patient showed minimal improvement, and that was a 56 year old male patient with severe chronic rheumatoid arthritis.

Conclusion

15 [0079] Administration of lidocaine, targeting a subject's lymphatic system, appears effective in treating COVID-19 and long-covid. The sublingual/ oromucosal approach is a simple, effective, non-invasive approach. A high concentration low volume unit dose of greater than 10% lidocaine in a small volume, less than 0.5ml, is optimal.

CLAIMS

1. Lidocaine or a salt thereof, or articaine or a salt thereof, for use in the treatment of COVID-19 or an autoimmune disease or a condition in which an immune response
5 caused by a disease or infection causes a cytokine storm.
2. Lidocaine or a salt thereof, or articaine or a salt thereof, as claimed in claim 1 for use in the treatment of COVID-19 and/ or long -covid.
3. Lidocaine or a salt thereof, or articaine or a salt thereof, as claimed in claim 1 for use in the treatment of Acute Respiratory Distress Syndrome (ARDS).
- 10 4. Lidocaine or a salt thereof, or articaine or a salt thereof, as claimed in claim 1 for use in the treatment of an autoimmune disease.
5. Lidocaine or a salt thereof, or articaine or a salt thereof. as claimed in claim 4 for use in the treatment of one or more
- scleroderma;
 - 15 • dermatomyositis;
 - parkinson; and
 - psoriasis.
6. Lidocaine or a salt thereof, or articaine or a salt thereof, as claimed in any of the preceding claims which is formulated for oromucosal or sublingual delivery.
- 20 7. Lidocaine, or a salt thereof, or articaine, or a salt thereof, as claimed in claim 6 which is in a high dose/ low volume unit form.
8. Lidocaine, or a salt thereof, or articaine, or a salt thereof, as claimed in any of the preceding claims which targets the lymphatic system.
9. Lidocaine, or a salt thereof, or articaine, or a salt thereof, as claimed in any of the
25 preceding claims which comprises, as a unit dose from 40-100mg of lidocaine, or salt thereof, or articaine, or a salt thereof.
10. A pharmaceutical formulation comprising lidocaine, or a salt thereof, or articaine, or a salt thereof, which is formulated to facilitate uptake by the lymphatic system with one or more suitable excipients.
- 30 11. A pharmaceutical formulation as claimed in claim 10 wherein the one or more suitable excipients comprise a lipophilic excipient.

12. A pharmaceutical formulation as claimed in claim 11 wherein the lipophilic excipient is menthol.
13. A pharmaceutical formulation as claimed in any one of claims 10 to 12 which further comprises a polar solvent.
- 5 14. A pharmaceutical formulation as claimed in claim 13 where the polar solvent is ethanol.
15. A pharmaceutical formulation as claimed in any one of claims 10 to 14 further comprising one or more co-solvents.
16. A pharmaceutical formulation as claimed in claim 15 wherein the one or more co-solvents comprise polyethylene and polypropylene glycol.
- 10 17. A pharmaceutical formulation as claimed in any one of claims 10 to 16 further comprising a sweetener and a flavourant.
18. A pharmaceutical formulation as claimed in any one of claims 10 to 17 comprising from 60-100mg of lidocaine, or a salt thereof, or from 40 – 100mg of articaine, or a salt thereof, in a unit dose.
- 15 19. A pharmaceutical formulation as claimed in any one of claims 10 to 18 comprising a unit dose with a volume of less than or equal to 0.5ml.
20. A pharmaceutical formulation as claimed in any of claims 10 to 19 comprising at least a 20% by weight solution of lidocaine, or a salt thereof, in a volume of less than or equal to 0.5ml.
- 20 21. A pharmaceutical formulation as claimed in any of claims 10 to 19 comprising at least a 10% by weight solution of articaine, or a salt thereof, in a volume of less than or equal to 0.5ml.
22. A method of treating a subject suffering from COVID-19 or an autoimmune disease or a condition in which an immune response caused by the disease or an infection causes a cytokine storm, comprising administering to the subject an effective dose of lidocaine, or a salt thereof, or articaine, or a salt thereof, targeted to the lymphatic system, in a suitable high dose/ low volume unit dosage form.
- 25 23. A method as claimed in claim 22 wherein the lidocaine, or a salt thereof, or articaine, or a salt thereof, is administered oromucosally or sublingually.
- 30 24. A method as claimed in claim 22 or 23 wherein the lidocaine, or a salt thereof, or articaine, or a salt thereof, is provided in a unit dose in an amount of from 40-100mg.
25. A method as claimed in claim 24 wherein the unit dose has a volume of less than or equal to 0.5ml.

26. A method as claimed in any of claims 22 to 25 which is for the treatment of COVID-19 or long-covid.

27. A method as claimed in any of claims 22 to 25 which is for the treatment of Acute respiratory distress syndrome (ARDS).

5 28. A method as claimed in any of claims 22 to 25 which is for the treatment of an autoimmune disease.

29. A method as claimed in any of claims 28 wherein the autoimmune disease is selected from

- scleroderma;
- 10 • dermatomyositis;
- parkinson; and
- psoriasis.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/167 A61K9/00 A61P31/14 A61P37/06 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 A61P		
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 practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE, 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.
X	WO 2007/072923 A1 (KOWA CO [JP]; TAKEMAE KAZUHISA [JP]) 28 June 2007 (2007-06-28)	10-15
Y	paragraphs [0072] - [0081]; claim 4x8; example 1	10-21
X	CN 106 692 120 A (LIU LI) 24 May 2017 (2017-05-24) paragraphs [0008], [0011]; example 27	10-16,19
	----- -/--	
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "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 5 September 2022		Date of mailing of the international search report 31/10/2022
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Allnutt, Sarah

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2022/055134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. K. HUANG ET AL: "Surfactant Lavage with Lidocaine Improves Pulmonary Function in Piglets after HCl-Induced Acute Lung Injury", LUNG, vol. 182, no. 1, 1 January 2004 (2004-01-01), pages 15-25, XP055751929, US ISSN: 0341-2040, DOI: 10.1007/s00408-003-1041-y cited in the application See Abstract and Discussion -----	10, 11, 13, 15, 20
X	RU 2 742 505 C1 (OBSCHESTVO S OGRANICHENNOJ OTVETSTVENNOSTYU INST TERMOLOGII [RU]) 8 February 2021 (2021-02-08) -----	1-3, 6, 8-10, 13, 18, 21-24, 26, 27 10-21
Y	paragraphs [0001], [0002], [0025], [0026], [0047], [0053], [0070] -----	
A	CN 111 150 738 A (THE SECOND AFFILIATED HOSPITAL OF COLLEGE OF MEDICINE OF XI'AN JIAOTON) 15 May 2020 (2020-05-15) example 3 -----	1-3, 6-27
A	SIRAIT ROBERT HOTMAN ET AL: "Lidocaine suppressed hyperinflammation in BALB/c mice model sterile injury via downregulation of toll-like receptor 4", EGYPTIAN JOURNAL OF ANAESTHESIA, vol. 34, no. 4, 1 October 2018 (2018-10-01), pages 135-137, XP055955041, DOI: 10.1016/j.egja.2018.07.002 abstract -----	1-3, 6-27
A	CN 104 127 397 B (DONG YINGYING) 27 April 2016 (2016-04-27) -----	1-3, 6-27
A	WO 2007/109192 A2 (RENOVIS INC [US]; KELLY MICHAEL G [US] ET AL.) 27 September 2007 (2007-09-27) paragraph [0143] -----	1-3, 6-27
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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2022/055134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OKURA DAN ET AL: "Lidocaine Preferentially Inhibits the Function of Purinergic P2X7 Receptors Expressed in Xenopus Oocytes", ANESTHESIA AND ANALGESIA, vol. 120, no. 3, 1 March 2015 (2015-03-01), pages 597-605, XP055955097, US ISSN: 0003-2999, DOI: 10.1213/ANE.0000000000000585 abstract -----	1-3, 6-27
Y	KANG LISHENG ET AL: "Physicochemical studies of lidocaine-menthol binary systems for enhanced membrane transport", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER, NL, vol. 206, no. 1-2, 25 September 2000 (2000-09-25), pages 35-42, XP002294480, ISSN: 0378-5173, DOI: 10.1016/S0378-5173(00)00505-6 See summary -----	10-21
X,P	HASAN DJO ET AL: "A novel definition and treatment of hyperinflammation in COVID-19 based on purinergic signalling", PURINERGIC SIGNALLING, SPRINGER VERLAG, DE, vol. 18, no. 1, 10 November 2021 (2021-11-10), pages 13-59, XP037697925, ISSN: 1573-9538, DOI: 10.1007/S11302-021-09814-6 [retrieved on 2021-11-10] the whole document -----	1-3, 6-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/055134

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-3, 6-27 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 6-27(all partially)

Lidocaine or a salt thereof, or articaine or a salt thereof,
for use in the treatment of COVID-19

2. claims: 4, 5, 28, 29(completely); 1-3, 6-27(partially)

Lidocaine or a salt thereof, or articaine or a salt thereof,
for use in the treatment of an autoimmune disease

3. claims: 1-3, 6-27(all partially)

Lidocaine or a salt thereof, or articaine or a salt thereof,
for use in the treatment of a condition in which an immune
response caused by a disease or infection causes a cytokine
storm.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2022/055134

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WO 2007072923 A1	28-06-2007	CN 101340916 A JP 5111117 B2 JP WO2007072923 A1 KR 20080080387 A WO 2007072923 A1	07-01-2009 26-12-2012 04-06-2009 03-09-2008 28-06-2007
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