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(72) Inventor; and

(71) Applicant: FERRAZZA, Paolo [IT/IT]; Via Ottorino Lazarini 11, I-00136 Roma (RM) (IT).

(74) Agent: FIAMMENGHI, Eva et al.; Via delle Quattro Fontane, 31, I-00184 Roma (IT).

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(54) Title: COMPOSITION FOR THE TREATMENT OF SKIN LESIONS AND IRRITATIONS

(57) Abstract: Composition for use in the treatment of skin lesions and irritations comprising: Water, EDTA 2Na, Allantoin, urea, propolis, 1% Sodium hyaluronate, Marine collagen, glycerine, propylene glycol, 18-β glycyrrhetic acid, Chlorhexidine digluconate up to 20% solution, Hypericum oil, Melaleuca oil, Calendula e.g. Aloe e.g Mallow e.g., Polyethylene glycol sorbitan monolaurate.



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“Composition for the treatment of skin lesions and irritations”Description5 Field of the art

The present invention regards the medical industry and in particular the dermatological and chronic skin lesions industry in general. More in detail, the present invention regards a particular composition for use in the treatment of skin lesions and irritations of various nature such as: redness of the skin due to cold, own irritations, irritations from contact and rubbing; grazes and abrasions that do not extend past the dermis; wounds from superficial cutting and with joined edges; dry and cracked skin; reddened and irritated psoriasis plaques; eczema of various nature even with exudate; mild acne; scalds and burns up to the second degree; radiation burns, decubitus ulcers, venous insufficiency ulcers, diabetic ulcers. Wounds from avulsions with healing by secondary intention.

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State of the art

The treatment of skin lesions is undoubtedly one of the most discussed issues in clinical studies in the dermatological industry. Of particular interest is the study aimed at the treatment of lesions such as: decubitus ulcers; acute and chronic wounds; open wounds (post-surgical and non-surgical); ulcers in general, including decubitus ulcers. The latter are the ones of greatest clinical interest, since the impact on the population, especially bedridden population, is very high and, in addition, no definitive treatment has been found to date, nor has uniformity been achieved in terms of therapeutic and care behaviour, despite the numerous studies carried out on the subject, the various professional figures involved, the countless number of aids and devices used, including the most technologically advanced ones. The only thing that is certain is that adequate prevention plays a decisive role in preventing the occurrence or progression of the lesions. It should be borne in mind that decubitus ulcers can be prevented with the help of family members or competent health

personnel, attentive to the needs of the patient: every two to three hours the subject should be helped to change the position, in order to stimulate blood circulation; the diet should be very scrupulous and regular, as should the hygiene of the body: not excessive but adequate. In addition, specific and targeted ulcers prevention aids, such as pillows, mattresses, 5 disinfectants, bandages, dressings, etc. should be used. In addition, hospital staff or family members, should also consider possible pre-existing diseases (e.g. liver, metabolic, neurological disorders).

Prevention of decubitus ulcers is crucial towards the good health of the subject; as a matter of fact, the lesions which can arise from forced immobility can cause very serious effects, 10 also affecting the muscular and bone tissue. Pressure ulcers cannot be considered “normal” wounds, because they do not heal spontaneously, rather they tend to become chronic. Natural remedies (for mild ulcers) or drugs (if the ulcers degenerate in the critical stages reaching the muscle and bone) can be used depending on the severity of the ulcers. Since decubitus ulcers tend to predominantly occur in subjects with diseases that jeopardise neuromotor function, 15 and in elderly bedridden subjects, such problem is likely to grow as the as the old age population increases, hence entailing an undeniable prospect of increasing demand for effective therapeutic alternatives. Specifically, the expression decubitus ulcer or wound is used to indicate a tissue lesion with necrotic evolution which affects the skin, dermis and subcutaneous layers, up to reaching - in the most severe cases - the muscle, cartilage and 20 bone. The event is caused by a prolonged and/or excessive pressure exerted between the support surface and the bone surface, to an extent of causing a mechanical stress on the tissues and an alteration of the local blood circulation. Clinically, lesions are observed in particularly predisposed sites, such as bone prominences, and they arise following prolonged decubitus in a compulsory position. They are facilitated by general and local events. All 25 conditions leading to decreased mobility are therefore an important risk factor for the onset of lesions. Patients immobilised due to impaired neuromotor function and elderly bedridden patients represent the most exposed categories. The latter also due to the ageing of the tissues which are hypotrophic, less elastic and characterised by greater capillary fragility. The

- presence of concomitant systemic diseases such as diabetes mellitus, renal failure, immunodepression, circulatory disorders, etc. are a further aggravating factor. The main physiopathological mechanisms that determine the onset of decubitus ulcers are pressure and stretching. Other conditions that play a contributing role are rubbing and moisture: The
- 5 pressure exerted on the tissues is considered the main pathogenetic factor. Besides the extent and duration of pressure, the effects of pressure vary also depending on the site, the thickness of the skin and the soft tissues. For example, a pressure of 60-70 mmHg maintained for 2 hours may be sufficient to cause irreversible damage. If the skin tissue can respond to the insult caused by the pressure with compensatory hyperaemia (increased blood
- 10 supply), in the elderly patient this is generally insufficient to protect the latter from the risk of hypoxia (oxygen deficiency). In the absence of oxygen, cells use an anaerobic metabolism, which produces toxic substances and local acidosis, increased vascular permeability, formation of transudate and oedema, as well as further cellular suffering up to the onset of necrosis.
- 15 The stretching forces occur for example when the patient is seated on the chair without sufficient support for the legs or when the headrest of the bed is raised, with a tendency of the trunk to fall and body segments to slide from one position to the other.
- Rubbing does not seem to play a major pathogenetic role. It causes the removal of the outermost layer of the skin, the stratum corneum, with ensuing reduction of the fibrinolytic
- 20 activity of the dermis, making it more susceptible to pressure necrosis.
- Moisture enhances the action of other factors because it makes the skin more fragile and easier to attack. Prolonged exposure of the skin to moisture causes maceration and alteration of the pH, reducing the shielding function of the skin, as it for example occurs in the presence of incontinence and excessive sweating.
- 25 Typically, a correct approach to the treatment of decubitus ulcers is to consider it as a continuous solution of the skin, i.e. a wound, which must be put in the best conditions to heal. Repair is a vital event. It occurs through the formation of connective tissue which is covered through the multiplication of the epithelial cells and migration thereof from the

edges of the wound towards the centre thereof.

It is affected by both local factors (blood supply, the presence of oxygen, the presence of bacteria or the presence of tissue damage, the type of dressing) and systemic factors (malnutrition, diabetes, vitamin deficiency, drug use, hypoxia, hypovolemia, etc.).

- 5 Given that there is no optimal method for the treatment of decubitus ulcers, it can vary depending on the patient's condition, the type of lesion and its evolution. The basic principle is to promote healing by taking care of the natural environment in which tissue repair processes occur, such as granulation and re-epithelisation, and by avoiding the conditions that slow it down, such as changes in moisture, pH and temperature.
- 10 When choosing the most appropriate treatment, certain general principles relating to these processes must therefore be taken into account; in particular:
- Oxygen: it has been proven that the wound healing rate is directly proportional to the local oxygen tension; as a matter of fact, epithelial cells need oxygen to move and reproduce. Therefore, the lesion should be kept clean by the presence of fibrin,
15 necrotic tissue or pressure ulcers that take away the necessary oxygen.
 - Moisture: the concept of healing in a moist environment is a relatively recent acquisition of research on wound repair. In a moist environment, cell proliferation appears to start after 6 hours as opposed to the 18 hours required in a dry environment.
 - Temperature: it greatly affects cell regeneration. The optimum temperature is 37° C. A
20 decrease of even only two degrees is sufficient to inhibit leukocyte mobility. After a dressing, it takes approximately 40 minutes for the cleansed lesion to resume normal temperature and 3 hours to resume mitotic activity. Therefore, dressings which do not require frequent changes and the use of solutions at room temperature for cleaning are preferred.
 - 25 - Cell repair: in the early stages of healing the epithelial cells migrating across the surface of the lesion have poor adhesion to the underlying dermis, hence they can be easily removed. Therefore, as part of the dressing operations, movements of the lesion margins and too frequent dressing changes are to be avoided, as they may hinder

healing.

So ultimately, the requirements for an ideal dressing can be summarised as follows:

- keep a moist micro-environment and the surrounding skin dry
- allow gaseous exchange
- 5 - protect from bacterial contamination
- protect from mechanical damage
- ensure optimal temperature conditions
- allow and facilitate the removal of exudates and necrotic tissues
- be biocompatible
- 10 - be easy to handle.

There are many treatments used to treat decubitus ulcers. Each type of treatment has peculiar characteristics, which make it more suitable for a certain type of lesion (granulating, bleeding, secreting, dry, etc.).

a) Drugs

- 15 - Local antiseptics. The scope of use of local antiseptics has been reviewed recently, which, given the toxicity of the latter to many chemotactic factors, reserves their use to clearly infected lesions and post-escharotomy phases. As a matter of fact, local antiseptics are irritating to skin and mucous membranes, they inactivate the action of proteolytic enzymes and they destroy fibroblasts.
- 20 They therefore slow down the scarring processes and hinder re-epithelisation. In cases where disinfection is required, the preferred antiseptic is chlorhexidine gluconate in 0.05% aqueous solution, with good antiseptic activity, excellent tolerability and low cytotoxicity. The following are not to be used: hydrogen peroxide, as it destroys cells at the re-epithelialisation phase up to 50%;
- 25 povidone iodine, due to the possible cytotoxic activity on fibroblasts, due to the onset of hypersensitivity reactions and due to the risk of triggering thyrotoxicosis; cetrimide and sodium hypochlorite, due to cytotoxic activity; ethyl alcohol, because it is irritating and causes dryness of the skin; silver nitrate,

because it is irritating and it confers a brown colour to the skin.

- Antibiotics. The use of topical antibiotics is the subject of controversial opinions because it entails the risk of sensitization and bacterial resistance. Most authors argue that accurate and frequent cleansing is sufficient for the treatment of colonized and/or infected lesions as well. Some authors argue that the use of topical antibiotics should be reserved exclusively for the treatment of clearly infected lesions, limited to cases where the use of antiseptics and thorough cleansing, continued for 2-4 weeks, did not heal the lesion completely. In serious infections, with muscular or bone involvement, everyone agrees on the use of antibiotics via systemic route, with targeted spectrum of action.

- Proteolytic enzymes. Proteolytic enzymes act by removing necrotic fragments from the enzyme digestion lesions of denatured collagen bridges. They are active in a moist environment and they are inactivated by hydrogen peroxide and antiseptics. Their action time varies from 8 to 24 hours depending on the active ingredient used. They are recommended for moist or suitably moistened lesions with presence of necrotic areas or fibrin accumulation at the bottom of the lesion and in the phases following escharotomy. They should not be used on infected lesions.

- Ringer's lactate solution. The solution is used to irrigate decubitus ulcers. It contains lactic acid, calcium chloride, potassium chloride, sodium chloride and sodium hydroxide; potassium is alleged to have skin trophism facilitating properties.

b) Medical devices

The ideal dressing must create an environment favourable to cell division and replication processes on the surface of the lesion, i.e. ensure optimal temperature (37°C), humidity and oxygenation conditions, be biocompatible and protect the ulcer from mechanical damage and bacterial contamination, preserving the skin surrounding the lesion.

Dressings available in the market:

1. Gauzes
2. Adsorbent dressings
3. Dressings favouring granulation
4. Hydrogels
- 5 5. Occlusive dressings
6. Semi-occlusive dressings

I. GAUZES. Gauzes can be made of cotton or TNT. They are distinguished in:

- simple gauzes, which represent conventional dressings, should not be applied directly to the ulcer, but used as secondary covering dressings, as they require frequent dressing changes and, moreover, adhering to the lesion, they increase the risk of removal of the granulation tissue;
- non-adherent gauzes impregnated with fatty substances to reduce adhesion and traumatism in dressing operations;
- antiseptic gauzes containing antiseptic substances;
- 15 - medicated gauzes containing or carrying active substances.

II. ADSORBENT DRESSINGS The adsorbent dressings, consisting of hydrocolloid pastes and granules - alginates - hydrofibres, are characterised by the ability to remove excess exudate (extravascular inflammatory liquid), absorbing it or trapping it in the weft thereof. Their duration of use is determined by saturation and it is directly proportional to the amount of exudate present in the lesion. The optimal product should be capable of absorbing excess exudate, maintaining the lesion-dressing interface always moist so as to facilitate the repair process.

III. DRESSINGS FAVOURING GRANULATION. By acting through a gelation process, these products maintain a moist microenvironment, favouring the development of the granulation tissue. They are non-occlusive and do not guarantee thermal stability. These are collagen or alginate or hydrofibre-based dressings that become active after gelation. Collagen provides a favourable weft for the development of fibroblasts and it is recommended for well-cleansed, moist and granulating superficial and deep lesions.

It should not be used on dry or hyperexuding lesions. Alginates and hydrofibres have both adsorbing and granulation-promoting properties and the above applies.

IV. HYDROGELS. Hydrogels are structural polymers, formed from synthetic, semi-synthetic, or natural materials, or from mixtures of several polymers, capable of retaining and incorporating significant volumes of water. They act by moisturising necrotic tissues and favouring their autolysis. Given that their absorbent capacity is rather limited, they should be used on dry or slightly exuding lesions. Hydrogels that also contain adsorbent substances have greater efficacy. They are available as gels or plaques. They are recommended for the treatment of lesions covered with fibrin and yellow necrotic tissue and for the rehydration of dry pressure ulcers. The time of use varies from 1 to 3 days. They release a bad odour. They always require a secondary dressing, preferably a polyurethane film or hydrocolloid or polyurethane foam-based dressings.

V. OCCLUSIVE DRESSINGS. Occlusive dressings are advanced dressings, which maintain a moist microenvironment and do not allow oxygen to pass through. They have medium-low adsorbing capacity and they promote the cleansing of the lesion. They can also be used on infected wounds, but require careful monitoring for possible anaerobic infections. They are represented by occlusive hydrocolloids. Hydrocolloids are mixtures of natural or synthetic polymers, in granules suspended in an adhesive matrix. These granules have the property of absorbing water in a slow and controlled manner hence they are recommended selectively in dry or moderately exuding lesions. When the dressing is hydrated, a physical transformation called phase inversion occurs, forming a gel. This gel is characterised by an unpleasant smell, it does not adhere to the injured skin and it keeps the environment moist, favouring the repair process, promoting autolysis, angiogenesis, granulation and therefore healing. The gel allows the dressing to be changed without damaging the newly formed granulation tissue or epithelium. Plaques may remain in site until efficacy is exhausted, i.e. from 3 to 7 days, depending on the amount of exudate, and they are the option of choice in

the treatment of many cases of decubitus ulcers.

VI. SEMI-OCCLUSIVE DRESSINGS. Semi-occlusive dressings are advanced dressings which maintain a moist microenvironment and they allow oxygen, but not liquids and bacteria, to pass through. They are characterised by semi-permeable films, polyurethane foams and semi-occlusive hydrocolloids. They act by maintaining a microenvironment that is moist and isolated from the external. Semi-permeable films are normally transparent films, made of polyurethane, covered with a thin acrylic adhesive layer, permeable to gases. Unlike foams, they have no adsorbing capacity. They can be used as a single dressing in grade I lesions, as a prevention of rubbing or maceration damage due to prolonged exposure to moisture or as secondary dressings in the fixation of other products. The transparent ones allow to inspect the wound without having to remove the dressing. The dressing should be replaced in the event of detachment or approximately every 7 days, depending on the amount of exudate. Polyurethane foams are high-absorption materials, coated with a soft, perforated layer that does not adhere to the lesion, in the form of circular or tubular plaques or pads. They are used for flat or cavitory lesions with medium/abundant exudate, they maintain a moist environment and they promote the development of scar tissue. They are not recommended in case of infection. After cleansing, the dressing should be replaced at saturation (1 to 7 days depending on the amount of exudate). Pads require a secondary fixing dressing (e.g. semi-permeable films).

Further types of skin lesions are acute and chronic wounds.

A wound is a continuous solution of one or more tissues of the body and it is defined depending on how it is determined and the time of healing. The main types of wounds, classified according to the time of healing, are acute wounds and chronic wounds: acute wounds that the healthcare professional most frequently has to treat are surgical wounds; chronic skin lesions are all skin lesions that do not reach the tissue repair state within 8/10 weeks from their onset. In addition to the above-mentioned decubitus ulcers, the following are also worth mentioning: vascular ulcers, diabetic foot ulcers and surgical wounds.

Vascular ulcers are defined as cutaneous wounds with venous, arterial and/or mixed vascular aetiology, which are found, in 75% of cases, on the lower limbs, starting from the knee to the foot and which manifest themselves with a duration equal to or greater than eight/ten weeks.

Vascular ulcers in turn are divided into:

- 5 - Venous ulcers: continuous solutions that may only affect dermo-epidermal surfaces, due to varicose disease and/or post-thrombotic syndrome that causes abnormal venous return, associated with oedema;
- Arterial ulcers: trophic ulcers of the lower limbs that occur in subjects suffering from obliterating arteriopathy that causes ischaemia. They are characterised by pain;
- 10 - Mixed ulcers: skin lesions due to microcirculatory alterations resulting from microvascular diseases of both arterial and venous type.

A very common disease in the Western world, chronic leg ulcers mainly affect the elderly, resulting in a high social cost. The prevalence data of vascular ulcers are in a range from 1.8 to 3.05 per thousand, with increasing prevalence as age increases. In Western countries, it

15 has been calculated that 10 per thousand of the adult population has been affected by lower limb ulcer at least once in their lives. Though less studied and having received less attention than chronic arterial insufficiency, chronic venous disease is believed to affect the adult population 10 times more. Despite this, the treatment of venous ulcer is often neglected or completely inadequate. Venous leg ulcer usually manifests itself as a loss of irregular shaped

20 skin substance, with the surface covered with a yellowish exudate, with well-defined margins, surrounded by erythematous or hyperpigmented and liposclerotic skin. Patients with venous ulcer may experience severe pain, even in the absence of infection. The pain is aggravated by the upright position and decreases until it disappears upon lifting the lower limb.

25 Venous ulcer is a chronic condition characterised by slow repair and a tendency to relapse, hence the objective of the therapy is not only healing, but also, and above all, prevention of relapse. At the same time, it is of fundamental importance to improve the patient's psychological condition, for acceptance and collaboration in the therapeutic program as well

as for the quality of life. The therapy of a venous ulcer may involve one or more of the following treatments:

- Basic treatment. Basic treatment should conform to the general rule of considering the patient as a whole and not focus solely on the treatment of the ulcer. In this context, the modus vivendi, the ambulatory capacity, the work, the possibility of obesity, diabetes or other concomitant diseases of the patient are of great importance;
- Pharmacological therapy. It should be used, always associated with pressure, when the surgical solution is not usable or when it has not given the expected result. Profibrinolytic, bioflavonoid, prostanoid and pentoxifylline agents are commonly used;
- Compression Therapy. A systematic review of controlled and randomised studies has shown that compression facilitates recovery of venous ulcers, that in venous ulcers high pressure compression is better than low pressure compression and that multicomponent systems are more effective than single component systems, especially if one of the components is elastic. In addition to reducing the diameter and venous reflux and increasing the venous pump function, compression can increase lymphatic drainage, improve microcirculation, reduce chronic oedema, and thus facilitate the healing of the ulcer. Compression therapy can be carried out using bandages or elastic stockings.
- Topical dressing. Topical treatment of the venous ulcer must ensure the cleansing of the lesion, preservation of the microenvironment, protection from infectious agents and stimulation of cell repair mechanisms. The ideal dressing should have the following characteristics:
 - not stick or leave residue on the bottom of the ulcer;
 - keep the surface of the ulcer moist;
 - be impermeable to liquids but permit gaseous exchanges;
 - create a barrier against bacteria and fungi;
 - stimulate the growth of the granulation tissue

- relieve pain.
- Surgery. Venous ulcer surgery is not to be considered either exclusively nor alternatively, but complementary to conservative management. Surgical ulcer therapy has two fundamental objectives:
 - 5 • correction of basic haemodynamic alteration;
 - ulcer cover by skin grafts in order to reduce healing time.

The choice of the most suitable procedure must always be preceded by an accurate morphological and haemodynamic study of the venous system both superficial and deep using the usual diagnostic methods.

- 10 Diabetic foot ulcers occur when diabetic neuropathy or lower limb arteriopathy compromise the function or structure of the foot. The two profiles, also referred to as neuropathic foot or ischaemic foot, are profoundly different from each other: however, in most subjects, especially in old age, both coexist giving rise to the so-called neuroischemic foot. In case of diabetic neuropathy, the damage may cause insensitivity or loss of ability to feel pain and
- 15 temperature changes at the level of the lower extremities. This means that a diabetic patient tends not to notice the presence of cuts, wounds, burns, freezing, and so on at the foot, precisely because the response thereof to pain is weakened.

- If, besides diabetic neuropathy, we also have poor circulation at the lower limbs (arteriopathy and vascular ulcers), it is easily clear that a small scratch on the foot can cause
- 20 exaggerated damage, bleeding ulcers which, can induce gangrene in the long run. Rapid degeneration in ulcers and foot infections from a small lesion in a diabetic patient derives from poor circulation at the lower extremities (arteriopathy). Not receiving due blood supply, the feet of a diabetes patient struggle to repair the damage the skin has suffered. Furthermore, the skin of the diabetic foot becomes thin, fragile and extremely delicate and
- 25 therefore more subject to traumas and injuries of all kinds.

Foot ulcers are undoubtedly the most common complication that occurs in the feet of a diabetes patient. The danger of ulcers is closely linked to the poor circulation induced by the of the diabetes patient: not receiving the due amount of blood, the ulcers struggle to heal. As

a result, a cascade mechanism is triggered leading to bleeding and/or infections. When the infection spreads, the patient runs the risk of tissue death (tissue necrosis), and thus gangrene.

In the latter case, the limb requires immediate medical-surgical operation, which involves the administration of antibiotics to kill bacteria, the removal of infected tissue and, when necessary, amputation of the limb (or part of it) so as to prevent the damage from spreading even to the neighbouring regions.

The World Health Organization's predictions estimated that the number of diabetic patients in 2025 will be more than 300 million as compared to the 120 million calculated in 1996, which makes it easy to see the magnitude of this problem. Estimates of this disease indicate that about 15% of diabetic patients will experience a foot ulcer in their lives that will require medical care. In addition to the relevant impact in terms of frequency, it is emphasised that the foot ulcer in diabetes patients is burdened by a greater risk of higher level amputation, i.e. performed above the ankle; although the diabetic population accounts for about 3% of the general population, more than 50% of all higher level amputations specifically regard diabetes patients. The optimal treatment of diabetic foot ulcers occurs through: either local treatment of the lesion by dressing; or the treatment of possible infections; or discharge of the ulcerative lesion (i.e., avoid that it is burdened by the weight of the body while walking); or possible revascularisation.

If the treatment of the diabetic foot is based on the following principles, 80-90% recovery rates can be achieved. The best local treatment cannot compensate for the presence of minor trauma linked to the persistence of the hyperloading and, it does not allow to overcome an ischaemia or infection condition if not adequately treated.

The choice of the right treatment requires classification of the lesion, in particular Wagner's is the standard classification, even though the "Texas wound classification system", which allows the lesions to be stage lesions also based on parameters such as depth, infection, ischaemia, and therefore able to provide more prognostic information than other classifications, has been recently reported in literature.

WAGNER CLASSIFICATION

Class 0 = Non-ulceration, presence of possible deformity, oedema, cellulitis, etc.

Class 1 = Superficial ulcer

Class 2 = Deep ulcer up to the tendon, to the joint capsule, to the bone, without infection

5 Class 3 = Deep ulcer with abscess, osteomyelitis, septic arthritis

Class 4 = Gangrene localised to the fingers or heel

Class 5 = Gangrene of the whole foot or a significant portion thereof.

Table 1.

Texas Wound Classification

Grade	0	I	II	III
Stage A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendons, capsule, bone	Wound penetrating to capsule or tendon	Wound penetrating to bone or joint
Stage B	With infection	With infection	With infection	With infection
Stage C	With ischemia	With ischemia	With ischemia	With ischemia
Stage D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

10

As far as surgical wounds are concerned, first and foremost it should be pointed out that the surgical wound is a solution of continuity of the tissues produced by a mechanical agent. In clinical practice there are 2 main types of surgical wounds:

- wounds that heal by primary intention in which the edges have been approached by stitching. They repair rapidly generally developing a linear scar that is often not very visible;
- wounds that heal by secondary intention in which the flaps are often not approached due to an infection. Healing is slow and the scar that forms can take on varying

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dimensions. Dehiscence of the surgical wound indicates a post-operative complication represented by the spontaneous reopening of a previously sutured wound. It may be partial and thus involve one or more stitches or full. A very serious form regards laparotomy wounds, in which the complete opening of all the layers of the wall entails the removal of the movable viscera out of the abdominal cavity or evisceration. Optimal treatment of surgical wounds is achieved through proper preparation of the skin and patient for the operation and local treatment of the wound through dressing.

The difference between lesion, wound and ulcer should be emphasised, in particular:

- lesion: reversible or irreversible alteration of the anatomy and histological characteristics of a tissue or organ that alters the integrity of the organism;
- Wound: a continuous solution, with or without loss of substance, of cutaneous or internal tissue, caused by various external factors;
- Ulcer: A skin lesion characterised by deep loss of substance and poor healing tendency that occurs leading to scars. It is the expression of degenerative processes caused by inflammatory, infectious events, circulatory disorders or by tissue damage due to chemical and physical causes.

The treatment of the wound must allow restitutio ad integrum, that is, it must ensure a complete restoration of the functions of the skin, it must reduce the risk of infection and it must make the wound acceptable from an aesthetic point of view. This objective is achieved both by adopting some solutions in the preoperative period and through the correct treatment of the wound. In particular, it is necessary to remove any necrotic material from the wound bed, reduce the bacterial load, the excess exudate, while simultaneously protecting the edges and using advanced dressing technologies. The choice of one treatment rather than another depends on the type of surgical wound which in turn depends on the type of surgical procedure performed which may affect the risk of wound infections. Surgical procedures can therefore be classified according to the risk of wound infection as follows:

Table 2.

Wound classification	Type of operation	Definition
I	Clean	Operations in which no phlogistic process is observed, the continuity of the respiratory, intestinal, genitourinary mucosa is not breached and in which the rules of asepsis in the operating theatre are not breached.
II	Clean-contaminated	Operations in which the continuity of the respiratory, intestinal or genitourinary mucosa is breached, but without loss of material toward the external.
III	Contaminated	Operations where there are signs of acute phlogosis (without pus), or where contamination of the wounds is visible.
IV	Dirty or infected	Operations carried out in the presence of pus or on a previously perforated hollow viscera or on compound/open wounds occurring more than 4 hours before the operation.

In the case of a “clean” wound, it is assumed that the wound environment, whose edges are normally closed using stitches, is clean and with low bacterial contamination. There arises
5 the need to keep the wound in good cleaning conditions, avoiding bacterial over-contamination, and protect the suture from contact with clothing and with dirt.

Thus:

- Unless otherwise prescribed, disinfect the wound regularly using a specific antiseptic;

- Apply a sterile prepared dressing with high absorbency of exudates.
- Change the dressing whenever necessary (e.g. when it is dirty, soaked with exudate or when it has lost adhesiveness).
- If you have to wet the skin (for example, for a shower), use suitable waterproof dressings.

In the case of skin injury caused by sharp objects, in the specific case due to surgical scalpel, skin healing occurs faster than when fortuitous events cause skin injury and they do not require external applications to facilitate the mating of the two outer edges of the wound.

The healing of surgical wounds is facilitated by the use of stitches that fill the cut portion and, in a short time, allow for healing of the cut in a few weeks.

It is also true that there are considerations to be made in this case; the physician will instruct the patient on several measures to be taken so that the wounds heal in the best possible way without further complications for the subject in question.

As a matter of fact, in order to avoid uncomfortable and sometimes serious side effects, the patient must avoid:

- lifting weights,
- practising sports,
- carrying out heavy work in the immediate weeks close to surgery,
- All in the modalities and times communicated by the specialised medical staff.

Wound healing may also depend on the presence of any infectious symptoms: if for any reason the wound appears infected, recovery times will certainly be longer and it may also be necessary to use drugs against infections and pain killers, if the wound causes the person physical pain that is stronger and more persistent than usual.

This possibility may occur due to the presence of pathogenic agents which have altered the condition of the wound; bacterial infection can occur when applying the stitches with the presence of some bacteria either inside the human body or present on the equipment used or in subsequent dressings due to failure to comply with good hygiene practice. An accurate and perfect hand cleansing, use of sterile material (gloves, gauzes, etc.) are good bacterial

infection prevention standards in the post-surgical period.

In any case, there are daily actions that can be taken in order not to risk irritating the scars and to improve their healing:

- Gentle cleansing;
- 5 - Attention to heat and cold;
- Comfortable clothing, avoid rubbing;
- Avoid exposure to the sun;
- Repair oil and ointments;
- It is important to choose an extremely delicate cleansing of the part by choosing
10 washing ointments or cleansing oils that do not dry or dehydrate the area, but,
guarantee nourishment and strengthen the hydrolipidic mantle.
- Heat and cold can infect scars; heat, such as sauna temperatures, can damage scars;
likewise, it is good to pay attention to the temperatures that are too cold, protecting the
scars from the strong frost which, just like heat, can further damage it, making
15 treatment even more difficult;
- The clothing used is of remarkable importance; it is good not to use clothes that are too
elastic and restrictive in the vicinity of the scar; the fibres can irritate the epidermal
tissue of the scar. Exposure to sunlight in summer should be more cautious if there are
scars on the skin. High protection against the harmful rays of the sun must always be
20 used. In the presence of scars, attention must be greater. Avoid direct exposure of the
scars to sunlight where possible. However, the scar should always be protected
abundantly.
- Specific repair oils act reducing the reddening of the scar and making the skin softer,
more elastic and smoother. It should be borne in mind that the treatments suitable to
25 eliminate scars should start as soon as possible. After an operation, as soon as the scar
can be treated, that is, immediately after eliminating the stitches, it is advisable to start
the treatment immediately. It must be applied twice a day paying keen attention to
what you are doing;

- some basic rules must be followed in order to achieve the desired effects: the scar must be completely healed;
 - it must be massaged carefully starting from the centre of the scar to reach up to the external until complete absorption. The treatment of scars requires daily constancy;
 - 5 - The duration of treatment depending on the nature and “age” of the scar. Generally, the first treatment period is eight weeks, after which the first positive effects of the application should be visible;
 - For more severe situations with older scars, treatment and application should be extended several months from approximately three to six months.
- 10 An object of the present industrial invention patent application is to propose a new pharmaceutical composition for use in the treatment of the above-mentioned skin lesions which proves to be particularly effective in the process of healing such lesions.

Description of the invention

The present description refers to a particular pharmaceutical composition suitably formulated
15 in spray for topical use, specifically designed to favour the formation of a film-forming barrier capable of exerting on the skin a protective, lenitive and transpiring action.

In more detail, it is an Allantoin spray which, thanks to the muco-adhesive properties of its components, favours the formation of a barrier on the skin useful to protect it from the attack of external agents.

20 The barrier function, in addition to Allantoin, is ensured by the presence of hydrolysed Marine collagen and Sodium hyaluronate which, thanks to its film-forming properties, allows to retain hydrophilic molecules ensuring skin hydration. The synergistic action between dry extract of Propolis, Hypericum oil and Calendula, ensures a dermoprotective and regenerating effect which, together with Chlorhexidine, contributes towards protecting
25 the environment from bacterial infections. Even more in detail, the spray-formulated composition according to the present invention can be used in the treatment of:

- Any type and level of redness of the skin due to cold, irritation, contact and rubbing;
- Grazes and abrasions that do not extend past the dermis;

- Small superficial cut wounds and with joined edges;
 - Dry and cracked skin;
 - Red and irritated psoriasiac plaques;
 - Eczema of various nature also with exudate;
- 5 - Support for the treatment of mild and moderate acne;
- Treatment of scalds and burns up to the second surface degree (maintaining the transpiring capacity without causing occlusive effect on the sunburn);
 - Treatment of radiation burns;
 - Prevention in the formation of decubitus ulcers (back, heels and glutei) and also in the
- 10 prevention of ulcers caused by the use of the diaper.

Being based on natural substances and not containing alcohol, the spray can also be used for localised irritations in the skin folds due to rubbing and in delicate areas such as armpits and groin.

Its method of use in the treatment of such lesions provides for: cleaning and drying the

15 affected part before application. Dispensing the product from a distance of 5-10 cm from the part concerned and allow to dry for one minute.

Said spray is preferably to be applied 2/3 times a day on the area to be treated taking care to have it washed and dried thoroughly before. It is not necessary to massage, but rather to let it dry in the air.

20 It is important not to exceed the recommended doses without the advice of the physician and it is advisable to stop using the product in case of irritation.

It should also be pointed out that the product must be shaken before use on the skin to be treated. With regard to possible contraindications and side effects, the studies carried out have shown that no overdose events have been reported. Although the product has been

25 tested without any adverse effects, the spray-formulated composition according to the present invention should not be used in the event of a known hypersensitivity to one or more components of the formulation and it is therefore advisable to contact the treating physician or pharmacist for any possible adverse effect. It should also be pointed out that said

composition is not to be used on wounds, infected lesions, deep lesions, burns or on the face. It should not be inhaled and it is also important not to massage the treated area after application. It should also be noted that this composition should not be used during pregnancy, breast-feeding and in children without consulting the physician. Said

5 composition comprises: 18- β glycyrrhetic acid, Water, Allantoin, Aloe Vera, Calendula, Chlorhexidine digluconate 20% solution, hydrolysed Marine Collagen, EDTA 2 Na, Glycerine, Propylene Glycol, Hypericum oil, Mallow, Propolis, Sodium hyaluronate 1% solution, Tea Tree oil (Melaleuca oil), Tween 20 (Polyethylene glycol sorbitan monolaurate) Urea. In its preferred embodiment, the composition according to the present invention,

10 formulated in spray, is made available to the user in 50 ml spray bottles.

Detailed description of the invention

The composition for use in the treatment of skin lesions, subject of the present invention, has the following quantities of its components indicated in Table 3.

Table 3.

15

Substance	%
Water	74.5
EDTA 2 Na	0.3
Allantoin	0.1
Urea	2
Propoli hrd	0.5
Sodium hyaluronate 1% solution	0.7
Marine collagen	0.7
Glycerine	4.3
Propylene glycol	3.6
18- β glycyrrhetic acid	0.1
Chlorhexidine digluconate 20% solution	3
Hypericum oil	0.7

5	Tea tree oil	0.7
	Calendula e.g. (glycolic extract)	0.4
	Aloe e.g.	3
	Mallow e.g.	0.4
	Tween 20 (Polyethylene glycol sorbitan monolaurate)	5
	TOTAL	100

10 Of the aforementioned components indicated in Table 3 the hydrolysed marine collagen is a protein of marine origin, it creates an effective protective barrier between the wound and the external environment. Collagen is an abundant protein in the human body. Its functions are mainly structural, allowing the anchoring of complex molecules such as proteoglycans or fibronectin and conferring the tissues their structural conformation.

15 In brief, collagen is mainly involved in maintaining the cohesive, elastic and regenerative properties of the skin and in structuring various tissues and, mainly, the extracellular matrix. An integration of collagen strengthens endogenous collagen by stimulating its renewal. It also strengthens the elasticity of the skin.

Hydrolysed Collagen owes its pharmacokinetic properties mainly to the hydrolysis process
 20 carried out chemically using acids or bases or enzymes. The fruit of this digestion is a mixture of peptides of different molecular weight, therefore characterised by equally different biological functions and pharmacokinetic characteristics. More precisely, peptides of high molecular weight, thanks to the excellent surfactant properties, have proved particularly valuable in order to maintain the qualitative properties of the skin, avoiding the
 25 dispersion of water therefrom and thus maintaining an excellent skin hydration condition, necessary to maintain the correct degree of moisture in the wound, such to make the environment suitable for repair. Therefore, the hydrolysis process confers collagen a greater water absorption capacity, suitable for the reconstruction of exogenous collagen.

The hydrolysed marine Collagen allows to recover the significant losses of ceramides and glycosaminoglycans that the skin can undergo. It also has major antioxidant properties and helps to repair endogenous collagen synthesis.

Allantoin is a natural substance, present both in the natural world and in the plant world. It is
5 also naturally found in the human organism where it performs essentially antioxidant functions. Allantoin action has been shown to actively participate in the healing process of inflammations, wounds and grazes, thanks to its ability to promote cell proliferation, even quickly. In particular, the healing mechanism occurs through the regulation of the inflammatory response, further guaranteeing a stimulation of fibroblast proliferation and the
10 synthesis of the extracellular matrix, which are fundamental components for the tissue regeneration of open wounds. Allantoin also participates in the formation of epithelial tissue, avoiding the formation of disfiguring scars, and can therefore also be used for the treatment of burns scars, as well as for the topical treatment of postoperative scars. To this end, it can constitute actual patch on the wound, not only performing an antibacterial and protective
15 action against contamination by external agents, but also allows the transpiration of the tissue. Therefore, besides performing an important dermo-repair action, it also has moisturising properties, thus being suitable for the treatment of dry, dull and cracked skin.

In high concentrations, it has a certain keratolytic activity, i.e. loosens the junctions between cells in the stratum corneum, hence the superficial necrotic elements can be removed, with
20 the advantage of softening and regenerating the skin.

It is one of the main constituents of the snail drool and its antioxidant, lenitive, moisturising and healing capacities make it one of the perfect molecules to promote physiological cellular regeneration.

In addition, safety tests and assessments were conducted on the use of allantoin with
25 concentrations up to 2% with positive outcomes.

It acts helping to eliminate the stratum corneum of the skin, also providing an emollient action of hyperkeratotic areas. It performs a so-called “debridement” action: that is, it removes necrotic tissue, devitalized tissue, infected tissue, hyperkeratosis, pus, haematoma,

debris, or any type of bacterial load of a wound with the aim of promoting healing. The body also reacts to Endogenous urea in the same way as it reacts to the Urea produced by the body: when it penetrates into the tissues it removes dead skin cells, thus favouring cell renewal but above all by accessing the lower layers of skin, carrying out an in-depth
5 emollient effect. Urea has been shown to be useful in wound therapy for mucus and other exudates, crusts and necrotic tissue removal capabilities. Furthermore, excellent results have been obtained regarding the use of urea as bactericide. Furthermore, the use of urea has not shown any deterioration effects of the wounds on which it has been applied. The best results were obtained by applying urea to chronic and infected ulcers.

10 Chlorhexidine is a bactericidal antiseptic disinfectant for topical use, of synthetic origin and bis-guanidine structure. It is used more in the prevention of inflammatory and infectious diseases of the oral cavity and as an adjuvant in the prevention of gingivitis and periodontitis.

It can alter the integrity of the normal structure of the bacterial membrane, increasing the
15 permeability thereof and inducing cell death through osmotic lysis. A variety of formulations are available and chlorhexidine gluconate is the most widely used in the healthcare industry. The spectrum of action is wide being active toward Gram-positive, Gram-negative, yeast and lipid-enveloped viruses. Numerous empirical studies have also shown activity against Candida Albicans. A potent sporicidal activity can be induced by temperature increases, pH
20 changes and addition of ethanol. Thanks to its wide range of action and excellent safety profile, it has been used for many decades for hand hygiene and for disinfecting the skin of the patient before a surgical procedure or before a catheter is inserted. Chlorhexidine has been shown to significantly reduce the microbial load present on the skin by showing persistent activity for many hours even after application. Chlorhexidine is occasionally
25 associated with contact dermatitis and rarely associated with anaphylaxis and hypersensitivity reactions.

A study conducted to reduce the risk of infection at the surgical site due to bacterial load of the skin, comparing the activity of an innovative polyester cloth impregnated with 2%

Chlorhexidine gluconate with the application of a standard procedure of a topical antiseptic of 4% Chlorhexidine in the preparation of the skin prior to surgery. The bacterial flora of the skin often includes numerous species of Staphylococcus and in particular Staphylococcus epidermidis.

- 5 Hand washing with Chlorhexidine has been shown to reduce the bacterial flora present by 86% - 92%. In addition, Chlorhexidine has a residual activity on the skin which helps prevent rapid regrowth of bacterial organisms by improving the skin's antiseptic action.

In particular, the presence of Chlorhexidine in the composition in question allows the medical device, or said composition formulated in spray or plaster, to have a great
10 effectiveness not only for treating but also for preventing infections which can often occur on open wounds, burns and sores of all kinds. In particular, clinical studies have shown a significant reduction in infections in wounds of patients treated with Chlorhexidine in a preventive manner. However, even on already infected wounds, Chlorhexidine has proved effective in the treatment thereof.

- 15 Sodium hyaluronate derives from the reaction between hyaluronic acid and sodium metal. Its main mechanism of action is to create a film-forming effect given that it forms, on the skin surface, a film that prevents the loss of transdermal water, thus preserving moisture. Sodium hyaluronate is suitable to promote the healing of epithelium wounds, as has been verified through in vivo and in vitro studies on animals. Studies have also been conducted on cultures
20 of human cells treated with Sodium hyaluronate and a significant increase in cell migration has been demonstrated. The beneficial effect of sodium hyaluronate in wound healing is therefore due to the rapid cell migration facilitated by the latter.

The Tea Tree Oil, also called Melaleuca, is extracted from an Australian plant and has always been used for herbal purposes, but in recent decades demonstrations of its medicinal
25 capabilities, as an added treatment for wounds, have emerged in scientific literature. Its properties are portentous and effective from the first use: antiviral, antibacterial, anti-parasitic, calming and balsamic. In particular, it is used as an antiseptic and wound disinfectant.

In particular, the antibacterial action of Melaleuca oil against Staphylococcus infections has been demonstrated and no adverse effects of topical use have been reported.

Mallow shows a marked emollient activity, it helps to hinder and reduce the inflammatory processes associated with the evolution of wounds, sores and ulcerations. The mechanisms of action of Mallow are therefore synergistic and adjuvant with those of Allantoin.

Hypericum oil is extracted from a plant also called St John's-wort (*Hypericum perforatum*), which is a medicinal plant and which has a marked eudermic action, that is, it is capable of improving the physiological condition of the skin. Its reputation as a support for healing wounds, bruises, and ulcers, alone or contained in a topical formulation, is well documented in literature.

Propolis essentially consists of a mixture of aromatic and phenolic compounds enriched by numerous heterogeneous substances (fatty acids, terpenes, amino acids, vitamins, mineral salts, etc.) whose percentage distribution varies a lot depending on the seasons and type of vegetation.

Propolis is a bee product with a very complex chemical composition. It is a resinous substance that bees collect from the buds and bark of plants. It is therefore a substance of plant origin even if bees, after harvesting, process it with the addition of wax, pollen and enzymes produced by their organism.

It has antibacterial, anti-inflammatory, cicatrising, anaesthetic, anticariogenic, antifungal, antiprotozoal and antiviral activity. In vitro antibacterial activity has been tested against several Gram-positive and Gram-negative bacteria and proved to be synergistic among propolis, pinocembrin compounds mainly and flavonoids, galangina. Other flavonoids, such as chrysin and kaempferol have shown antiviral activity with reduction of intracellular proliferation of some viruses, such as herpes simplex.

A wide variety of natural products are used in the treatment of wounds due to their harmlessness, low cost and bactericidal/bacteriostatic effect. Propolis is widely used in dermatology for wound healing and acceleration in tissue repair.

Many studies show that treatment with Propolis induces better epithelial healing, reducing

the inflammatory response. Wound healing is directly related to the inflammatory process and regenerative property appears to cause the antioxidant activity thereof because whenever free radicals are produced, they hinder or even block cell regeneration. The removal of free radicals from the flavonoids contained in propolis would therefore allow tissue regeneration.

- 5 Aloe Vera is a succulent plant similar to cactus, belonging to the Liliaceae family that grows in arid and tropical regions.

Aloe Vera leaves contain a wide range of biologically active substances, the most documented among which surely being: acetylated mannans (Acemannans), polymannans, C-glycosylated anthraquinones, anthrones and lectins.

- 10 Aloe Vera is believed to be effective in wound healing and some studies confirm its effectiveness. A recent meta-analysis dating back to 2007, which took several studies into consideration, concluded that Aloe Vera is effective in healing first and second grade wounds.

Aloe in topical preparations was also effective against genital herpes and psoriasis.

- 15 Aloe Vera extracts have antibacterial and antifungal properties useful in minor skin infections, such as tinea capitis, pedis, etc. As antibacterial, the ability of Aloe Vera gel to inhibit the growth of Streptococci and Shigelle colonies has been demonstrated in vitro.

- Calendula has anti-inflammatory, antibacterial, antiviral, immunostimulant activity; it also promotes wound healing by influencing the various phases of the process leading to their
20 healing. The healing activity has been demonstrated in various experimental models and most of the positive results have been obtained using an alcoholic extract. Carotenoids are believed to be, at least in part, responsible for the healing action of calendula and that this action is assisted by the antibacterial and anti-fungal action of polysaccharides and essential oil. Lastly, the anti-inflammatory activity, demonstrated in several experimental models, was
25 mainly attributed to the triterpenoid fraction, in particular to faradic and its derivatives. Aqueous extracts of calendula can inhibit influenza and herpes simplex virus.

Calendula is recommended by the German E commission for the treatment of inflammatory conditions of the oral cavity as well as for accelerating the healing of wounds and burns. In a

randomised study of 254 patients with grade 2 (or higher than grade 2) acute dermatitis following radiotherapy (required for breast cancer) skin application of calendula was shown to be even superior than the reference drug in reducing the incidence of dermatitis and pain. Calendula was usually applied twice a day starting from the first day of radiotherapy and
5 until the cycle was completed. No adverse effects or contraindications related with the use of calendula are known.

18- β glycyrrhetic acid is extracted from liquorice roots and its essential anti-inflammatory as well as lenitive and adjuvant properties in skin repair processes have been pharmacologically demonstrated.

10 The anti-inflammatory effects of 18- β glycyrrhetic acid can be attributed to its ability to enhance the effects of glucocorticoids on the one hand and to inhibit the generation of neutrophils, potential mediators of inflammation.

Claims

1. Composition comprising water, EDTA 2Na, Allantoin, Urea, Propolis, 1% Sodium hyaluronate, Marine collagen, Glycerine, Propylene glycol, 18- β glycyrrhetinic acid, Chlorhexidine digluconate in 20% solution, Hypericum oil, Melaleuca oil, Calendula e.g. Aloe e.g. Mallow e.g., Polyethylene glycol sorbitan monolaurate.
5
2. Composition according to the preceding claim, wherein Water is present at 74.5% by weight, EDTA 2Na at 0.3% by weight, Allantoin at 0.1% by weight, Urea at 2% by weight, Propolis, in the form of granules, at 0.5%, sodium hyaluronate, in a 1% solution, at an amount equal to 0.7%, glycerine at 4.3% by weight, propylene glycol at 3.6%, 18- β glycyrrhetinic acid at 0.1% by weight, Chlorhexidine digluconate in solution up to 20% at an amount of 3% by weight, Hypericum oil at 0.7% by weight, Melaleuca oil at 0.7%, calendula e.g. at 0.4%, aloe e.g. at 3%, Mallow e.g. at 0.4%, Polyethylene glycol sorbitan monolaurate at 5%, all the components completing 100% by weight of said composition.
10
15
3. Composition according to any one of the preceding claims, formulated as a spray.
4. Composition according to any one of the preceding claims for use as a medicament.
20
5. Composition according to any one of claims 1 - 3 for use in a method of treatment of skin lesions and/or irritations.
6. Composition for use according to the preceding claim in a method of treatment of:
25 redness of the skin due to cold, to own irritations, irritations from contact and rubbing; grazes and abrasions that do not extend past the dermis; superficial cut wounds and with joined edges; dry and cracked skin; reddened and irritated psoriasis plaques; eczema of various nature even with exudate; mild acne; scalds and burns up to the second degree;

radiation burns.

7. Composition according to any one of claims 1 to 3 for use in a method for preventing the formation of decubitus ulcers.

5

8. Composition for use according to any one of claims 4 to 7, wherein said composition is to be administered through topical route.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/70 A61K31/00 A61K36/00 A61K47/36 A61K47/42
A61P17/00

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 practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IT UB20 159 582 A1 (VALITUDO PHARMA SRLS) 21 June 2017 (2017-06-21) page 9, line 16 - page 16, line 22 examples claims -----	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

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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

van de Wetering, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/050077

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
IT UB20159582	A1	21-06-2017	-----