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(71) Applicant(s)
Sinclair Pharmaceuticals Limited

(72) Inventor(s)
Mastrodonato, Marco

(74) Agent/Attorney
Lord and Company, 4 Douro Place, WEST PERTH, WA, 6005

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(71) Applicant (for all designated States except US): SIN-
CLAIR PHARMA S.R.L. [IT/IT]; Viale Marche, 15,
I-20125 Milano (IT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): MASTRODONATO,
Marco [IT/IT]; Via E. Boschetti, 7, I-20121 Milano (IT).

(74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Mi-
noja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF MUCOSITIS, STOMATITIS AND BEHICET'S
SYNDROME

(57) Abstract: Pharmaceutical compositions comprising as active ingredients effective doses of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone, for the treatment of painful, inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis and Behcet's syndrome.

**PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF
PAINFUL, INFLAMMATORY AND ULCERATIVE CONDITIONS OF
MOIST EPITHELIAL SURFACES SUCH AS MUCOSITIS,
STOMATITIS AND BEHCET'S SYNDROME**

The present invention relates to pharmaceutical compositions containing hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone for the management of painful ulcerative and inflammatory conditions of moist surfaces including the mouth, oropharynx, oesophagus, vagina and rectum 5 (including, but not limited to, mucositis, stomatitis, Behcet's syndrome).

TECHNICAL BACKGROUND OF THE INVENTION

The terms mucositis and stomatitis are often used interchangeably but may include some general distinctions. Mucositis describes a toxic inflammatory reaction affecting the gastrointestinal tract, which may result 10 from exposure to chemotherapeutic agents or ionising radiation. Mucositis typically manifests as an erythematous, burn-like lesion or as random, focal-to-diffuse, ulcerative lesions.

Stomatitis refers to an inflammatory reaction affecting the oral mucosa, with or without ulceration, that may be caused or intensified by 15 pharmacological, particularly chemotherapeutic treatments, or by radiotherapy. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth.

Many women get oral aphthous ulceration at specific times of the menstrual cycle and simultaneously get the same kind of ulcers in the genital 20 tract, in particular the vulva and vagina. This is sometimes very severe and can cause retention of urine and require strong painkillers and sedatives. The most severe form is called Behcet's syndrome.

In the following description, the more general term mucositis will be

employed also to indicate stomatitis proper. The study in mucositis exemplifies the action and supports the claim.

Erythematous mucositis may appear as early as three days after exposure to chemotherapy or radiotherapy, but more typically within five to seven days.

5 Progression to ulcerative mucositis typically occurs within seven days after the start of chemotherapy and may sometimes reach such severity as to make it necessary to discontinue the pharmacological treatment. Mucositis may involve the mouth and oropharynx as well as the gastro-intestinal tract from the mouth to the anus. Here we confine the experience to mucositis affecting the easily

10 accessible regions such as mouth, oropharynx, oesophagus and rectum.

As a high percentage (from 30 to 40%) of patients who receive chemotherapy will develop mucositis to varying degrees, there is a strong need for an effective, convenient treatment. To date, no effective treatments are in fact available and attempts have been made to solve the problem by use of

15 analgesics, antiseptics and oral hygiene measures or palliation of symptoms.

Furthermore, the problem is not restricted to cancer patients, as mucositis frequently also occurs in HIV patients, particularly when associated with Kaposi's sarcoma, in patients affected with non-Hodgkin's lymphoma, in debilitated elderly patients and in patients receiving BRM treatments like

20 interleukin-2, TNF, interferons, lymphokine-activated lymphocytes and the like.

DISCLOSURE OF THE INVENTION

It has now been surprisingly found that the topical administration of a pharmaceutical formulation containing hyaluronic acid, glycyrrhetic acid and

25 polyvinylpyrrolidone provides an effective therapeutical and preventive treatment for mucositis and stomatitis of various origin and severity and, more generally, of the lesions of the oro-pharynx cavity and oesophagus, particularly those caused by dental devices and by radio- or chemotherapy.

Therefore the present invention, in a first aspect, provides pharmaceutical compositions comprising as active ingredients effective doses of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone, in mixture with excipients and adjuvants to form a viscous and lubricating substance that 5 remains adherent to the surface epithelium suitable for topical administration to epithelial surfaces such as, but not limited to, the oropharynx and oesophagus.

A further aspect of the invention concerns the use of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone for the preparation of medicaments for the topical treatment of inflammatory states of epithelial 10 surfaces such as, but not limited to the oral mucosa, particularly mucositis and stomatitis.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention are in the form of a slightly viscous aqueous liquid (gel) which provides a film-forming and coating effect on the 15 epithelial surfaces such as, but not limited to the oral mucosa.

Hyaluronic acid is present in weight percentages ranging from 0.01 to about 5%, preferably about 0.1%. Hyaluronic acid can also be in the form of the sodium salt, and preferably of biotechnological origin, with the molecular weight ranging from 1.6 and $2.2 \cdot 10^6$ Da.

20 Polyvinylpyrrolidone or povidone (PVP), a suspending and binding agent widely used in pharmaceutical technique. It is present in the formulations of the invention in weight percentages ranging from 1 and 20% by weight, preferably between 5 and 10%.

Glycyrrhetic acid can be present in weight percentages ranging from 25 0.01 to 3% by weight.

High molecular weight povidone is preferably used, for example povidones of K-30 to K-120, preferably povidone K-90, having an average molecular weight of about 1,000,000.

The compositions of the inventions can contain suitable excipients for topical administration such as:

- viscosity-increasing agents;
- surfactants;
- 5 - stabilising agents - preservatives;
- flavours, fragrances, sweetening agents;
- bioadhesives;
- co-solubilisers.

Examples of said excipients comprise cellulose derivatives, acrylic or 10 methacrylic acids polymers or copolymers, ethylene or propylene glycols, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrans, sodium saccharin, aspartame and other excipients conventionally used in the formulation of collutaries or liquid oral forms.

The compositions of the invention may further contain other active 15 ingredients with complementary or anyway useful activity, such as antibacterials/ disinfectants, antifungals, analgesics, anti-inflammatories, emollients, local anaesthetics and the like. Suitable antimicrobials include quaternary ammonium salts such as benzalkonium chloride.

Finally, the compositions of the invention can be presented as single- or 20 multi-dose forms, for example in sachets, vials, ampoules, bottles and the like.

Dosage will depend on a number of factors, such as severity, type and extension of the disease to treat: in principle, however, a wash or gargle with 10-50 ml of solution, optionally diluted in water, for a time of about up to two or three minutes three times or more daily, preferably before meals, will be 25 sufficient to provide an optimal therapeutical or preventive response. The treatment can be protracted until remission of symptoms, usually for 5-10 days. More prolonged treatments are not contraindicated, considering the poor, if any, toxicity of the components of the formulations of the invention.

The favourable therapeutical results obtained by use of the formulations according to the invention are due to both the synergic interactions between hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone and the capability of the formulation of adhering to the oral mucosa providing a protective coating for the exposed nerve endings, and therefore reduction of pain and promoting cicatrisation and healing of the lesions. Furthermore, the moisturising effect of the compositions has beneficial effect as it protects mucous membranes from further irritating lesions.

The following examples illustrate the invention in greater detail.

10 Example 1

Quali-quantitative composition percent composition

	Sodium hyaluronate	0.1
	Glycyrrhetic acid	0.06
	PVP	9.0
15	Maltodextrin	6.00
	Propylene glycol	2.94
	Potassium sorbate	0.3
	Sodium benzoate	0.3
	Hydroxyethyl cellulose	1.5
20	Hydrogenated castor oil PEG-40	0.27
	Disodium EDTA	0.1
	Benzalkonium chloride	0.5
	Perfume (Glycyrrhiza Comp. 2717)	0.16
	Sodium saccharin	0.1
25	Depurated water	78.44

For the preparation, water is placed in a turboemulsifier, then a mixture of potassium sorbate, sodium benzoate and disodium EDTA is added, followed by hyaluronic acid and maltodextrin. The mixture is stirred after each addition

until complete dissolution of the components. After that, PVP is slowly added under stirring and vacuum (30 mm Hg) until complete solvation. Then sodium saccharin and hydroxyethylcellulose are subsequently added, the whole is subjected to vacuum and left under stirring until complete solvation.

5 Afterwards, hydrogenated castor oil 40/OE and perfume, benzalkonium chloride, and a mixture of propylene glycol and glycyrrhetic acid are added in this order, stirring after each addition until complete dissolution of the components. When the additions are completed, the mixture is stirred under vacuum for 30 minutes.

10 For the concentrated version of the invention, 10 ml or 15 ml of the composition reported above are distributed in sachets or mono-dose vials, to be diluted with 30-50 ml of water before use; for the ready-to-use version of the invention, the composition reported above is diluted with depurated water to a concentration of 50% and 200 ml or 300ml are distributed in bottles.

15 **Example 2**

Clinical trials

Thirty patients, of age range from 30 to 60 years, were evaluated, 10 of them being AIDS patients, of age of 30 to 40 years, receiving anti-retroviral therapy. Patients were affected with inflammatory pathologies of the oral 20 cavity of various aetiology:

12 cases of oro-pharyngeal mucositis;
4 cases of aphthous lesions of the oral cavity;
4 cases of post-traumatic lesions;
3 cases of Lichen Planus of the oral cavity;
25 3 cases of radiotherapy-induced stomatitis;
3 cases of oral cavity surgery side effects;
1 case of leukoplakia.

Patients were treated with the composition of Example 1 in 15 ml sachets

diluted in water in a 1:4 ratio. The slightly viscous solution was retained in the mouth for 2-3 minutes during which it was gargled and swirled about to obtain homogeneous distribution on the whole surface of the oral mucosa. The solution was then discharged.

5 The formulation was used three times a day 60 minutes before meal times for seven consecutive days.

At the end of the treatment, the extent of inflammation and lesions, the decrease or disappearance of dysphagia for solid and semi-solid foods, and liquids, and the duration of the activity of the product were evaluated.

10 Already after the first administration, more than 80% of patients perceived within a few hours reduction of pain so as to permit food intake. The effect lasted three or four hours.

15 Healing of the lesions of the oral mucosa already occurred after 3-4 days of treatment in about 60% of treated cases. The percentage reached 90% at the end of the treatment. In the remaining three cases only a pathological condition persisted, but with improved symptoms compared with the beginning of the treatment, providing anyway a remarkable improvement of life quality and restoring a normal, differentiated diet.

Example 3

20 Two patients with throat pain (sore throat) were unable to obtain relief with analgesics or other topical agents. Patients were treated with the composition of Example 1 in 15 ml sachets diluted in water in a 1:4 ratio. The solution was retained in the mouth for about one minute during which time it was gargled to obtain good contact with the tissues of the throat. The solution 25 was then discharged. Within ten minutes the patients experienced dramatic relief of their sore throat symptoms, which relief persisted for several hours.

CLAIMS

1. Pharmaceutical compositions comprising as active ingredients effective doses of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone, in mixture with excipients and adjuvants suitable for topical administration.
2. Compositions as claimed in to claim 1, further comprising viscosity-increasing agents, surfactants, stabilising agents-preservatives, flavours, fragrances, sweetening agents, bioadhesive agents, co-solubilisers.
3. Compositions as claimed in claim 2 further comprising cellulose derivatives, acrylic or methacrylic acids polymers or copolymers, ethylene or propylene glycols, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrans, sodium saccharin, aspartame.
4. Compositions as claimed in any one of claims 1 to 3 further comprising other active ingredients with complementary or anyway useful activities.
- 15 5. Compositions as claimed in claim 4, comprising antibacterials/disinfectants, antifungals, analgesics, anti-inflammatories, emollients, local anaesthetics.
6. A composition according to claim 1 having the following percentage composition:

	Sodium hyaluronate	0.1
	Glycyrrhetic acid	0.06
20	PVP	9.0
	Maltodextrin	6.00
	Propylene glycol	2.94
	Potassium sorbate	0.3
	Sodium Benzoate	0.3

	Hydroxyethyl cellulose	1.5
	Hydrogenated castor oil PEG-40	0.27
	Disodium EDTA	0.1
	Benzalkonium chloride	0.5
5	Perfume (Glycyrrhiza Comp. 2717)	0.16
	Sodium saccharin	0.1
	Depurated water	78.44

7. The use of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone for the preparation of medicaments for the topical treatment of inflammatory conditions of the 10 oral mucosa and lining of the oropharynx and oesophagus, particularly mucositis and stomatitis, and the mucosa of the vagina and rectum (including, but not limited to, vestibulitis and Behcet's syndrome).

8. Pharmaceutical compositions substantially as hereinbefore described with reference to the accompanying Examples 1 to 3.

15 9. The use of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone for the preparation of medicaments substantially as hereinbefore described with reference to the accompanying Examples 1 to 3.

DATED THIS 2ND DAY OF OCTOBER 2003.
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Sinclair Pharmaceuticals Limited
By their Patent Attorneys
25 LORD & COMPANY
PERTH, WESTERN AUSTRALIA