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Method of treating symptoms of common cold, allergic rhinitis and infections relating to the respiratory tract

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(54) Title: METHOD OF TREATING SYMPTOMS OF COMMON COLD, ALLERGIC RHINITIS AND INFECTIONS RELATING TO THE RESPIRATORY TRACT

(57) Abstract: The present invention relates to methods of treating conditions and/or symptoms related to common cold of the upper and/or lower respiratory tract and/or eyes. In particular the invention relates to the methods of treating conditions and/or symptoms related to common cold comprising administration of a flavonoid or administration of a flavonoid in combination with a metal. The invention furthermore describes compositions comprising a metal and a flavonoid useful for the treatment of conditions and/or symptoms relates to common cold.

METHOD OF TREATING SYMPTOMS OF COMMON COLD, ALLERGIC RHINITIS AND INFECTIONS RELATING TO THE RESPIRATORY TRACT.

Field of the Invention

The present invention relates to the use of a therapeutical effective amount of a flavonoid and/or a flavonoid derivative such as for example troxerutin or Veneruton® (a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to 10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside); and/or a pharmaceutical acceptable salt thereof, together with a pharmaceutically acceptable carrier for the preparation of a medicament for treatment of one or more conditions related to common cold of the upper and/or lower respiratory tract and/or eyes. Such conditions comprises "common cold", a virus infection or bacterial infection related to the syndrome of common cold, an allergic condition having one or more symptoms similar with the symptoms of a common cold for example allergic rhinitis initiated by rhinovirus infection, asthma like exacerbations and/or other abnormal airway functions derived from various dysfunctions of the immune system, such as for example hay fever or the like.

The present invention further relates to a medicament for prevention and/or treatment of infections and optionally inflammations accompanying infections of the respiratory tract initiated by microorganisms. The invention relates more specifically to a medicament comprising a flavonoid and/or a flavonoid derivative, for example Venoruton®; or Troxerutin, as the active substance in said medicament.

The present invention further relates to a medicament comprising zinc and a flavonoid for the treatment of conditions relating to common cold and/or symptoms relating to common cold, as well as to a method of treatment of conditions relating to common cold or symptoms relating to common cold involving administration of zinc and a flavonoid.

Background Art

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

In the prior art no fast working and efficient composition has been provided for preventing and/or treating common colds initiated by viral infections caused by the so-called cold viruses, such as rhino virus, corona virus, adenovirus, coxsackie virus, RS-virus,

echovirus or other cold viruses yielding the usual well known cold syndromes in patients. Practically all humans suffer 2 to 3 times a year from infections in the upper respiratory passages, such as cold and flu. In general, in Denmark the majority of common colds occurring in September, October and November are caused by rhinovirus infection, whereas the majority of common cold occurring in January, February and March are caused by Coronavirus infections.

Furthermore, there is a great need for effective remedies in the increasing number of patients suffering from allergic syndromes, for example asthma, which may be initiated by common cold viruses, especially the rhinovirus.

Recent observations from a polymerase chain reaction (PCR)-study (Johnston, 1993) with naturally rhinovirus infected persons indicates that the actual range for rhinovirus infections involved in common cold syndrome probably is at least twofold higher, compared to findings obtained via the traditional cell culture techniques (40%). This indicates that up to 70-75% of all patients suffering from common colds have a rhinovirus infections ongoing either as a single infection or co-infection (Spector, 1995).

It has been estimated that the average pre-school child experiences 6-10 upper respiratory infections or common colds per year whereas the average adult experiences 2-4 (Sperber, 1989). The effects of the common cold can be uncommonly disruptive, forcing otherwise normal persons to miss work, school, etc. Individuals who are at increased risks, such as individuals suffering from bronchitis or asthma, may also experience a life-threatening exacerbation of their underlying conditions. The average annual expenditure for various cold treatments exceeds USD 2 billion in the United States, alone (Spector, 1995); in the EU a similar figure is expected.

Currently, there is no efficient treatment to offer common cold patients. Some offered treatments may even worsen the cold; for example, it has been demonstrated that the administration of aspirin and acetaminophen may have detrimental effects on cold treatment, neutralising antibodies and even increase nasal problems (Graham, 1990). Oral alpha-agonist may relieve congestions in many individuals and antihistamines may sometimes be helpful (Spector, 1995) but no real cure is observed. Prevention or treatment with artificial soluble receptors has not been as successful as hoped (Hayden, 1988); several trials treating common cold patients with interferon have been completely

negative (Monto, 1989; Sperber, 1989). Plecarnil ® which recently (March, 2000) was investigated in several trials and which inhibits the binding of the rhinovirus via its attachment site, termed also negatively.

All these trials, which involved treatment of the syndrome common cold were negative, despite the fact that adequate drug concentrations were present in the nose of the treated persons. These results indicate that reversal of the pathogenic events in rhinovirus colds requires more than just the inhibition of viral replication.

Unfortunately, research in development of novel strategies to treat common cold is complicated by the fact human rhinoviruses only have been reported to infect primates successfully and hence no practical animal model has been developed for rhinovirus infections (Rotbart, 2000).

The development of natural and experimentally induced rhinovirus infections in normal persons are initiated by selected events which can be considered to occur sequentially. The steps in the rhinovirus pathogenesis are believed to include viral entry into the outer nose, mucociliary transport of virus to the posterior pharynx, and initiation of infection in ciliated and non-ciliated epithelial cells of the upper airway. Viral replication peaks on average within 48 h of initiation of infection and persists for up to 3 weeks; Infection is followed by activation of several inflammatory mechanisms, which may include release or induction of interleukins, bradykinins, prostaglandins and possibly histamine, including stimulation of parasympathetic reflexes (the cytokines may counteract each other at certain levels resulting in a very complex pathway). The resultant clinical illness is a rhinosinusitis, pharyngitis, and bronchitis, which on average lasts one week (Gwaltney, 1995).

Occasionally, a secondary bacterial or microbial infection may follow subsequently to the viral infection and a sustained and more serious inflammation may result.

Previously, it was believed that the major part of the virus was produced in the upper nose region and excreted (Winther, 1993a). However, subsequent studies, comparing recovery of virus in nasopharyngeal wash specimens, nasal swabs and pharyngeal swabs showed that the nasopharyngeal wash specimens was consistently superior to the other two specimens in yielding virus (Cate, 1964). From a series of in-depth investigations

(Winther, 1984a; Winther, 1984b; Winther, 1984c; Turner, 1984; Farr, 1984; Hayden, 1987; Winther, 1987a; Winther, 1987b; Winther, 1993b; Arruda, 1995; Winther, 1998) it was concluded that:

(i) the virus was first recovered, at the highest concentrations, from the nasopharynx before it could be recovered in the upper nose region (turbinates).

(ii) no evidence for rhinovirus induced damage of the surface ciliary lining of the inferior turbinate was noted which is in agreement with other investigators suggesting that the virus may be transported to the nasopharynx in the overlaying mucus by mucociliary clearence.

(iii) there was a significant increase of the influx of neutrophils in the same area as in (ii)

(iv) infection of the lining of the nasal cavity was not uniform after intranasal inoculation and seemed not to result in any cell damage at all, cf. (ii) above.

(v) the rate of viral shedding in the nasopharynx was high by day 1 (post infection), whereas cold symptoms did not peak until day 3. The symptoms waned during the first week, but rhinovirus was present during the following 3 weeks.

(vi) The increase of neutrophils correlate with the onset of symptoms, including sore throat. The symptoms include oedema-like symptoms which, in turn, may trigger sneezing and coughing.

In summarising the above findings, it should be stressed that the highest concentration of virus can be recovered from the nasopharynx, and virus usually appears on the turbinate(s) one or two days later, despite the fact that virus is innoculated via the nose (in volunteers); no visible damage of the cell lining in the upper airways was ever demonstrated. Furthermore, as "sore throat" usually develops simultaneously with the appearance of virus in the nasopharynx it can be reasoned that "signal molecules" or the like (Van Damme, 1988) will be made by the relatively few rhinovirus cells infected and that these "cytokine-like molecules" subsequently may activate the "lymphatic ring" - which is located just beneath the nasopharynx - leading to the well-known sore throat which in turn triggers a complex pattern of inflammatory reactions, involving an array of

different interferons and cytokines the interaction of which is currently under in-depth investigation. Some of these factors, such as for example Il-1, induce fever in patients. Bradykinines per se may be responsible for the sore throat which is frequently associated with common cold.

The fact that interferon is known to be part of the non-specific innate immune response against viral infections in man has lead to several publications as a number of groups have investigated how much interferon is produced locally during viral infections of the upper-airways. One of the earliest and probably most thorough, *in vivo*, investigations in man was performed by Cate et al. (Cate, 1969) on volunteers (healthy adult males from federal correctional institutions in USA): the authors were able to demonstrate that most of the persons involved, produced interferon (as demonstrated in nasal washings) during common colds at a level which, at least theoretically, should have been enough to block the viral infection, per se. It is tempting to speculate that if no interactions from the numerous inflammatory actions (including oedemas) had taken place, the infected persons might not had experienced a traditional cold at all.

It has been demonstrated in a recent publication, that the immune system also takes "active part" in the spread of the inflammatory actions since experimental evidence supports the notion that rhinovirus may use some of the effector cells from the immune system as a mean for spreading the inflammatory reactions to the lower airways (Gern, 1996) via initiation of local TNF-alpha production; it is tempting to speculate that the allergic rhinitis is initiated via this mechanism as it has been found that the pathogenesis for asthma is linked to local TNF-alpha production (Broide et al.1992). Several quarters have thus argued that the asthma syndromes are rhinovirus manifestations of post-infectious events triggered by an array of different cytokines in connection with a "switch" between the Th1 vs. Th2 response (Gern, 1999; Winther, 1998; Grünberg, 1999).

Generally speaking, air-way infections or allergic rhinitis and/or asthma may pose a serious health problems as it can be potentially life-threatening for susceptible groups such as elderly people with chronic airway problems or persons suffering from a deficient immunity, such as AIDS-patients, cancer patients etc. Thus, a simple method of treating these symptoms/syndromes (and possibly also the underlying infections would be of immense importance).

Viral and/or other microbial infections are known to initiate a complex inflammatory response (Ginsburg, 1988) from the patient which probably is mediated by several groups of responder cells including the neutrophile granulocytes, which are specifically increased during a cold. The latter represents approximately more than 95% of all the effector cells ; each min. about 6-9 millions neutrophiles enter the upper-airways and slowly pass down the interior surfaces encompassing the upper airways; it may be assumed that the neutrophiles, which are able to release very aggressive enzymes and toxic substances upon proper stimulation will keep the bacterial load of the upper-airways to an acceptable level ; the small numbers of S. pyogenes or S. aureus found in nasopharynx, which otherwise is almost sterile, may stimulate the neutrophiles via the so-called superantigens to a certain degree thereby limiting the numbers of bacteria in said areas (dynamic equilibrium/symbiosis).

According to Ihrcke and co-workers (Ihrcke, 1993) the very early steps in a virus infection (or any other abnormality in the cell lining) can be related to the content and metabolism of heparan sulfate proteoglycan (the major proteoglycan associated with intact endothelial cells). The first element of the model derives from the observation that heparan sulfate is released from the intact endothelial lining of blood vessels during the very first step in an inflammatory response initiated by a viral infection. Accordingly, this loss may seriously compromise the vascular integrity and result in a local edema attracting further neutrophiles via the up-regulation of ICAM-1 markers on the endothelial cells increasing the inflammatory response further. Thus, in a separate experiment, activated neutrophiles were able to release 70% of all cell-associated heparan sulfate proteoglycan within one hour via the subsequent release of heparanase. One important function of heparan sulfate is the maintenance of the endothelial cell integrity. Loss of heparan sulfate partially abrogate the barrier properties of the endothelium and contributes to the edema and exudation of plasma proteins that characterise inflammation.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

Disclosure of the Invention

According to the present invention, it is believed that the explanation for the therapeutic failure of the said prior art antiviral therapies is, that the viral infections per se trigger inflammatory responses which can not be expected to respond at all to antiviral drugs, *per*

se. The existence of inflammatory events in rhinovirus induced common colds is substantiated by the finding of elevated concentrations of inflammatory mediators, such as bradykinins, IL-8 in the nasal secretion of persons with colds (Proud, 1990; Naclerio, 1988) and the partial reduction of cold symptoms by treatment with selected antiinflammatory drugs that have no antiviral activity (Gaffey, 1988).

Flavonoids are polyphenolic compounds isolated from a wide variety of plants with over 4000 individual compounds known. They comprise a range of C_{15} aromatic compounds and are found in virtually all land-based green plants. According to one theory, upon administration of flavonoids to an individual theflavonoid molecules are build into a part of the outer layer of the endothelial cell layer and thereby cause a reduction in microvascular hyperpermeability and hence a reduction of the migration of granulocytes through the endothelial layer. Accordingly, flavonoids can be used to inhibit oedemas and to downregulate inflammatory reactions.

WO 01/03681 describes the anti-viral effect of a number offlavonoids for the purpose of treatment of infections, in particular viral infections. Althoughseveral flavonoids have been shown to comprise an antiviral effect, a number of flavonoids do not comprise any antiviral effects in laboratory tests. Never the less the present invention discloses that such non-antiviral flavonoids surprisingly are very effective in the treatment of common cold.

According to a first aspect of the present invention there is provided use of a therapeutically effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier for the preparation of a medicament for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever.

According to a second aspect of the present invention there is provided use of a therapeutically effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier for the preparation of a medicament for treatment of symptoms of conditions related to common cold of the upper and/or lower respiratory tracts and/or eyes, wherein said symptoms are selected from the group consisting of: cough, sneezing, muscle pain, sore throat, hoarseness, headache, malaise, chilliness,

nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis and bronchitis.

According to a third aspect of the present invention there is provided a pharmaceutical composition comprising a pharmaceutically-effective amount of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, as well as a Zn^{2+} salt and/or Zn^{2+} complex, wherein said composition is formulated for topical administration to the mucosal membrane of the oral cavity.

According to a fourth aspect of the present invention there is provided a kit-of-parts comprising a pharmaceutically-effective amount of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex, when used in a method for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever.

According to a fifth aspect of the present invention there is provided use of a pharmaceutical composition comprising a pharmaceutically-effective amount of a hydroxyethylrutoside or a pharmaceutically-acceptable salt thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex or of the kit-of-parts according to any one of claims 16 to 22 for the preparation of a medicament for treatment of one or more conditions and/or symptoms of conditions, wherein said conditions are selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis and hayfever.

According to a sixth aspect of the present invention there is provided a method for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever, said method comprising applying to a patient in need thereof, a therapeutically-effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier.

According to a seventh aspect of the present invention there is provided a method for treatment of symptoms of conditions related to common cold of the upper and/or lower respiratory tracts and/or eyes, wherein said symptoms are selected from the group consisting of: cough, sneezing, muscle pain, sore throat, hoarseness, headache, malaise,

chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis and bronchitis, said method comprising applying to a patient in need thereof, a therapeutically-effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier.

According to an eighth aspect of the present invention there is provided a method for treatment of one or more conditions and/or symptoms of conditions, wherein said conditions are selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis and hayfever, said method comprising applying to a patient in need thereof, a pharmaceutically-effective amount of a hydroxyethylrutoside or a pharmaceutically-acceptable salt thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex or of the kit-of-parts according to the fourth aspect.

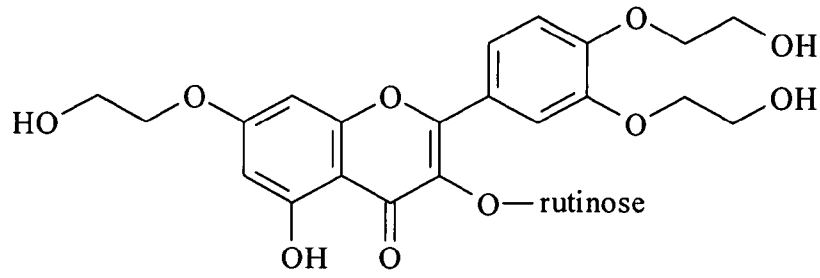
In an embodiment, the present invention provides use of a therapeutically effective dosage of a flavonoid and/or a flavonoid derivative selected from the group comprising hydroxyethylrutosides, troxerutin, Veneruton®, genistein, taxifolin, eriodyctol, catechin,epicatechingallate, pharmaceutical acceptable salts thereof and functional derivatives thereof, together with apharmaceutically acceptable carrier for the preparation of a medicament for treatment of one or more conditions and/or symptoms of conditions relating to a common cold of the upper and/or lower respiratory tract and/or eyes.

In another embodiment, the present invention provides a method of treatment of an individual, including a human being, comprising administering to said individual a therapeutically effective dosage of a flavonoid and/or a flavonoid derivative selected from the group comprising hydroxyethylrutosides, troxerutin, Veneruton®, genistein, taxifolin, eriodyctol, catechin, epicatechin, epigallocatechin, epicatechingallate, pharmaceutical acceptable salts thereof and functional derivatives thereof, for prevention and/or treatment of one or more conditions and/or symptoms of conditions relating to a common cold of the upper and/or lower respiratory tract and/or eyes.

Preferably, said flavonoid and/orflavonoid derivative does not comprise antiviral activity when tested *in vitro*. It is furthermore preferred that said flavonoid is soluble in water. More preferably, said flavonoid is a hydroxyethylrutoside, which does not comprise antiviral activity when tested *in vitro*. Yet more preferably, said flavonoid and/or flavonoid

derivative is selected from the group consisting of troxerutin, Veneruton®, pharmaceutical acceptable salts thereof and functional derivatives thereof. Most preferably, said flavonoid and/or flavonoid derivative is selected from the group consisting of troxerutin and Veneruton®. Veneruton® is a registered trademark of NOVARTIS and comprise a mixture of hydroxyethylrutosides, wherein around 50% is troxerutin.

In one especially preferred embodiment of the present invention the flavonoid is troxerutin of the formula:



Even though treatment of common cold patients with zinc gluconate lozenges in one trial performed by Mossad *et al.* lead to a reduction in the number of days the patients were suffering from common cold symptoms, after 4 days treatment with zinc gluconate lozenges the total symptom score was still more than 50% of the original symptom score. Interestingly, the present invention discloses a synergistic effect between administration offlavonoids and the administration of a metal, i.e. a combination therapy with flavonoids and metal is much more efficient than either one alone.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutical effective amount of a flavonoid and/or a flavonoid derivative and/or a pharmaceutical acceptable salt thereof, as well as a pharmaceutical acceptable metal and/or metal salt and/or metal complex.

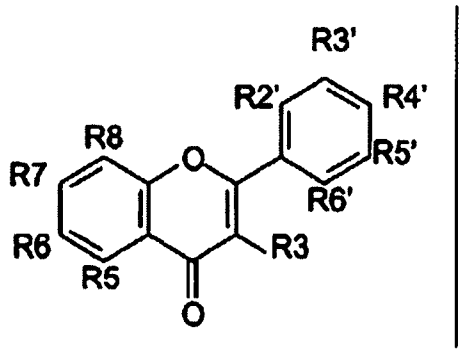
In another embodiment, the present invention provides a kit of parts comprising a pharmaceutical effective amount of a flavonoid and/or a flavonoid derivative and/or a pharmaceutical acceptable salt thereof, as well as a pharmaceutical acceptable metal and/or metal salt and/or metal complex.

In an embodiment, the present invention provides a therapeutically effective amount of a flavonoid and/or a flavonoid derivative and/or a pharmaceutical acceptable salt thereof,

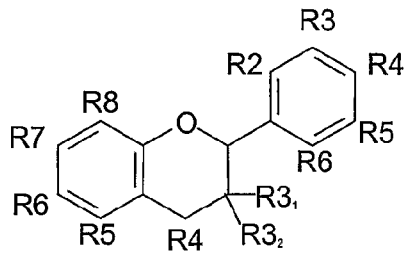
together with a therapeutically effective amount of a metal and/or metal salt and/or metal complex and a pharmaceutically acceptable carrier for the preparation of a medicament for treatment of one or more conditions and/or symptoms relating to a common cold of the upper and/or lower respiratory tract and/or eyes.

In another embodiment, the present invention provides a method of treatment of an individual, including a human being, comprising administering to said individual either simultaneously as separate or combined formulation or sequentially in any order, a therapeutic effective amount of a flavonoid and/or a flavonoid derivative and/or a pharmaceutical acceptable salt thereof as well as a pharmaceutical acceptable amount of a metal and/or metal salt and/or metal complex for ameliorating, curative and/or prophylactic therapy of one or more conditions and/or symptoms relating to a common cold of the upper and/or lower respiratory tract and/or eyes.

In combination with metal, flavonoid and flavonoid derivatives according to the present invention includes flavonoids of the general formula:



or the general formula:



Wherein

R2' can be selected from: -H
-OH

R3' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R4' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R5' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R3 including $R3_1$ and $R3_2$ can be selected from:
-H
-OH

-O-rutinose
-O-glucoside
-O-glucose-p-coumaric acid
-SOH
-O-rhamnose

R4 can be selected from: -(O)
-OH

R5 can be selected from: -H
-OH
-O-CH_2CH_2OH

R6 can be selected from: -H
-OH
-OCH_3

R7 can be selected from: -H
-OH
-O-glucose
-OCH_3
-OCH_2CH_2OH
-O-glucuronic acid
-O-rutinose
-O-rhamnoglucoside

R8 can be selected from: -H
-OH

Furthermore, flavonoid and/or flavonoid derivatives could be stereoisomers of the above mentioned. Additionally flavonoid and/or flavonoid derivatives could be dimers comprising two flavonoid subunits.

Additionally, flavonoids and/or flavonoid derivatives of the present invention to be used in combination with metal could be any flavonoid and/or flavonoid derivative known to the person skilled in the art. For example such flavonoid and/or flavonoid derivative could be any of the flavonoid and/or flavonoid derivative mentioned in WO 01/03681, which is hereby incorporated in its entirety by reference.

Preferably, the flavonoid and/or flavonoid derivatives are selected from molecules with the above general formulas with the proviso,

that when R3' is selected from	-OH $-OCH_3$ $-OCH_2CH_2OH$
then R5' is selected from	-H
and when R5' is selected from	-OH $-OCH_3$ $-OCH_2CH_2OH$
then R3' is selected from	-H

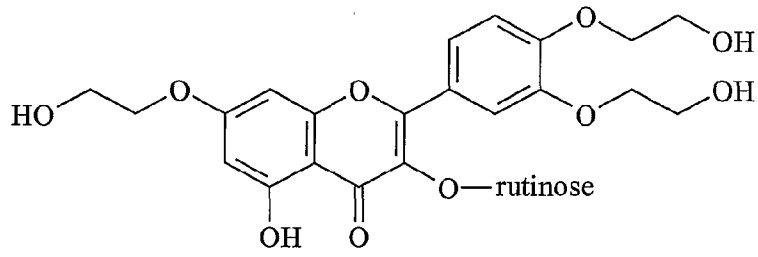
Semi-synthetic flavonoids are also within the scope of the present invention.

Preferably, the flavonoid according to the present invention could be selected from the group consisting of: troxerutin, venoruton, hydroxyethylrutosides, hesperitin, naringenin, nobiletin, tangeritin, baicalein, galangin, genistein, quercetin, apigenin, kaempferol, fisetin, rutin, luteolin, chrysin, taxifolin, eriodyctol, catecithin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, flavone, sideritoflavone, hypolaetin-8-O-Gl, oroxindin, 3-hydroxyflavone, morin, quercetagetin-7-O-Gl, tambuletin, gossypin, hipifolin, naringin, leucocyanidol, amentoflavone and derivatives thereof and mixtures thereof.

More preferably, one or more of the R chains are $-OCH_2CH_2OH$, yet more preferably, at least two R chains are $-OCH_2CH_2OH$, most preferably three R chains are $-OCH_2CH_2OH$.

Preferably, said flavonoid and/or flavonoid derivative does not comprise antiviral activity when tested in vitro. Furthermore, it is preferred that said flavonoid is soluble in water. More preferably, said flavonoid is a hydroxyethylrutoside, which does not comprise antiviral activity when tested in vitro. Yet more preferably, said flavonoid and/or flavonoid derivative is selected from the group consisting of troxerutin, Veneruton, pharmaceutical acceptable salts thereof and functional derivatives thereof.

In one especially preferred embodiment of the present invention the flavonoid derivative to be used is troxerutin of the formula:



Troxerutin

Mixtures of more than one flavonoid and/or flavonoid derivative is also comprised within the present invention. For example such a mixture may comprise 2, such as 3, for example 4, such as 5, for example 6, such as 7, for example 8, such as 9, for example 10, such as more than 10 different flavonoids. Preferably, such a mixture comprise 8 to 10 different flavonoids.

In one preferred embodiment the flavonoid derivatives according to the invention comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides. More preferably, the mixture comprise 1% to 15% monohydroxyethylrutoside, such as from 5% to10% monohydroxyethylrutoside, and from 25% to 50% dihydroxyethylrutoside, such as from 30% to 38% dihydroxyethylrutoside, and from 30% to 70% trihydroxyethylrutoside, such as from 45% to 55% trihydroxyethylrutoside and from 1% to-20% tetrahydroxyethylrutoside, such as from 3% to 12% tetrahydroxyethylrutoside. Most preferably, said mixture of hydroxyethylrutosides is Venoruton.

Figures

Figure 1. The number of "events" in each category (symptoms 1-4) were counted every day. Day 0: no treatment; day 1= 24 h treatment, etc. Symptom 4 (very strong), symptom 3 (strong), symptom 2 (not pleasant), symptom 1 (minimal symptoms), symptom 0 (no symptoms):

Figure 2. The total scores from all patients under the symptom "malaise" were calculated for each day and graphed vs. a so-called "non-treated" group taken from Jackson et al, 1958 (day 2 in Jackon's study is here used as day 0)

Figure 3. The scores for the symptom "sore throat" were calculated for each day as in the preceding figure.

Figure 4. The corresponding scores for the "sneezing" symptom were calculated as in the preceding figures as an average from 7 patients.

Figure 5. The mean total scores from a control trial (Hertz) and the trial described in example 1 (KB) are compared as %-reduction in mean total symptom score per patient.

Figure 6. Average symptom score per patient during a 3 days treatment with preparation C (ImmumaxZn).

Figure 7. The antiviral activity of natural HuIFN-α vs. Rhinovirus-T39

Detailed description of the invention

According to the present invention conditions relating to a common cold of the upper and/or lower respiratory tract and/or eyes comprises common cold, a viral infection and/or a bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis, an allergic condition having one or more symptoms similar with the symptoms of a common cold for example allergic rhinitis initiated by rhinovirus infection, asthma like exacerbations

and/or other abnormal airway functions derived from various dysfunctions of the immune system, such as for example hay fever or the like.

Furthermore, conditions relating to a common cold may comprise secondary bacterial infection(s) that follow soon after a primary viral infection. Secondary bacterial infections may for example be initiated by the normal bacterial flora present in the upper and/or lower respiratory tract and/or eyes.

Symptoms of conditions relating to common cold can be selected from the group comprising, but is not limited to: coughing, sneezing, muscle pain, sore throat, hoarseness, irritated throat, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, fever, rhinitis, swelling of mucosal membranes, pharyngitis, astma, and acute as well as chronic bronchitis.

In the present invention the upper respiratory tract includes the mouth, nose, sinuses, throat, and the respiratory tract to epiglottis. The lower respiratory tract includes the rest of the bronchial tree including the bronchioles and lung vacuoles. The invention also relates to the treatment of eye symptoms related to the condition of the respiratory tract in that the condition may involve the mucosal lining of the respiratory tract as well of the eyes. By the term treatment as used herein is also meant prevention of symptoms whether the prevention is in fact a decrease in the development of symptoms or a prevention of the symptoms to arise in first place, e.g. upon exposure to infection.

According to the present invention a pharmaceutically effective amount or a therapeutically effective amount is to be understood as an amount sufficient to induce a desired biological result. The result can be alleviation of the signs, symptoms, or causes of a disease, for example of common cold, preferably, the result is a significant alleviation of signs, symptoms or causes of common cold. For example, an effective amount is generally that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer, preferably such a relief of symptoms is a significant relief. The relief may for example be evaluated based on a symptom score as disclosed herein in the examples. Accordingly, effective amounts can vary widely depending on the individual, on the disease or symptom to be treated.

Most common cold patients produce interferon following infection of the respiratory tract (Cate et al., 1969), which per se in principle should be sufficient to alleviate the infection.

Hence, in one preferred aspect of the present invention the treatment of a viral infection is not to be regarded as a direct antiviral effect but as a modification or inhibition of cytokines or other factors relevant for the establishment or continuation of a viral infection located in the mucosal membrane of the respiratory tract or eyes. Furthermore, the treatment preferably inhibits inflammation processes in the mucosal membrane of the respiratory tract or eyes and thereby alleviates symptoms of common cold. Accordingly, the invention relates to use of a flavonoid and/or a flavonoid derivative for the treatment of symptoms of viral infection of the upper and/or lower respiratory tract and/or eyes, wherein the flavonoid and/or flavonoid derivative has no antiviral effect in vitro.

Thus, in one preferred embodiment of the present invention the flavonoid and/or flavonoid derivatives does not comprise an antiviral or anti bacterial effect in vitro. In vitro antiviral and/or antibacterial effect can be determined in various laboratory tests. Preferably, such laboratory tests comprise a cultured cell line capable of being infected with the bacteria or virus to be tested as well as said bacteria or virus. More preferably, said cultured cell line is WISH cells and said virus is a rhinovirus selected from the group consisting of: rhinovirus 1A, rhinovirus 15 and rhinovirus 39. Most preferably antiviral effect is determined using the MTS method as described in example 1. When antiviral effect is measured according to the MTS method as described in example 1, a protection of less than 10%, preferably less than 7.5%, more preferably less than 5%, even more preferably less than 3%, most preferably less than 2% is to be regarded as no antiviral effect in vitro.

Preferably, the effect of the flavonoid and/or flavonoid derivative is closely related to the living organism such as the effect is a modulatory effect on specific factors and biological reactions related to the affected mucosal membrane. The precise mechanisms are currently not known.

Very often common cold is initiated by, associated with or followed by a viral infection which is involved in the common cold or symptoms of the common cold. In one embodiment of the present invention the condition relating to common cold is associated with a viral infection of the upper and/or lower respiratory tract and/or eyes.

The virus infection which a common cold is most often associated with or initiated by, is infection by one or more virus selected from the group consisting of: adenoviruses, parvoviruses, picornaviruses, reoviruses, orthomyxoviruses, paramyxoviruses, arenaviruses, caliciviruses, coronaviruses, orthomyxoviruses, rhinovirus, influenza virus, including influenza virus type A and B, echovirus, respiratory syncytial virus (RSV), and coxsackie virus. Rhinovirus is the most common virus identified in relation to common cold. The term rhinovirus is meant to comprise any rhinovirus for example any of the rhinoviruses 1-113. However, very often the above virus may be present in individuals with no symptoms of common cold. Preferably, the virus infection associated with common cold according to the present invention is infection by rhinovirus or coronavirus.

Very often the common cold is associated with or followed by a bacterial infection, which is involved in the common cold or symptoms of the common cold. Such a bacterial infection may in one embodiment of the present invention be a secondary infection following a primary infection with for example a virus. In one embodiment of the present invention the condition relating to common cold is associated with a bacterial infection of the upper and/or lower respiratory tract and/or eyes.

The bacterial infection which may be associated with a common cold or with the symptoms thereof is most often infection by one or more bacteria selected from *Streptococcus pheumoniae, Streptococcus Haemolyticae, Haemophilus influenxae,* and *Moraxella catarrhalis.*

Furthermore, common cold may be initiated by a microbial infection. Such a microbial infection may lead to similar inflammatory responses as viral infections involving the same effector cells for example neutrophiles. Accordingly, such microbial infections may be treated in a fashion similar to viral infections associated with common cold.

Many allergic reactions are associated with symptoms similar to the symptoms of a common cold and it has surprisingly been shown that such symptoms of an allergic disorder may also be effectively treated by the method and use as disclosed herein. Hence, in one embodiment of the present invention the condition relating to common cold is an allergic disorder.

The allergic conditions according to the present invention is preferably selected from rhinitis, asthma, acute and chronic bronchitis, and hay fewer, and the most common symptoms in this respect is one or more symptom selected from nasal discharge, nasal congestion, sneezing, cough, swelling of mucosal membranes, rhinitis. More preferably, the allergic condition according to the present invention is selected from the group consisting of rhinitis and hay fewer. In a further aspect of the present invention the individual may have relief from the symptoms based on a decreasing effect of said flavonoid derivatives on the mucosal swelling associated with the infection or condition mentioned herein. In a still further aspect the present invention encompass acute allergic reactions related to insect bites and sticks and in a still further aspect to the allergic reactions from food or other allergens leading to swelling of the mucosa of the mouth and/or throat in such acute reactions.

It is furthermore contained within the present invention to treat allergic conditions that is initiated by one or more agents selected from the group consisting of: pollution, house dust, common dust mite such as Dermatophagoides Farinae or Dermatophagoides Pteronyssinus, pollen such as grass pollen, tree pollen or weed pollen, mold, animal danders or feathers, fungal spores and chronic inhalation of for example, wheat flour.

Accordingly, the conditions related to common cold of the present invention could be an infection or common cold or allergic condition characterised by one or more symptoms selected from the group comprising: coughing, sneezing, muscle pain, sore throat, hoarseness, irritated throat, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis, astma, and acute as well as chronic bronchitis.

When the condition relating to common cold is an allergic condition, preferably such a condition is treated by administration of flavonoid without simultaneous administration of metal to the individual in need thereof. More preferably said flavonoid is selected from the group consisting of troxerutin and Veneruton®.

The classical common cold results in symptoms, which lasts for approximately one week. However, in certain cases conditions relating to common cold results in symptoms, which lasts for much longer. Such long lasting common colds for example last for more than 10 days, such as more than 2 weeks, such as more than 3 weeks, for example more than

one month, such as more than 6 weeks. Individual suffering from long lasting common cold are preferably treated by administration of flavonoid without simultaneous administration of metal. More preferably said flavonoid is selected from the group consisting of troxerutin and Veneruton®.

In contrast, individuals suffering from a classical common cold wherein treatment is initiated 1 to 5 days following the onset of common cold symptoms, preferably 1 to 3 days following the onset of common cold symptoms are preferably treated by administration of both a flavonoid and metal according to the present invention.

In one preferred embodiment the flavonoid and/or flavonoid derivative is not able to potentiate interferon mediated antiviral activity. Preferably, determination of potentiation of interferon mediated antiviral activity is performed using a laboratory test measuring antiviral effect as described herein above. Such laboratory test preferably includes measuring the antiviral effect of interferon in the presence and absence of said flavonoid and/or derivatives. More preferably such test is performed as described in example 3 and 4.

The interferons could be any interferon known to the person skilled in the art. Such interferon could be derived from a mammal including a human being. Such interferon could be naturally occuring interferon and/or recombinant interferon. Preferably such interferon could be selected from the group consisting of: IFN-α, IFN-β, IFN-γ and native human leucocyte interferon. More preferably, such interferon could be HuIFN-α-2b.

The effective dosage of said flavonoids and/or flavonoids derivatives and/or a pharmaceutically acceptable salt thereof is preferably from 5 to 5000 mg daily. More preferably, the effective dosage is from 10 mg to 4000 mg, such as from 30 mg to 3000 mg, even more preferably from 40 mg to 2000 mg daily, yet more preferably, from 50 mg to 1000 mg daily.

Furthermore, the effective dosage of said flavonoids and/or flavonoids derivatives and/or a pharmaceutically acceptable salt thereof could be a dosage equivalent of a dosage of troxerutin of from 5 mg to 5000 mg daily.

The effective dosage of Venoruton or troxerutin or a pharmaceutically acceptable salt or a

functional derivative thereof is from 5 to 5000 mg. In general the effective dosage is from 10 mg to 4000 mg, such as from 30 mg to 3000 mg, preferably from 40 mg to 2000 mg daily, more preferably, from 50 mg to 1000 mg daily, yet more preferably from 50 to 500 mg daily, most preferably from 100 to 300 mg daily.

The administration of flavonoids and/or flavonoid derivatives according to the present invention is preferably a very frequent administration during the day. Accordingly, the daily dosage may be administered in divided dosages of 1 to 36 individual dosages daily, preferably 2 to 24 times daily, more preferably 3 to 12 times daily, such as 5 to 8 times daily, for example around 6 times daily. Preferably, the first 2 doses are administrated simultaneously. The specific number of daily applications may be correlated to the individual way of administration and the severity of the symptom in question. The preferred treatment is a treatment where the medicament is present in the mucosal membrane as constant as possible due to the theory that the individual factors involved in the maintenance of the symptoms are constantly produced in the affected mucosal membrane during the illness.

In one embodiment the flavonoids or the composition or kit-of-parts comprising flavonoids and metals according to the present invention are administrated in combination with a second treatment such as in combination with an antiviral treatment including treatment against influenza such as TaMiFlu®, treatment against rhinitis such as Picovir®; or treatment with antibodies against streptococcus; or treatment with interferons (alpha, beta or gamma) and mixtures thereof. The antiviral agents include TamiFlu or other neuraminidase inhibitors or rimantadine or antibodies against RSV.

In another embodiment of the present invention the second treatment is administration of an anti-microbial agent. Preferably, the anti-microbial agent is distinct and specific, however the anti-microbial agent may also be a general antibiotic. In particular, an anti-microbial agent may be administrated to treat conditions associated with bacterial infections.

However, the flavonoids according to the present invention may be administrated alone or in combination with a metal (see below). In particular, the flavonoids according to the present invention are preferably not administrated in combination with a vitamin.

In one preferred embodiment the flavonoids are comprised in a composition or a kit of parts that further comprises a therapeutic effective amount of a metal and/or metal salt and/or complex or derivatives thereof.

The metal according to the present invention is preferably selected from the group consisting of zinc, manganese, cadmium, cobalt, iron and selenium. The metal may for example be in the form of Zn^{2+}, Mn^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+} and Se^{2+}. Most preferably the metal is zinc. Preferably zinc is Zn^{2+}, given in the form of a salt and/or complex or derivatives thereof.

Within the scope of the present invention, zinc could be in any suitable form for example as ZnGluconate, as $Zn(acetate)_2$, as Zn^{2+} aminochelates , as Zn^{2+} amino acid chelates, as Zn^{2+} DL-methionine, as Zn^{2+} L-methionine, as histidine derivatives or as a complex with amino acids in combination with histidine, or the like such as for example PolaPreZinc ®. Furthermore zinc could be in the form of zinc sulfate, zinc chloride, Nitric-acid zinc, phosphoric-acid zinc, ulmin acid zinc, zinc fluoride, zinc iodide, a zinc hydroxide, zinc carbonate, a zinc chromate, benzoic-acid zinc, zinc acetate, p-aminobenzoic-acid zinc, p-dimethylamino benzoic-acid zinc, p-zinc phenolsulfonate, p-methoxy cinnamic-acid zinc, lactic-acid zinc, gluconic-acid zinc, citric-acid zinc, salicylic-acid zinc, a zinc stearate, lauric-acid zinc, myristic-acid zinc, Oleic-acid zinc, 2, 5-pyridine dicarboxylic-acid zinc, 2, 6-pyridine dicarboxylic-acid zinc, 4-pyridine dicarboxylic-acid zinc, 2, 4-dicarboxy pyridine zinc, 3-hydroxy-2-carboxy pyridine zinc, 3-n-propoxy-2-carboxy pyridine zinc, 3-n-hexyloxy-2-carboxy pyridine zinc, 5-n-propoxy-2-carboxy pyridine zinc, 5-n-butoxy-2-carboxy pyridine zinc, 5-(2-ethyl-hexyloxy)-2-carboxy pyridine zinc, 6-n-butoxy-2-carboxy pyridine zinc, 3-methoxy-2-carboxy pyridine zinc, 5-methoxy-2-carboxy pyridine zinc, 6-methoxy-2-carboxy pyridine zinc, 6-n-hexyloxy-2-carboxy pyridine zinc, 3-methyl-2-carboxy pyridine zinc, 4-methyl-2-carboxy pyridine zinc, 4-tert-butyl-2-carboxy pyridine zinc, 5-methyl-2-carboxy pyridine zinc, 5-n-hexyl-2-carboxy pyridine zinc, 3-n-undecyl-2-carboxy pyridine zinc, 4-n-undecyl-2-carboxy pyridine zinc, 5-n-butyl-2-carboxy pyridine zinc, 6-n-undecyl-2-carboxy pyridine zinc, 4-nitroglycerine-2-carboxy pyridine zinc, 5-hydroxy-2-carboxy pyridine zinc, 4-fluoro-2-carboxy pyridine zinc, 2-carboxy pyridine N-oxide zinc, picolinic-acid zinc, Nicotinic-acid zinc, nicotinamide zinc, 3, 4-dihydroxy benzoic-acid zinc, Screw histidine zinc, hinokitiol zinc, protoporphyrin zinc, porphyrin zinc or picolinic-acid amide zinc.

It is contained within the present invention that zinc could be a combination of the above mentioned zinc salts and/or a zinc complexes. Such combination could comprise two or more sorts. Preferably zinc is selected from the group consisting of Zn^{2+} aminochelates , Zn^{2+} amino acid chelates, $Zn(acetate)_2$, Zn^{2+} DL-methionine, Zn^{2+} L-methionine, ZnGluconate and PolaPreZinc ®. Preferably, zinc is in the form of ZnGluconate or PolaPreZinc ®.

The effective dosage of Zinc depends upon the form of zinc component which is adminstrated. Preferably between 0.1 mg and 500 mg Zn^{2+} is administrated, such as between 0.5 mg and 250 mg, for example between 1 mg and 150 mg, such as between 5 mg and 100 mg, for example between 10 mg and 50 mg per dose. If the zinc compound is ZnGluconate , preferably between 5 mg and 1000 mg, more preferably between 10 mg and 500 mg, even more preferably between 10 mg and 100 mg, yet more preferably between 20 mg and 80 mg, even more preferably between 30 mg and 70 mg, most preferably around 50 mg ZnGluconate is administrated per dose. If the zinc compound is PolaPreZinc, preferably between 1 mg and 500 mg, more preferably between 5 mg and 250 mg, even more preferably between 10 mg and 100 mg, most preferably around 25 mg.

The administration of a flavonoid and/or a flavonoid derivative and/or a pharmaceutical acceptable salt thereof and a pharmaceutical acceptable amount of a metal and/or metal salt and/or metal complex may be either simultaneously as separate or combined formulations or it may be sequential.

It is preferred to present flavonoids and/or flavonoid derivatives and/or metals according to the present invention in the form of a pharmaceutical formulation. Accordingly, the present invention further provides pharmaceutical formulations, either as a single composition or as a kit of parts, for medicinal application, which comprises a flavonoid and/or flavonoid derivative as well as a metal and/or metal salt and/or metal complex according to the present invention or a pharmaceutically acceptable salts thereof, as herein defined, and a pharmaceutically acceptable carrier therefore.

The pharmaceutical formulations according to the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton,

Pa. The phamaceutical formulation may have any form known to the person skilled in the art. For example the pharmaceutical formulation may be in the form of a solution, dispersion, emulsion, suspension, bioadhesive and non-bioadhesive gel, powder, microphères, tablets, lozenges, chewing tablets, chewing gum, pills, capsules, cachets, suppositories, dispersible granules, drops, sprays, aerosols, insufflators, inhalators, patches, a lollipop, ointment, lotion, cream, foam, implant, syrup or balm. The skilled person may select the appropriate administration form based on the common knowledge within the field of delivery systems for pharmaceuticals.

It is believed that the optimal effect is obtained by a direct topical application of the flavonoids and/or metals according to the present invention on the mucosal membrane in question. Accordingly, it is preferred that the administration is topical administration directly to the mucosal membrane, more preferably, to the mucosal membrane of the upper and/or lower respiratory tract and/or of the eyes, even more preferably the mucosal membrane of the oral cavity. The formulation should generally be distributed to a major part of the mucosal involved in the specific condition or symptom to be treated.

The pharmaceutical composition and/or the kit of parts according to the present invention usually comprise pharmaceutically acceptable carriers, which can be either solid or liquid. Carrier can be one or more substances which may also act as diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders, preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material. Such carriers include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, lactose, pectin, dextrin, starch, gelatin, sucrose, magnesium carbonate, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Preferably, the pharmaceutical carrier is Magnesium stearate. In addition, the pharmaceutical formulations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

In powders, the carrier is a finely divided solid, which is a mixture with the finely divided active components. In tablets, the active components are mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contains from one to about seventy percent of the active compound.

Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. In one preferred embodiment the lozenges comprise sorbitol and/or peppermint oil.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

Surprisingly, the present invention discloses that even though common cold is usually caused by an infection of the upper and/or lower respiratory tract, it can be treated effectively by topical administration directly to the mucosal membrane of the oral cavity. Since administration directly to the mucosal membrane of the oral cavity is very convenient for the individual to be treated, it is a considerable advantage of the present

invention that administration can be performed directly to said mucosal membrane. In addition, the present invention discloses that allergic rhinitis also can be treated by applying the compounds according to the present invention directly to the musocal membrane of the oral cavity. Accordingly, the compounds according to the present invention are preferably formulated as lozenges, chewing tablets, chewing gum, drops, sprays and aerosols, which can be applied directly to the mucosal membrane of the oral cavity. Most preferably, the compounds according to the present invention are formulated as lozenges, which can be directly applied to the mucosal membrane of the oral cavity.

The individual in need of a treatment according to the invention could be any individual, however preferably, such individual is a human being. The individual will generally have a score relating to symptoms based on the score system as disclosed in Patients diary, (see examples) of at least 4 to 5, such as at least 6, preferably, at least 10, more preferably the patient would have a score of at least 15, whereas an individual with a score of 3 or less is not to be regarded as sick. Generally speaking a score around 5 to 6 or lower will allow the person to continue his/her work.

In a further aspect of the invention, the treatment results in a decrease in the severity of symptoms corresponding to a decrease of score as measured according to patients diary herein of at least 15% within 24 hours, such as least 25 %, more preferably of at least 30 % in 24 hours from the start of the treatment. After 48 hours of treatment the scores is preferably decreased with at least 20% in 48 hours, such as with at least 30%, for example with around 40% to 60%, more preferably with at least 40%, yet more preferably with at least 50%, even more preferably with at least 60% in 48 hours from the start of the treatment. 72 hours of treatment preferably results in a decrease of score as measured according to Patients Diary herein of at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 55%, yet more preferably at least 59%, even more preferably at least 65%, most preferably at least 70% in 72 hours from the start of the treatment. However, the preferred decrease in symptom score is dependent on the condition relating to common cold to be treated, the scheme of treatment and the individual patient.

Flavonoids are known to possess anti-oxidative properties, and according to one further aspect, the flavonoid is a flavonoid having a singlet Oxygen Quenching measured as the rate constant of $^1O_2$ quenching K of from 10^4 to 10^9 M^{-1} s^{-1}. Preferably, the rate is 10^4 to

10^8 M^{-1} s^{-1}. The singlet oxygen quenching can be measured using a variety of solvents known to the person skilled in the art. Preferably, the solvent is selected from the group consisting of CD_3OD, a mixture of CCl_4 and CH_3OH of 1:3 and CH_3CN.

Examples

Preparation A (Immumax)

Venoruton®	50 mg
Sorbitol	934 mg
Peppermint oil	8 mg
Magnesiumstearat	10 mg
In total	1000 mg

Preparation B

Troxerutin	50 mg
Sorbitol	934 mg
Peppermint oil	8 mg
Magnesiumstearat	10 mg
In total	1000 mg

Preparation C (ImmuMaxZn)

Venoruton ® (Novartis)	50 mg
Zn Gluconate (Fertin)	50 mg
Sorbitol	882 mg
Peppermint oil	8 mg
Magnesiumstearat	10 mg
In total	1000 mg

Patients diary

This scheme should preferably be filled out in the evening. How are your current condition with regard to the symptoms below. In the scheme below, please state the strength of your symptoms today by inserting an X at the appropriate place: every symptom should have points: 0 means that you have not had any symptoms at all; 4 means that you have had the worst symptoms available; etc. 0 = no symptoms, 1 = a minimum of symptoms; 2 = unpleasant symptoms; 3= considerably unpleasant symptoms; 4 = very unpleasant symptoms

Symptom points	0	1	2	3	4
Cough					
Headache					
Hoarseness					
Nasal discharge					
Sneezing					
Nasal obstruction					
Sore throat					
Irritated throat					
Malaise					
Sore muscles					
Fever					

Have you had any side effects of the treatment? Yes ☐ No ☐

Specify_____

Do you also take any other medical treatment or other kinds of treatment apart from this test treatment? Yes ☐ No ☐

Specify_____

The scheme above may preferable be used for identifying persons in need of a treatment according to the invention and to compare the effect with other treatments or placebo. A total score of 3 to 5 or less is regarded to be a normal condition.

Example 1

Virus titrations

Rhinovirus 1A, rhinovirus 15 and rhinovirus 39 were titrated according to the tetra zolium salt (MTS)-method (Berg et al., 1989; Berg and Owen, 2001a, Hansen et al., 1989). WISH cells were seeded in a micro tray at 3000 cells per well and incubated at 37° C, 5% CO_2 overnight; the following morning the medium was replaced with 10-fold dilutions of either rhinovirus 1A, rhinovirus 15 or rhinovirus 39, respectively, in fresh medium and the trays were incubated 4-5 days at 33°C; a microscopical examination confirmed that the CytoPathogenic Effect (CPE) was fully developed (CPE equal to 100%). The minimal amount of virus (i.e.: the highest dilution of the virus in question) which produced 100% destruction was used as "challenge virus" in the subsequent experiments. To quantitate the CPE in terms of % destruction, MTS (Berg and Owen, 2001a) was added to all cultures and after 3 h incubation at 37° C (without CO_2) the trays were read in a scanner as previuosly described (Berg et al, 1989, Hansen et al., 1989). Control cell cultures, that were not infected with virus, were included in the experiment; the latter gave the highest OD as these cells were not damaged; depending on the concentration of virus added to the different wells, the OD_{492} varied, accordingly: 100% CPE yielded a low OD(<0.200) ; 0% CPE corresponding to no infection at all (controls cell) gave a high OD (>1.200).

Example 2

No Antiviral activity of ZnGluconate as measured via the MTS-system.

WISH cells were seeded in wells in a microtray and incubated for 24 h at 34 °C, 5% CO_2; the medium was replaced with fresh medium comprising 2-fold dilutions of ZnGluconate (diluted 1:10 from a 1% stock dilutions) and incubated further for 3-4 days at 33 °C, 5% CO_2; on the following day challenge virus was added and after 3-5 days at 33° C, 5% CO_2, MTS was added and the microtray was measured in an OD-scanner (Berg et al., 1989; Hansen et al., 1989). Alternatively, instead of ZnGluconate WISH cells were incubated with other zinc salts/complexes or with the flavonoid derivatives, Troxerutin, Veneruton® or Quercetin.

No substantial protection against rhinovirus by addition of ZnGluconate could be detected (<2% protection). The OD signals from the wells, that were incubated in the presence of ZnGluconate were very close to the virus control curves (Figure 7). Similar results were observed when testing the antiviral effect of other zinc salts/complexes. When the flavonoid derivatives, Troxerutin and Veneruton were added to the WISH cells, they also did not show any antiviral activity (<1% protection). However Quercetin, had a moderate antiviral activity at levels not toxic to the cells (10 to 15% protection).

Example 3

Antiviral activity of Interferon-α (rHuIFN-α-2b) against Rhino virus (1A, 15 or 39).

3.000 WISH cells were seeded in a microtray and on the following morning, the medium was replaced with 2-fold dilutions (from a 0-30 units/ml stock solution) of HuIFN-α-2b (Intron A) in fresh medium comprising 2% serum. After incubation overnight, the medium was replaced with fresh medium comprising challenge virus and incubated at 33° C, 5% CO_2 for 3-5 days and processed further as described in Example 2.

The results in figure 7 clearly demonstrates that rhinoviruses are reasonable sensitive to HuIFN-α-2b (50% protection). However, 90-100% protection can be achieved at approx. 8-15 units/ml.

Example 4

Troxerutin and Interferon-α (rHuIFN-α-2b) vs. Rhino virus (1A, 15 or 39)

An experiment similar to Example 3 was carried out in which various, but constant concentrations of either Troxerutin or Veneruton or other relevant derivatives were added together with the 2-fold dilutions of interferon to WISH cells. A typical example from this series of experiments yielded no potentiation of the interferon system, (<1%) at all at Troxerutin levels below 2.5 mg/ml. Troxerutin concentrations higher than 2.5 mg/ml are toxic to the cells.

Example 5

RHINITIS AND COMMON COLD

Preliminary trial involving 2 persons.

Case 1

A) A 60 year old healthy man acquired a rhinitis with occasionally coughs. The person applied one tablet (preparation B) under his tongue and allowed the tablet to melt slowly during a period of 4-5 min. after the period of which the rhinitis sensation gradually disappeared within 10 min. (no more rhinitis, no more coughing).

The rhinitis started again after approx. 20-30 min. and the person applied 1-2 more tablets (preparation B) as described above after which no more rhinitis was observed. A mild headache disappeared. No side effects were noticed. The rapid effect of the treatment strongly suggests that the effect is caused by local action of the pharmaceutical rather than by systemic action.

The same person had previously on a few occasions treated himself with 1-2 lozenges (preparation B) when a mild rhinitis appeared and each time one lozenge stopped the rhinitis. .

Case 2

B) A 57 year healthy woman began coughing and an early rhinitis as described above appeared; the person applied one tablet (preparation B) under her tongue and kept it for 3-5 min. When asked about the result a few hours later she reported that the rhinitis had disappeared during 30-45 min. after one tablet, only. No side effects were noticed.

Preliminary conclusion on Case 1 and 2

It appears that the oral treatments comprising 1-3 preparation B tablets have been efficient as the early rhinitis and coughing disappeared. The persons did not catch new rhinitis or colds during the following 4-8 weeks period (ending December 15, 1999).

C) Preliminary trial involving 7 common cold patients at Doctor's Office

Based on the above results it was decided to go into a small controlled trial involving 10-15 patients who had acquired the infection naturally and were treated subsequently at a doctor's Office (HA). The optimal season for the classical common cold is from September to February but unfortunately it was not possible to arrange for a small controlled "trial" before the end of March, 2000.

Patient treatment.

Patients reporting to Doctor's Office (HA) complaining of a cold with rhinitis or a strong pharyngitis or other common cold syndromes (cf. Patient's Diary) were asked to fill out the Patients Diary (see above) which included relevant medical examinations (age, sex, patients on medical treatment were excluded, the date for the onset of the cold symptoms as listed in the diary – cf. enclosed copy. No specific efforts other than the usual symptoms of common cold were employed for characterisation of the patients enrolled. Thus most of the patients had experienced the cold for at least 1-2 days before reporting to the Doctor's Office. It is fair to assume that the patients probably represent a group of patient with a more severe cold than others not reporting to the Office.

A total of 7 patients with the usual characteristics for common cold – cf. the enclosed copy of the Patient's Diary above – were treated with the ImmuMax lozenges (preparation A) described above (50 mg Venoruton®) for a total period of 3 days, only. Each patient was instructed to fill out the patients diary every day (day 0= 1st visit to the Doctor's Office) and to follow the mode of administration: one lozenge should be applied on or under the patient's tongue and it should melt in a minimum period of 4-5 min. (no fluid or food should be taken the next 15-20 min.) If necessary, the patient could take the next lozenge after 30 min.; a total number of 5 lozenges per day was equal to the maximal dose per day.

The patients were asked to fill out the diaries and to return them to Doctor's Office a few days after the treatment.

Results

The results of this very limited and preliminary trial are shown in tables 1-8 and summarised in Figures 1-6. Events are defined as the number of marks noted in the 5 different symptoms categories. The data in table 1/fig. 1, which shows the number of events per day from the 7 patients in 5 symptom categories, supports the "early" preliminary "trial" as most of the severe symptoms have disappeared after 48 h; after further 24 h the patients have recovered almost completely. The curve for symptom 4 (very strong) drops within the first 24 h and stays at almost 0 for the remainder 48 h. The curve for symptom 3 (strong) had 15 counts on day 0; the curve drops in parallel to symptom 4 curve and at day 2(=48h treatment) no more counts with symptom 3 are reported from the 7 patients. The curve for symptom 2 drops in parallel with the two preceding curves, at day 3, three counts for symptom 2 were reported. The curve for symptom 1 reaches a plateau on day 1 and drops at day 3 to 8 counts. The symptom 0 curve shows 8 counts at day 1; then it rises in parallel to symptom curve 3 during the first 24 h, but it continues to rise to 45 on day 3.

In conclusion it can be stated that the fact that the symptom event score curve rises to a maximum for symptom zero supports the earlier findings with the two persons who were also cured within two days time.

As each patient fills out the diary each symptom receives a score graded from 0-4. These scores were compared with a "non-treated" control group taken from Jackson et al, Arch. Internal. Med. 101:267-278, 1958 (day 2 in Jackon's study is here used as day 0); The total scores from all patients under the syndrome "malaise" were compared with the so-called "non-treated" group The treated patients curve drops almost as a straight line in contrast to the non-treated, but infectious patients curve. At day 3 the treated group has significantly less scores compared to the non-treated group (fig. 2, table 2 and 3). Similarly the scores for sore throat are significantly reduced after 3 days treatment compared to the non-treated group (fig. 3, table 4 and 5). The scores for sneezing are close to zero after 3 days of treatment in contrast to the non-treated group (fig. 4, table 6 and 7).

Furthermore this study were compared with a controlled trial, designated Hertz, with 23 common cold patients who received a spray with another test drug for 6 days –the outcome was judged as negative although some minor effects were seen. This trial served as a control group for non-treated patients (placebo). When the mean total scores from these two groups are compared as percent reduction the present trial yielded a 50% reduction in symptom scores each day compared to the Hertz trial showing varying reductions. Based on this comparison it can be argued that the present trial yields a significant reduction in symptom scores compared to the placebo study.

Table 1

	x values day	A symptom 0 Y	B symptom 1 Y	C symptom 2 Y	D symptom 3 Y	E symptom 4 Y	sum
1	0	8	6	20	15	6	55
2	1	9	22	15	8	0	54
3	2	26	23	5	0	1	55
4	3	45	7	3	0	0	55

The number of events in each category (symptom 1-4) were counted every day, symptom 4 (very strong), symptom 3 (strong), symptom 2 (not pleasant), symptom 1 (minimal symptoms), symptom 0 (no symptom

Table 2

	A treated patients						
	X values day						
	X	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	0	2	3	3	2	1	4	2
2	1	2	2	1	1	1	3	1
3	2	1	1	1	0	1	1	1
4	3	1	0	0	0	0	1	1

Malaise scores from patient Y1-Y7 from day 0-3

Table 3

	B non-treated patients						
	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	2.240						
2	2.660						
3	2.450						
4	1.750						

Malaise scores from control group

Table 4

	A treated patients						
	X values day						
	X	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	0	0	2	2	3	3	1	3
2	1	0	2	1	1	0	0	2
3	2	0	1	1	0	0	0	3
4	3	0	0	0	0	0	0	2

Sore throat scores from patient Y1-Y7 from day 0-3

Table 5

	B non-treated patients						
	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	4.0						
2	4.0						
3	2.8						
4	2.1						

Sore throat scores from untreated group

Table 6

	A treated patients							
	X values day X	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	0	1	3	2	3	4	0	2
2	1	0	2	1	1	2	0	2
3	2	0	1	1	0	0	0	2
4	3	0	0	0	0	0	0	1

Sneezing scores from patient Y1-Y7 from day 0-3

Table 7

	B non-treated patients						
	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1	2.170						
2	1.680						
3	1.400						
4	1.300						

Sneezing scores from control group

Table 8

	X values	A	B	C	D	E
	day	% reduction	reduction	Data Set-C	Data Set-D	Data Set-E
		K	HE			
	X	Y	Y	Y	Y	Y
1	0	0	0			
2	1	50	22			
3	2	50	24			
4	3	48	37			

Percent reduction in total symptom score. K is this trial, HE is the Hertz trial

Conclusions from the Preliminary trial with 7 patients

Based on the findings in figures 1-5 it appears that the common cold patients are cured significantly faster than the non-treated group as the common cold period is cut down with approx. 50% from 6-7 days to 2-3 days. Furthermore, the more annoying symptoms seem to be cleared already during the first 24 h.

Example 6

Preliminininary trial with 3 patients suffering from allergic airway conditions

Case 1.

A 56-year old patient (BK/230244) who was allergic to grass and birch pollen was seeking advice at Doctor's Office; the patients had a rhinitis and irritated eyes; the condition had been unchanged during the last 2 weeks (no treatment was received during this period). The patient received the ImmuMax-treatment as described in example 1 and was asked to report after 5 days and to fill out the questionnaire in the patient's diary. The total symptom score had been reduced > 95% during the first 2-3 days of treatment.

Case 2

A 38-year old patient (CH/120962) who was notoriously allergic to birch pollen went to her Doctor's Office seek help; the exacerbations included rhinitis and irritated eyes; the symptoms had lasted for 2-3 days; no treatment was initiated at the time the patient went to Doctor's Office. The patient received the same treatment as in case 1 and was asked to fill in patients diary and reported back 5 days later: The initial patient score was very high for hoarseness, sore throat and scratchy throat, coughs, etc. After 2 days treatment with ImmuMaX a significant improvement was noted as the symptom score decreased > 75%.

Case 3

A 66-year old patient (ES/270334) had developed common cold symptoms which had sustained for 2 weeks; she received ImmuMaX as described above and reported back 5 days later: at day 0, the symptom score was approx. 50% of the total possible score; the symptom score was reduced >95% after 2-3 days of treatment.

Preliminary Conclusion.

Based on the results from this very limited group of allergic patients it seems as if Venoruton ® has a certain effect vs. allergy (pollen allergy and the like); furthermore, allergy which may have been induced via a slow upper airway infection (viral or bacterial or both) may also lend itself to an efficient treatment using the ImmuMax.

Commentary

The fact treatment was given exclusively by the oral/local route also deserves further exploitations as this manner of administration is rather surprising giving the fact that most

if not all treatments vs. allergic conditions are given either as spray or systemically. Our new administration form support the notion that one of the very early events initiating allergic reactions/asthma like syndromes could be the recruitment of the neutrophile granulocytes which as a matter of fact is in constant contact with the areas affected by infectious processes and/or inflammatory responses which in turn lend support to our current hypothesis namely, that it may be possible to control these events via drugs as Troxerutin or the like.

Example 7

Preliminary trial involving 7 common cold patients at doctors office treated with ImmuMaxZn

7 patients reporting at the Doctor's office, who had experienced the usual symptoms of common cold (sore throat, coughing, sneezing, running nose etc.) for 1-3 days, were treated. Each patient received 20 ImmuMaxZn tablets (containing 50 mg veneruton and 50 mg ZnGluconate, see preparation C) orally in the course of a 3 day treatment. On the first day patients received 5-7 tablets. Patients were asked to keep a patient's diary (see herein above). 7 out of 7 patients responded to the treatment with a 40-50% reduction in symptom score based on the patient diaries.

The results are shown in fig.6 and table 9. The curve demonstrates a marked decrease in symptom score after treatment. The reduction in symptom score made it possible for the patients to attend their normal duties.

Example 8

Trial including 42 patients suffering from common cold.

The trial was performed in Denmark, only adults participated in the trial. 42 patients suffering from common cold were treated with either Immumax (preparation A) or ImmumaxZn (preparation C). Each patient received a maximum of 5 lozenges daily and a total of 20 lozenges during the course of treatment. Each lozenge was administrated by

placing it under/on the tongue and allowing it to dissolve slowly (3-5 min.) and the following 10 min. the patient did not drink or eat.

Each patient was asked to fill in the patients diary (see herein above). The results of the trial is summarised in table 10 to 17.

There is a significant decrease in symptom score after 3 days of treatment with either Immumax or ImmumaxZn. However, when comparing the results of table 11 and table 15 it becomes clear that patients suffering from a typical common cold syndrome who started treatment within 3 days after the onset of the symptoms respond better to treatment with ImmuMaxZn than to treatment with ImmuMax. A mean reduction in symptom score of 59% after 3 days treatment with ImmuMax is observed, but 78% mean reduction in symptom score after 3 days treatment with ImmuMaxZn is observed.

Furthermore, it appears that the success of treatment is not dependent on the month in which the treatment was undertaken. Since the majority of common colds in Denmark occuring in September, October and November are caused by rhinovirus and the majority of common colds occuring in Denmark in January, February and March are caused by coronaviruses, this indicates that the treatment is effective against different kinds of virus infections. Accordingly, it is likely that the effect of ImmuMax or ImmuMaxZn is not a direct antiviral effect in vivo.

Table 10 Patients with a typical common cold syndrome presented within 24 h treated with ImmuMaxZn

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C Or NC)	Allergen	Patient's Remark
Nov	21-00	< 1	14	2	C	No	
March	12-01	<1	6	0	C	No	Good effect

Table 11 Patients with a typical common cold syndrome presented within 3 days treated with ImmuMaxZn

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C or NC)	Allergen	Patient's Remark
Nov.	22-00	3	11	4	C	No	
Nov.	27-00	3	14	0	C	No	Very good
Nov.	37-00	1	10	0	C	No	good
Dec.	41-00	3	30	3	C	No	
Dec.	42-00	1	10	7	Partial	No	Good !
Jan.	03-01	2	24	6	Partial	No	Good effect !
March	07-01	2	18	6	Partial	No	

Table 12 Patients with common cold syndrome /allergy treated with ImmuMaxZn

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C or NC)	Allergen	Patient's Remark
Nov.	29-00	3	15	3	C	Pollen	Average
Nov.	31-00	14	10	5	(C)	Birch	
Nov.	35-00	8	20	14	NC		
Dec.	46-00	3	10	2	C	Grass	Good
Dec.	47-00	3	20	15	NC	Grass	
March	08-01	2	16	5	(C)	Pollen	Good

Table 13 Patients (without any allergic background) with a typical common cold syndrome presented after 3 days treated with ImmuMaxZn

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C or NC)	Allergen	Patient's Remark
Nov.	28-00	6	21	9	PR	No	
Nov.	33-00	30	5	5	NC	No	
Nov.	34-00	4-5	29	29	NC	No	
Nov.	36-00	64	22	23	NC	No	
Jan.	48-00	6	9	2	C	No	
March	06-01	7	11	2	C	No	Good effect
March	09-01	14	7	3	C	No	Good effect

Table 14 Patients with a typical common cold syndrome presented within 24 h treated with ImmuMax

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C or NC)	Allergen	Patient's Remark
Oct.	17-00	< 1	18	21	NC	No	
Nov.	30-01	<1	5	5	NC	No	

Table 15 Patients with a typical common cold syndrome presented within 3 days treated with ImmuMax

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C) Or NC	Allergen	Patient's Remark
Jan.	13-00	2	20	1	C	No	
Oct.	14-00	2	33	2	C	No	
Nov.	15-00	2	11	9	NC	No	
Dec.	19-00	2	32	30	NC	No	
Nov.	20-00	2	23	9	Partial	No	
Nov.	38-00	3	9	3	C	No	good
March	07-01	2	18	6	Partial	No	

Table 16 Patients with common cold syndrome /allergy treated with ImmuMax

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C) Or NC	Allergen	Patient's Remark
Nov.	02-00	14	27	8	(C)		
Nov.	03-00	14	5	0	C		
Jan.	52-00	6	15	12	NC	grass	
Jan.	53-00	6	10	7	NC	grass	week

Table 17 Patients (without any allergic background) with a typical common cold syndrome presented after 3 days treated with ImmuMax

Month	Pt. No.	Days of Symptoms	Initial SS	SS on Day 3	Cured (C) Or NC	Allergen	Patient's Remark
Jan.	18-00	4	33	2	C	no	good
March	25-00	14	15	1	C	no	
Dec.	39-00	8	15	3	C	no	average
Dec.	40-00	6	17	5	C	no	average
Dec.	43-00	30	9	7	NC	no	
Jan.	18-00	4	33	2	C	no	good
March	25-00	14	15	1	C	no	

Table 10 to 17. SS symptom score, C cured, NC not cured, Pt. No. patient number, month indicates the month in which the treatment was performed, Days of symptom indicates the number of days the patient was suffering from common cold or a common cold related condition prior to the onset of treatment. Day 3 is day 3 of treatment.

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Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Although the invention has been described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

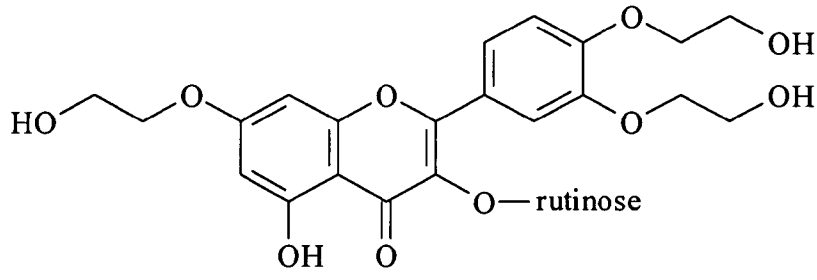
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. Use of a therapeutically effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier for the preparation of a medicament for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever.

2. Use of a therapeutically effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier for the preparation of a medicament for treatment of symptoms of conditions related to common cold of the upper and/or lower respiratory tracts and/or eyes, wherein said symptoms are selected from the group consisting of: cough, sneezing, muscle pain, sore throat, hoarseness, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis and bronchitis.

3. Use according to claim 1 or claim 2, wherein the pharmaceutical composition does not comprise any vitamin.

4. Use according to claim 1 or claim 2, wherein said flavonoid is troxerutin of the formula:



5. Use according to claim 1 or claim 2, wherein said flavonoid is a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to 10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside.

6. Use according to claim 1 or claim 2, wherein said treatment is in combination with a second treatment, wherein said second treatment is selected from the group consisting of: Tamiflu, Picovir, interferons, rimantadine.

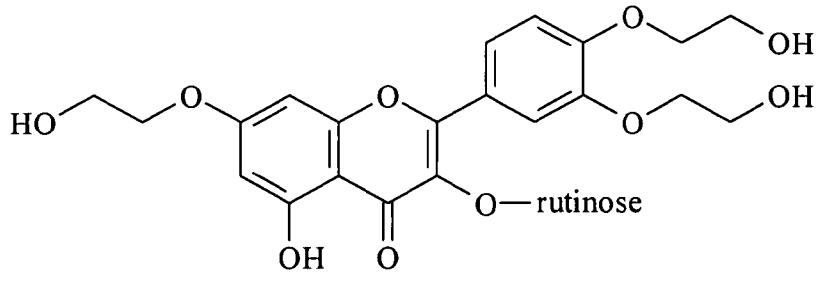
7. Use according to claim 1 or claim 2, wherein said treatment is in combination with a second treatment, wherein said second treatment is administration of a pharmaceutically-acceptable Zn^{2+} salt and/or complex.

8. A pharmaceutical composition comprising a pharmaceutically-effective amount of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, as well as a Zn^{2+} salt and/or Zn^{2+} complex, wherein said composition is formulated for topical administration to the mucosal membrane of the oral cavity.

9. A pharmaceutical composition according to claim 8, wherein said composition is formulated as lozenges, chewing tablets, chewing gum, drops, sprays or aerosols.

10. A pharmaceutical composition according to claim 8, wherein the flavonoid comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides.

11. A pharmaceutical composition according to claim 8, wherein the flavonoid is troxerutin of the formula:



12. A pharmaceutical composition according to claim 8, wherein said flavonoid comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to 10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside.

13. A pharmaceutical composition according to claim 8, wherein said Zn^{2+} complex is ZnGluconate.

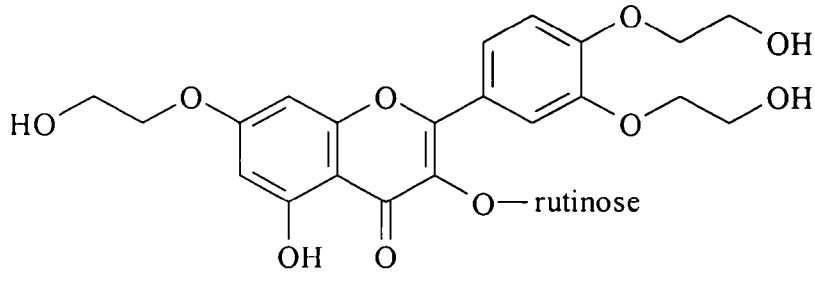
14. A pharmaceutical composition according to claim 8, wherein said composition comprises a Zn^{2+} complex.

15. A pharmaceutical composition according to claim 8, wherein said flavonoid is selected from the group consisting of: troxerutin and a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to 10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside and wherein the Zn^{2+} complex is ZnGluconate.

16. A kit-of-parts comprising a pharmaceutically-effective amount of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex, when used in a method for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever.

17. A kit-of-parts according to claim 16, wherein said flavonoid comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides.

18. A kit-of-parts according to claim 16, wherein said flavonoid is troxerutin of the formula:



19. A kit-of-parts according to claim 16, wherein said flavonoid comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to

10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside.

20. A kit-of-parts according to claim 16, wherein said Zn^{2+} complex is ZnGluconate.

21. A kit-of-parts according to claim 16, wherein said kit-of-parts comprises a Zn^{2+} complex.

22. A kit-of-parts according to claim 16, wherein said flavonoid is selected from the group consisting of: troxerutin and veneruton and the Zn^{2+} complex is ZnGluconate.

23. Use of a pharmaceutical composition comprising a pharmaceutically-effective amount of a hydroxyethylrutoside or a pharmaceutically-acceptable salt thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex or of the kit-of-parts according to any one of claims 16 to 22 for the preparation of a medicament for treatment of one or more conditions and/or symptoms of conditions, wherein said conditions are selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis and hayfever.

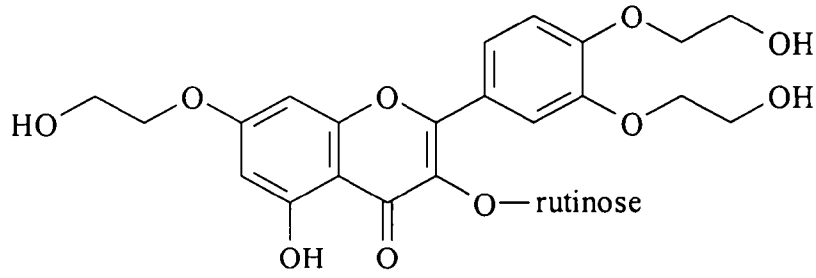
24. A method for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever, said method comprising applying to a patient in need thereof, a therapeutically-effective dosage of a flavonoid selected from the group consisting of: hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier.

25. A method for treatment of symptoms of conditions related to common cold of the upper and/or lower respiratory tracts and/or eyes, wherein said symptoms are selected from the group consisting of: cough, sneezing, muscle pain, sore throat, hoarseness, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis and bronchitis, said method comprising applying to a patient in need thereof, a therapeutically-effective dosage of a flavonoid selected from the group consisting of:

hydroxyethylrutosides and pharmaceutically-acceptable salts thereof, together with a pharmaceutically-acceptable carrier.

26. A method according to claim 24 or claim 25, wherein the pharmaceutical composition does not comprise any vitamin.

27. A method according to claim 24 or claim 25, wherein said flavonoid is troxerutin of the formula:



28. A method according to claim 24 or claim 25, wherein said flavonoid is a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides, wherein the mixture comprises 5% to 10% monohydroxyethylrutoside, 30% to 38% dihydroxyethylrutoside, from 45% to 55% trihydroxyethylrutoside and from 3% to 12% tetrahydroxyethylrutoside.

29. A method according to claim 24 or claim 25, wherein said treatment is in combination with a second treatment, wherein said second treatment is selected from the group consisting of: Tamiflu, Picovir, interferons, rimantadine.

30. A method according to claim 24 or claim 25, wherein said treatment is in combination with a second treatment, wherein said second treatment is administration of a pharmaceutically-acceptable Zn^{2+} salt and/or complex.

31. A method for treatment of one or more conditions and/or symptoms of conditions, wherein said conditions are selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis and hayfever, said method comprising applying to a patient in need thereof, a pharmaceutically-effective amount of a hydroxyethylrutoside or a pharmaceutically-acceptable salt thereof, as well as a Zn^{2+} salt and/or a Zn^{2+} complex or of the kit-of-parts according to any one of claims 16 to 22.

32. A method according to any one of claims 1, 2 and 23, wherein said condition is a viral infection of the upper and/or lower respiratory tracts and/or eyes.

33. A method according to any one of claims 1, 2 and 23, wherein said condition is a bacterial infection of the upper and/or lower respiratory tracts and/or eyes.

34. A method according to any one of claims 1, 2 and 23, wherein said condition is characterised by one or more symptoms of the group comprising: cough, sneezing, muscle pain, sore throat, hoarseness headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis and bronchitis.

35. A method according to any one of claims 1, 2 and 23, wherein said condition is a viral infection caused by or associated with one or more viruses selected from the group consisting of: adenoviruses, parvoviruses, picornaviruses, reoviruses, orthomyxoviruses, paramyxoviruses, arenaviruses, caliciviruses, coronaviruses, rhinovirus, influenza viruses comprising types A and B, echovirus, respiratory syncytial virus (RSV) and coxsackie virus.

36. A method according to any one of claims 1, 2 and 23, wherein said condition is a viral infection caused by or associated with one or more viruses selected from the group consisting of: coronaviruses and rhinoviruses.

37. A method according to any one of claims 1, 2 and 23, wherein said condition is a bacterial infection caused by the common cold or wherein said condition is associated with one or more bacteria selected from the group consisting of: *Streptococcus pheumoniae, Streptococcus Haemolyticae, Haemophilus influenxae,* and *Moraxella catarrhalis.*

38. A method according to any one of claims 1, 2 and 23, wherein said condition is selected from the group consisting of: rhinitis and hayfever.

39. Use of a therapeutically effective dosage of a flavonoid substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

40. A pharmaceutical composition substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

41. A kit-of-parts when used in a method for ameliorative and/or curative treatment of a condition selected from the group consisting of: common cold, viral and/or bacterial infection of the upper and/or lower respiratory tracts and/or eyes, rhinitis and hayfever, substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

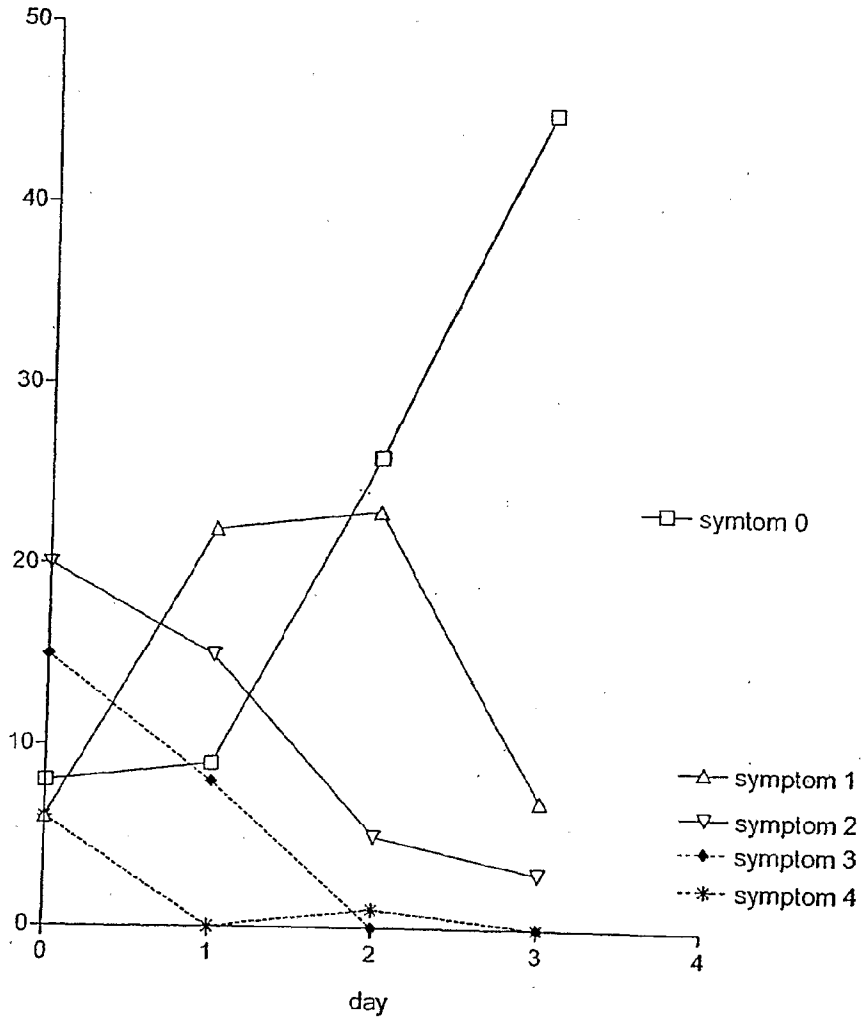
42. Use of a pharmaceutical composition substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

43. A method for ameliorative and/or curative treatment of a condition substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

44. A method for treatment of symptoms of conditions substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

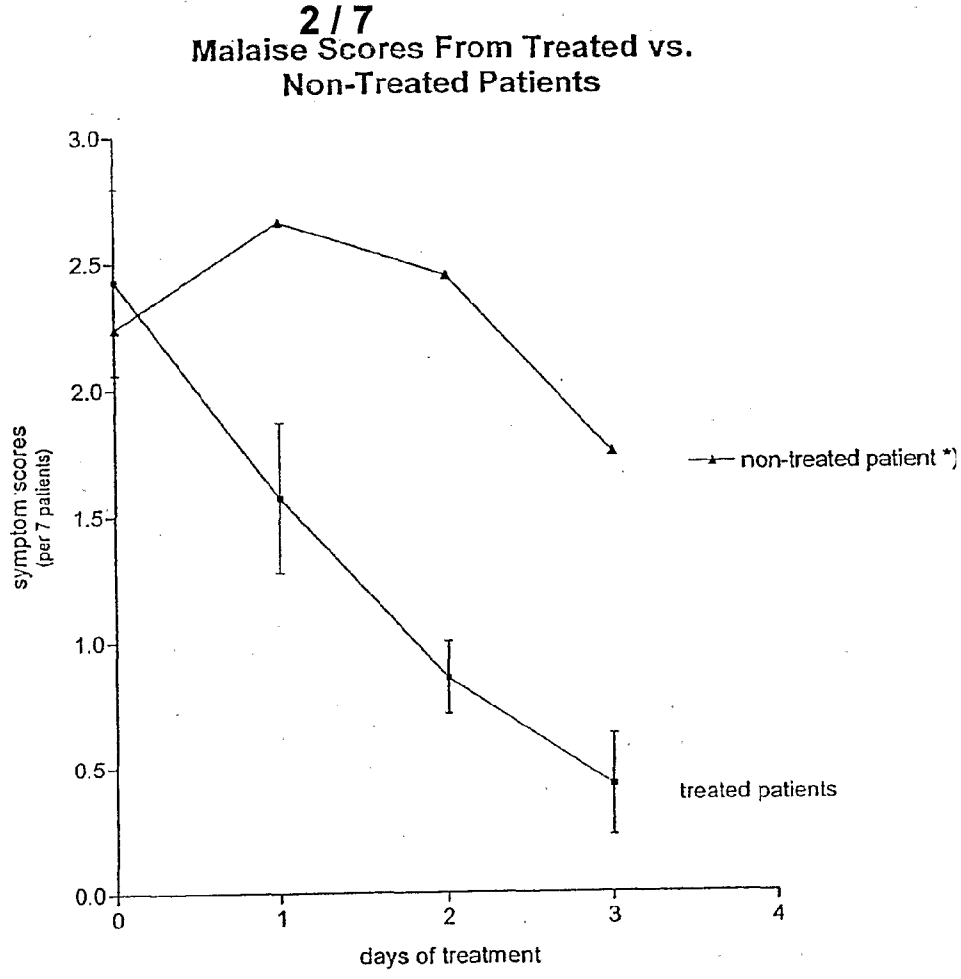
45. A method for treatment of one or more conditions and/or symptoms of conditions substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.

Dated this 13th day of July 2006
Shelston IP
Attorneys for: ImmuPharm ApS



Day 0: the status of the patient at the first visit at the doctor.
Day 1: 24 h after the 1st visit
Day 2: 48 h after the 1st. visit
Day 3: 72 h after the 1st. visit

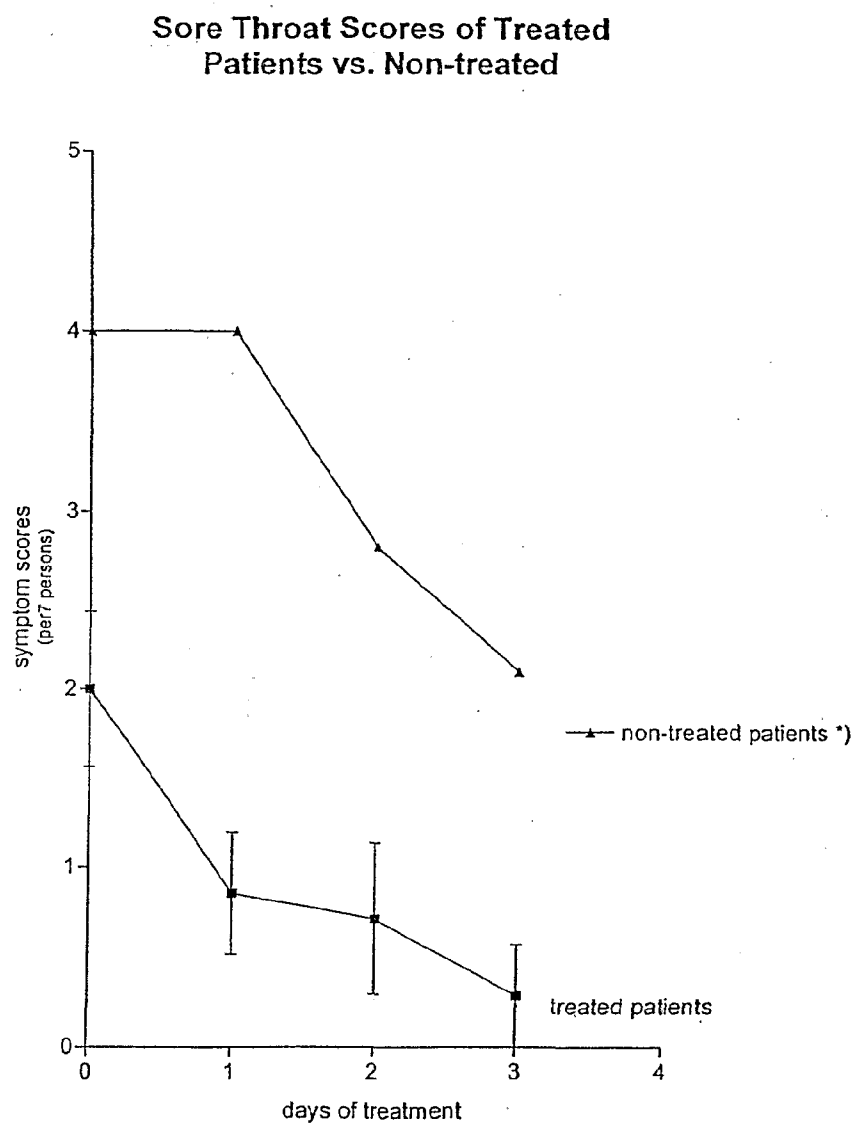
Fig. 1



day 0 : 1st. visit - treatment initiated
day 1: 24 h treatment
day 2: 48 h treatment
day 3: 48 h treatment

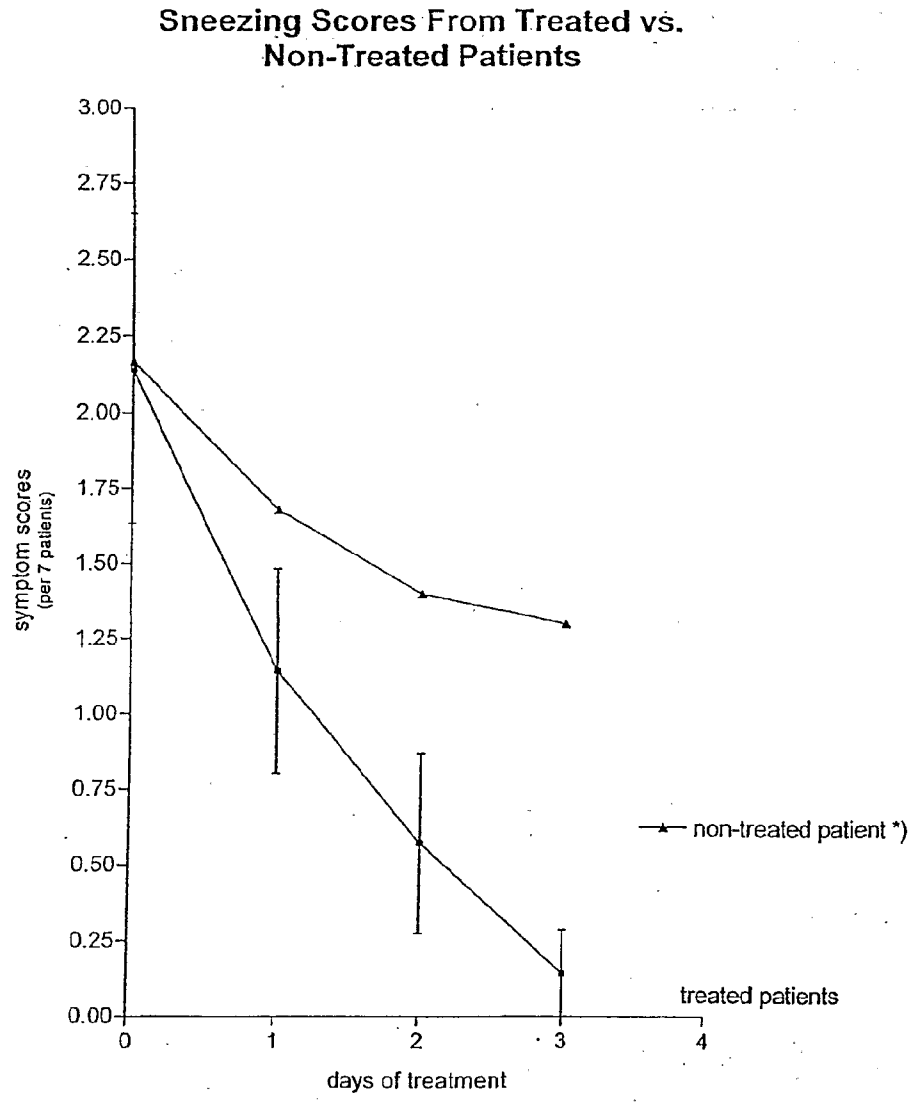
*) data taken from Figure 4 (day 2 is used as day 0 in this study) in Jackson et al.,Arch. Internal Med. 101; 267-278,1958

Fig. 2



day 0 : 1st. visit - treatment initiated
day 1: 24 h treatment
day 2: 48 h treatment
day 3: 48 h treatment

Fig. 3



day 0 : 1st. visit - treatment initiated
day 1: 24 h treatment
day 2: 48 h treatment
day 3: 48 h treatment

Fig. 4

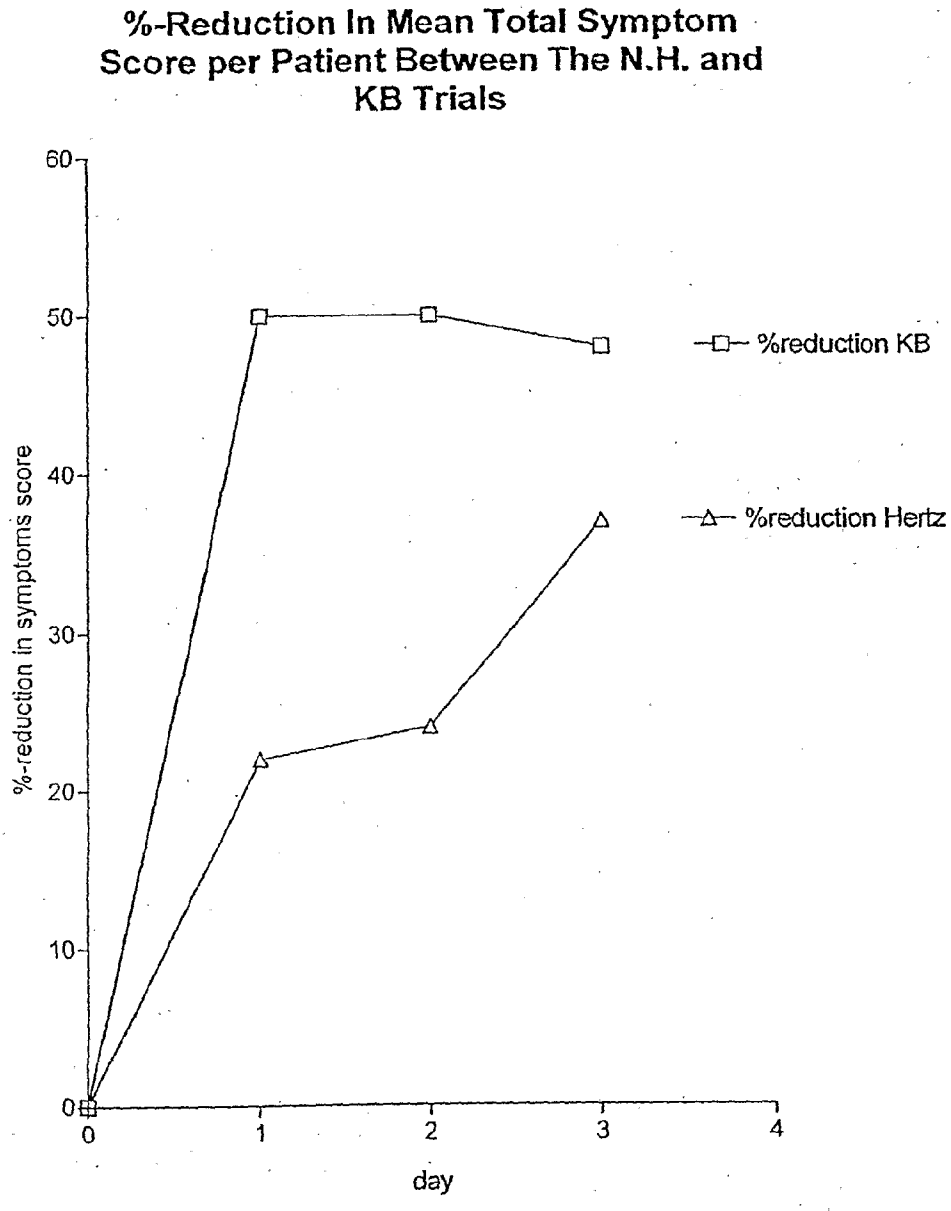

%-Reduction In Mean Total Symptom Score per Patient Between The N.H. and KB Trials
60
50
40
30
20
10
0
%-reduction in symptoms score
0
1
2
3
4
day
%reduction KB
%reduction Hertz

Fig. 5

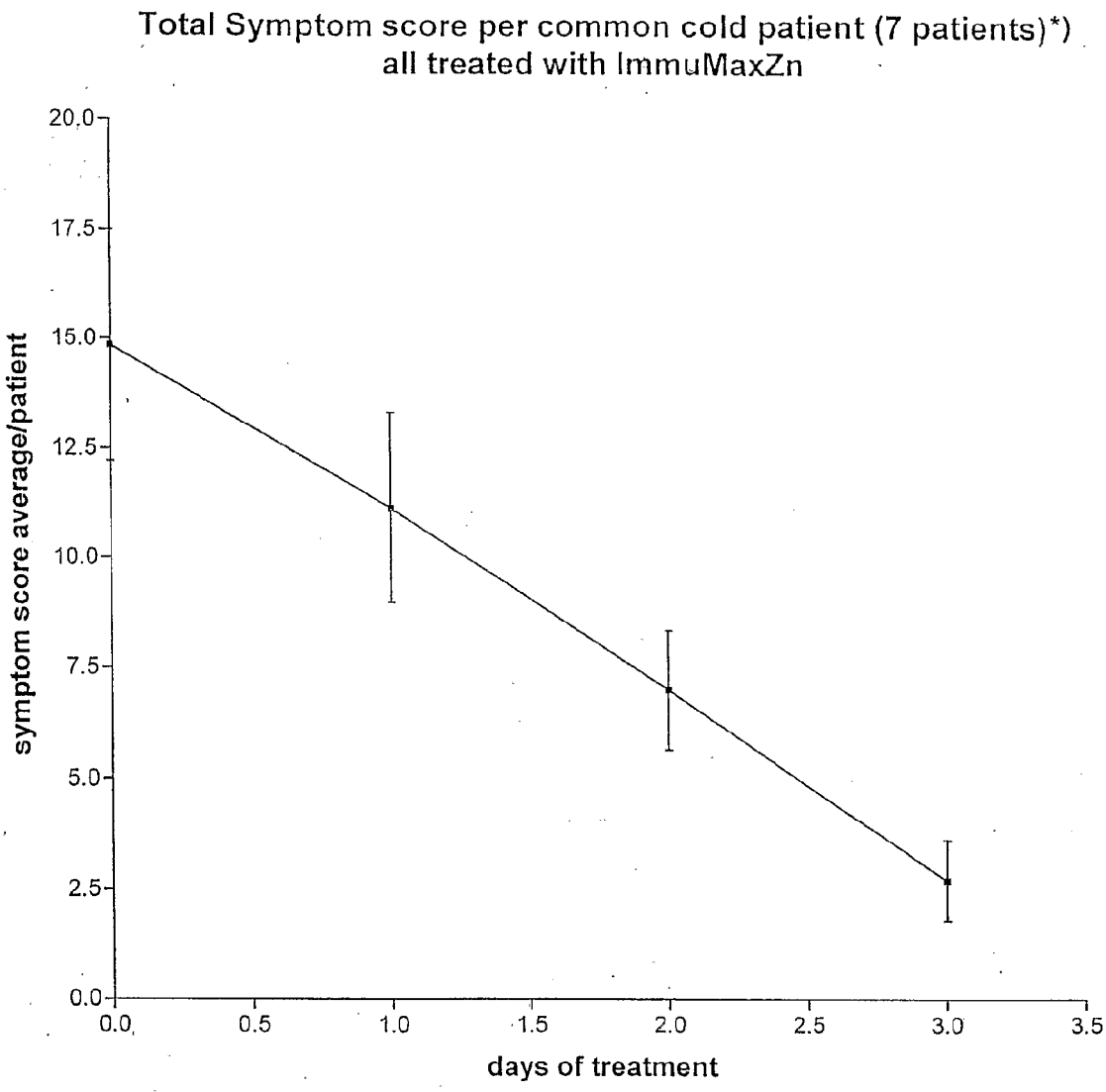

Total Symptom score per common cold patient (7 patients)*)
all treated with ImmuMaxZn
symptom score average/patient
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
days of treatment

Fig. 6

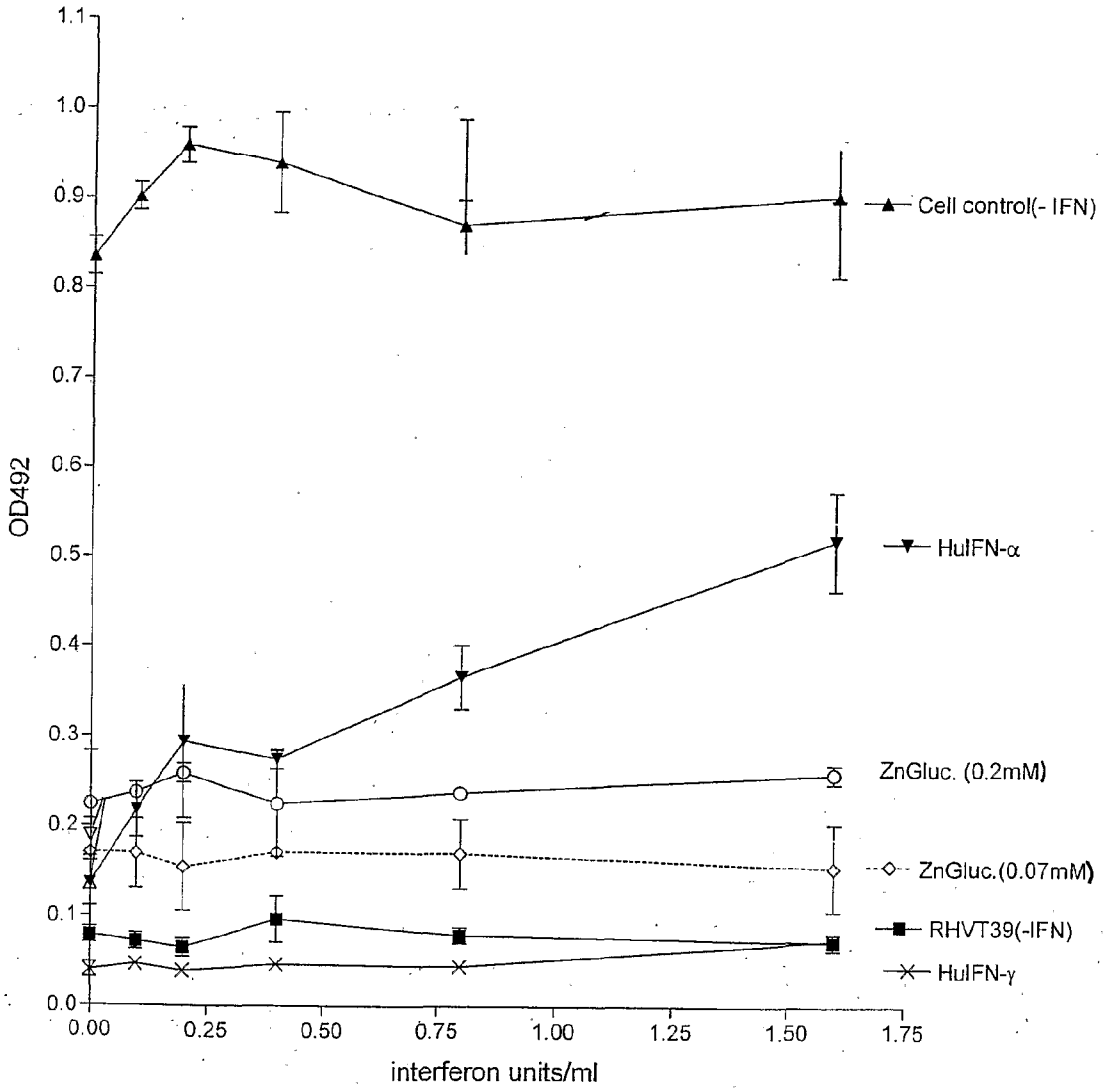

1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
OD492
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
interferon units/ml
Cell control(- IFN)
HuIFN-α
ZnGluc. (0.2mM)
ZnGluc.(0.07mM)
RHVT39(-IFN)
HuIFN-γ

Fig. 7