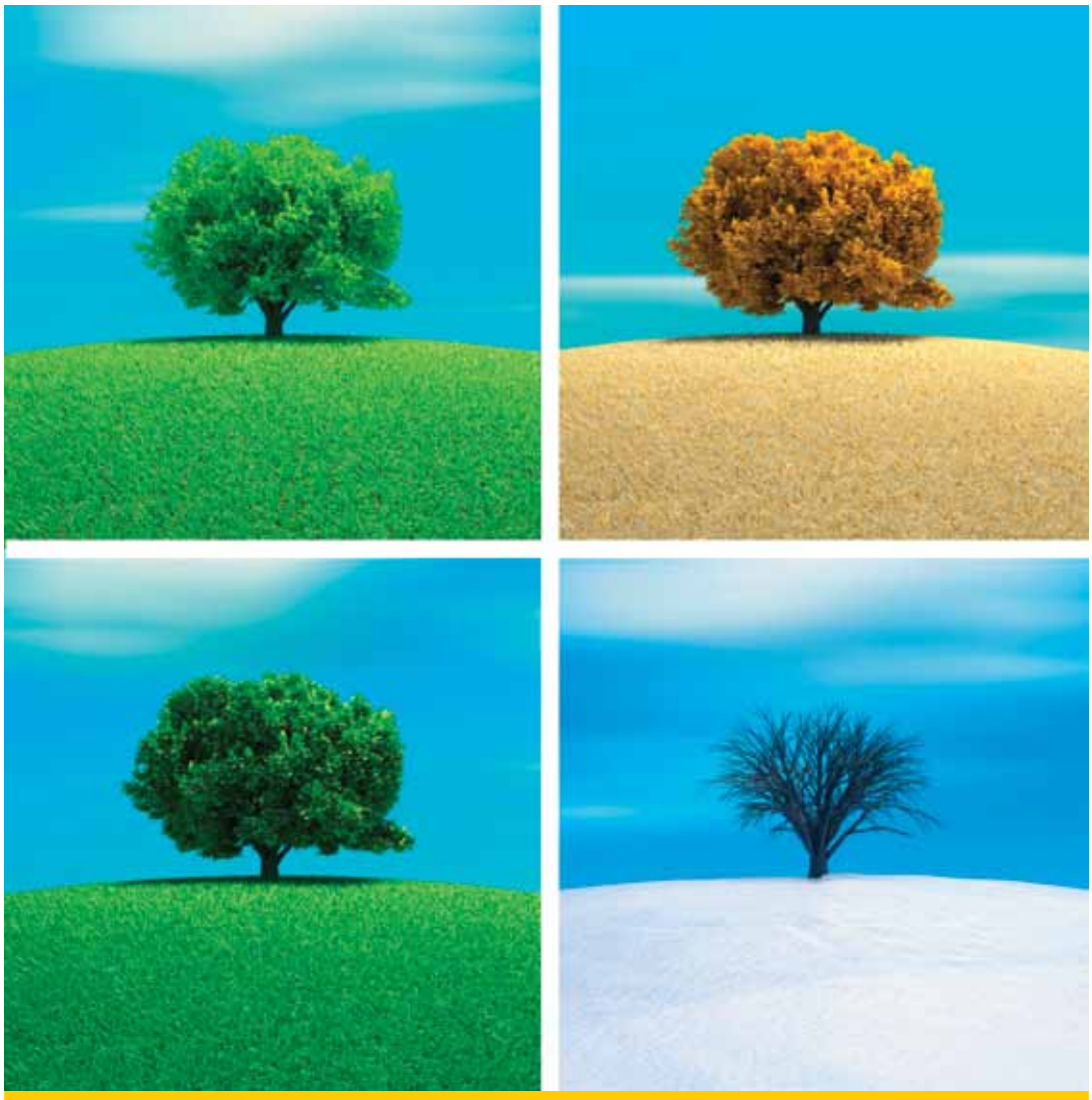
Product Monograph

Engystol®

An Antiviral Immunostimulator



Engystol®: consider a different approach in mild viral infections for all the family

Heel

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1 Overview

Engystol® has been used for more than 60 years. Today, it is available in over 50 countries worldwide. Each year, over half a million patients are treated with Engystol® worldwide. Engystol® can be used in patients of all ages.[1]

Engystol® can be used in patients of all ages.

Susceptibility to infections depends on numerous variables, including the status of the immune system. Engystol® is an **immunostimulating** medication with a broad range of therapeutic uses. It has been scientifically proven to significantly reduce the duration[2,3] and severity[4,5] of symptoms during an acute viral infection, and help protect against subsequent infections.[3]

The aim of treatment with Engystol® is to activate and support the body's endogenous defense mechanisms, i.e., to strengthen the natural immune response in cases of viral invasion, resulting in milder symptoms and shorter recovery times. Taken either preventively or at the first signs of a cold, Engystol® may prevent the development of acute symptoms.

Engystol® supports the immune system to reduce severity and duration of symptoms, particularly in early stages of viral infections, including colds and influenza-like illnesses.

Engystol® contains two main active ingredients:[6,7] *Vincetoxicum hirundinaria* (swallowwort) and sulfur (sulphur). Engystol® is available for use in oral tablet form, and as an injectable solution/drinkable ampoule.

The exact mechanism of action of Engystol® is still under investigation. *In vitro* tests have demonstrated that Engystol® stimulates the phagocytic activity of human granulocytes.[8,9] Further *in vitro* studies have demonstrated that Engystol® significantly increases the expression of interferon-γ producing T-lymphocytes suggesting that Engystol® causes an immunological stimulation mediated by the activation of T-lymphocytes.[10] Other studies have indicated that Engystol® is associated with a stimulation of the immune system in terms of granulocyte function and improved humoral response.[11,12] Examination of the effects of the individual components of Engystol® (sulfur and *Vincetoxicum hirundinaria*) may help to further elucidate its mode of action. Furthermore, recent research[13] has shown that Engystol® stimulates type 1 IFN release in different cell systems. These findings suggest that the antiviral activity of Engystol® may be mediated via modulation of the antiviral type 1 IFN host response.[13]

Basic research has revealed the activity of Engystol® against numerous respiratory viruses, such as influenza (flu) A virus, adenovirus type 5, Herpes Simplex Virus type 1 (HSV 1), human rhinovirus B serotype 14 (HRV-14) and Respiratory Syncytial Virus (RSV).[5,13,14]

Numerous studies with Engystol® demonstrate its excellent efficacy and tolerability, and the antiviral treatment and preventive benefits of Engystol® (alone or potentially in combination with Gripp-Heel®, due to its complementary action[13] in cases of infection and other pulmonary conditions with and without fever, such as bronchitis/asthma, RSV, upper respiratory tract infections, flu, etc.[1-5]

2 Viral infections and colds

Overview; general

Viruses are tiny parasites, ranging from 0.02 to 0.3µm. They depend completely on cells (bacterial, plant or animal) to reproduce. Viruses have an outer cover of protein, and sometimes lipid, and an RNA or DNA core. For infection to occur, the virus initially attaches to the host cell. The viral DNA or RNA enters the host cell and separates from the outer cover (uncoating). It then replicates inside the host cell. The host cell typically dies, releasing new viruses that can go on to infect other host cells.[15]

Several hundred different viruses infect humans. Viruses that infect primarily humans often spread via respiratory and enteric excretions.[15] Viral infections can cause illnesses as minor as the common cold and as severe as AIDS. Other common viral infections include influenza, viral gastroenteritis (e.g., from rotavirus or norovirus), non-polio enterovirus infections (e.g., viral meningitis, and hand, foot and mouth disease), viral pneumonia, measles, human parainfluenza, and Respiratory Syncytial Virus (RSV) (see below).

Treating and preventing viral infections; general

Antiviral drugs and interferons are used to treat specific viral infections.[15] Vaccines, immunoglobulins and protective measures are used for prevention.[15] For viruses that cannot be specifically treated or prevented, symptomatic therapy is used (see later).

Overview of viral respiratory infections

Viral infections can affect the upper or lower respiratory tract.[15] Upper respiratory tract infection (URI) represents the most common acute illness evaluated in the out-patient setting, and viruses account for most URIs.[16] Infections can be classified by the invading virus (e.g., influenza) or according to syndrome (e.g., the common cold, bronchiolitis, croup). Whilst specific viruses commonly cause characteristic clinical symptoms (e.g., rhinovirus typically causes the common cold, respiratory syncytial virus typically causes bronchiolitis), there is overlap and each respiratory virus can cause many of the viral respiratory syndromes.[15] Severity of viral respiratory illness varies widely; severe disease is more likely in the elderly and infants.[15]

Treating and preventing viral respiratory infections; general

Treatment of viral respiratory infections is usually supportive. Antibacterial drugs are ineffective against viruses, and should be only be given in cases of secondary bacterial infection. In some cases, antiviral drugs are useful but associated with issues of resistance (see later).[15]

Below we give an overview of some of the most common types of respiratory viruses that specifically relate to Engystol®.

A. The common cold[16,17,18]

What is it?

The common cold is a self-limited, contagious condition that can be caused by a number of different types of viruses. The common cold is medically referred to as a viral URI.

The common cold is the leading cause of acute morbidity and missed days from school or work.

What causes it?

More than 200 different viruses are known to cause the common cold. Typical viruses that cause URIs are rhinoviruses (causing approximately 30-50% of all adult colds) (see later), coronaviruses, adenoviruses and enteroviruses. With a few exceptions, similar agents cause URI in adults and children.

URIs involve direct invasion of the mucosa lining the upper airway. Person-to-person spread of viruses accounts for most URIs.

Symptoms

The patient's history is necessary for differentiating a common cold from conditions that require targeted therapy, such as group A streptococcal pharyngitis, bacterial sinusitis and lower respiratory tract infections.

Symptoms of the common cold usually begin 2-3 days after inoculation. Symptoms and signs of the common cold vary depending on the virus responsible for the infection. They may include coughing/hoarseness, sore throat, nasal congestion, runny nose, aching/headaches, low-grade fever, fatigue and sneezing.

Treatment

In most cases, the symptoms of the common cold will be self-limiting, self-diagnosed and self-managed, e.g., with rest, fluids, gargling, steam inhalations, vapor rubs, menthol-based sweets, adequate nutrition and symptomatic therapy, e.g., paracetamol, ibuprofen, aspirin (in over 16s) and/or decongestants (see later). The use of antibiotics is not recommended unless there are bacterial complications.

A 2011 Cochrane review[19] suggested that taking zinc supplements within a day of the symptoms starting will speed up recovery and lessen the severity of symptoms. However, long-term use of zinc is not recommended as it could cause side effects, such as vomiting and diarrhea.

B. Rhinoviruses[16,20,21]

What is it?

Rhinoviruses (RVs) are small (30nm), non-enveloped viruses that contain a single-strand RNA genome within an icosahedral (20-sided) capsid. Rhinoviruses belong to the Picornaviridae family, which includes the genera *Enterovirus* (polioviruses, coxsackieviruses groups A and B, echoviruses, numbered enteroviruses, parechoviruses) and *Hepatovirus* (hepatitis A virus).

What causes it?

Over 100 serotypes have been identified within the human rhinovirus A, B or C species, e.g., Human rhinovirus B serotype 14 (HRV-14). Although infections occur year-round, the greatest incidence occurs in the Autumn and Spring.

There are two modes of transmission: via aerosols of respiratory droplets and from contaminated surfaces, including direct person-to-person contact.

Human rhinoviruses occur worldwide and are the primary cause of common colds. Nasopharyngitis, croup and pneumonia are uncommonly caused by RVs. Rhinoviruses also play a significant role in the pathogenesis of otitis media and asthma exacerbations.

Symptoms

Since rhinoviruses are a predominant cause of common colds in humans, symptoms include sore throat, runny nose, nasal congestion, sneezing and cough; sometimes accompanied by muscle aches, fatigue, malaise, headache, muscle weakness, or loss of appetite. Fever and extreme exhaustion are more usual in flu-like illness (see above).

Treatment

Although the incidence and prevalence are high, most cases are mild and self-limiting; therefore, treatment is generally focused on the symptomatic relief and prevention of person-to-person spread and complications. The mainstays of therapy include rest, hydration, antihistamines and nasal decongestants.

There are no vaccines against these viruses. In terms of treatment, antibacterial agents are not effective unless bacterial superinfection occurs. Development of effective antiviral medications has been hampered by the short course of these infections and by the large number of rhinovirus immunotypes and the inaccessibility of the conserved region of the viral capsid (the most likely effective site for targeting a vaccine). There are also no antivirals which are currently effective against them. However, numerous agents are under investigation for the treatment of viral infections. Pleconaril is an orally bioavailable antiviral drug being developed for treatment.[22,23] In addition, 3C protease inhibitors are currently being evaluated in human trials.[24]

C. Flu-like illness[16,17, 18, 25]

What is it?

Numerous viruses that infect the respiratory tract can cause flu-like illness. In the majority of individuals, symptoms last for one to two weeks before recovery.

What causes it?

Many different viruses can cause a flu-like illness. Influenza viruses which cause the flu are divided into three types; type A, B and C. Influenza types A and B are responsible for outbreaks of respiratory illness that occur almost every winter, and are often associated with increased rates of hospitalization and death. Type C infection usually causes either a very mild respiratory or gastrointestinal illness or no symptoms at all.

Symptoms

Flu-like illnesses typically cause a high temperature, aches and pains in muscles and joints, a cough and various other symptoms. Most people recover fully, but complications, such as pneumonia, can develop particularly in more susceptible patients (e.g., the elderly, those with significant co-morbidities, <6 months of age).

Treatment

Treatment for flu-like illnesses is symptomatic, and often includes rest, keeping warm and fluids. Sufferers are advised to take paracetamol or anti-inflammatory medicines, such as ibuprofen, to lower fever and relieve aches. High-risk groups may be prescribed an antiviral medication. Antivirals (oseltamivir, zanamivir, amantadine, rimantadine) will not cure flu-like illnesses and there is widespread resistance to their use, e.g., to the adamantanes (amantadine and rimantadine) amongst influenza A (H3N2) virus strains. Drug resistance with neuramidase inhibitors is also a concern, although not to the same extent as the adamantine derivatives. During the 2007-2008 US influenza season, 10.9% of H1N1 viruses tested in the US were resistant to oseltamivir.

Whether to prescribe these agents should depend on the patient, the probable type of viral strain involved and the potential benefit. Advantages for prescribing these agents include significantly reducing illness severity, duration and secondary complications. Disadvantages include potential adverse effects, resistance and costs.

Whilst antibiotics are not prescribed for flu as they have no effect on viruses, occasionally they may be necessary to treat bacterial complications of flu-like illnesses, e.g., pneumonia, caused by the diminished host response to infection.

D. Adenoviruses[16,17,26]

What is it?

Adenoviruses are double-stranded DNA viruses that measure 70-90nm and have an icosahedral capsid.

There are at least 52 immunologically distinct types that can cause human infections. Young infants and immunocompromised patients are more susceptible to severe complications of adenovirus infection.

Adenovirus 14 (Ad14) is termed the 'killer cold virus' or 'super cold' because of the high incidence of hospitalizations and deaths attributed to this viral strain.

What causes it?

Adenoviruses are transmitted via direct inoculation to the conjunctiva, via a fecal-oral route, via aerosolized droplets or from exposure to infected tissue or blood.

The site of entry generally determines the site of infection; respiratory tract infection infections result from droplet inhalation, whilst gastrointestinal tract (GIT) involvement results from fecal-oral transmission.

Symptoms

Adenoviruses most commonly cause respiratory illness; however, depending on the infecting serotype, they may also cause various other illnesses, such as gastroenteritis, pharyngoconjunctival fever, acute hemorrhagic cystitis and epidemic keratoconjunctivitis. Symptoms of respiratory illness caused by adenovirus infection range in severity from those of the common cold (see above) to pneumonia, croup, bronchitis and fatal pneumonia.

Treatment

Other than supportive and symptomatic treatment, there is no specific therapy for adenovirus infection. However, most infections are self-limiting in non-immunocompromised patients. Several drugs, such as cidofovir, ribavirin, ganciclovir and vidarabine, have been used to treat adenovirus infections, particularly in immunocompromised patients. The use of these medications has been based on case reports and clinical studies, and no prospective controlled treatment trials have been conducted.

E. Herpes Simplex Virus types 1 & 2 (HSV-1, HSV-2)[16,17,27]

What is it?

Herpes simplex viruses belong to the family Herpesviridae and to the sub-family Alphaherpesvirinae. Herpes simplex viruses - more commonly known as herpes - are categorized into two types: herpes type 1 (HSV-1) and herpes type 2 (HSV-2). Both HSV-1 and HSV-2 can cause similar genital and orofacial primary infections after contact with infectious secretions containing either HSV-1 (usually oral secretions) or HSV-2 (usually genital secretions). Recurrent genital herpes is more common with HSV-2 infection.

What causes it?

HSV is transmitted via close personal contact. HSV infection occurs via inoculation of virus into susceptible mucosal surfaces (e.g., oropharynx, cervix, conjunctiva) or through small cracks in the skin.

Symptoms

Symptoms of HSV infection vary depending on its clinical course and stage, e.g., acute herpetic gingivostomatitis, acute herpetic pharyngotonsillitis, primary genital herpes, recurrent genital herpes or sub-clinical genital herpes. Symptoms can include lesions, fever, tenderness, pain, burning and tingling at the affected site.

Treatment

There is no cure for herpes simplex. Once a person has the virus, it remains in the body. The virus lies inactive in the ganglia until something triggers it to become active again.

Overall, medical treatment of HSV infection is centered on specific antiviral treatment. Whilst the same medications are active against HSV-1 and HSV-2, the location of the lesions and the stage of the infection dictate the dosage and frequency of medication. It is important to note that life-threatening HSV infections in immunocompromised patients and HSV encephalitis require high-dose intravenous acyclovir. When effects such as fever occur, symptomatic treatment can be used. Appropriate wound care is needed, and treatment for secondary bacterial skin infections may be required.

F. Respiratory syncytial virus (RSV)[16,26,28]

What is it?

Respiratory syncytial virus (RSV) infection, which mainly manifests as bronchiolitis and/or viral pneumonia, is caused by the respiratory syncytial virus. It is the leading cause of lower respiratory tract (LRT) infection in infants and young children.

What causes it?

RSV is the most common virus that causes lung and airway infections in infants and young children. However, the infection can occur in people of all ages. Peak incidence of occurrence of severe RSV disease is observed at 2-8 months. Virtually all children have had at least one RSV infection by their third birthday. More than 125,000 children are hospitalized annually in the United States because of this infection. Outbreaks of RSV infections most often begin in the Autumn and run into the Spring.

The virus spreads through tiny droplets that go into the air when an infected person blows their nose, coughs or sneezes.

Symptoms

Patients with respiratory syncytial virus (RSV) infection might present with fever (typically low-grade), cough, tachypnea, cyanosis, retractions, wheezing, rales or, in very young infants, a sepsis-like presentation or apneic episodes. Physical examination of infants with RSV LRT infection may show evidence of diffuse small airway disease. Low-risk, healthy infants infected with RSV often do not need to be hospitalized.

Treatment

Supportive care is the mainstay of therapy for RSV infection. Infants and children with a severe RSV infection may be hospitalized, where supportive care may include administration of supplemental oxygen, mechanical ventilation and fluid replacement. Bronchodilator therapy with beta-agonists is used, although data on their benefit in this condition are conflicting. Ribavirin is licensed for aerosolized treatment in children with severe RSV disease.

Palivizumab vaccine is licensed for the prevention of RSV infection in high-risk children, e.g., those with cystic fibrosis.

The World Health Organization (WHO) has targeted RSV for vaccine development, which is not surprising, given the prevalence and potential severity of this condition.

Current treatment options

Paracetamol, aspirin (in over 16s), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen) and decongestants (e.g., pseudoephedrine) are commonly used to manage the symptoms of viral infections and colds. There are many monotherapy and combination therapy options of these drugs available for purchase over-the-counter and by prescription.

However, the use of these agents is not without risk. For example, overdose or intolerance to paracetamol may give rise to states of excitation including convulsions, circulatory collapse and coma. Hepatic toxicity can result from overdose.[29] The therapeutic window between an active and a toxic dose is narrow with acetaminophen, particularly with multiple doses.[30] There are numerous reports that paracetamol use, particularly in children and pregnant women, is associated with an increased risk of asthma, atopy and allergy development.[31-33] There are also questions over the efficacy of pasracetamol in the common cold.[34]

NSAIDs and aspirin are associated with well-known gastrointestinal, clotting and renal effects, and contraindications in asthma. More serious reactions to the use of aspirin can also occur, particularly in children and infants. Indeed, while no causal link has been proven, studies show a significant association between aspirin use and Reye's syndrome (an acute, non-inflammatory encephalopathy and hepatotoxicity that often results in lasting neurological damage) in children and infants. The risk of contracting Reye's syndrome reduces dramatically throughout adolescence, and so the drug has been withdrawn from use as a treatment for fever and viral illness in infants and children.[35,36]

Decongestants can excessively dry nasal secretions leadibng to an increased risk of infection, and can cause a rebound effect leading to complications. They are also contraindicated in patients with cardiovascular disease, hypertension, diabetes, prostatic hypertrophy, and thyroid conditions.[25]

Furthermore, none of these agents have known immunostimulating or immunomodulating effects on viruses.[37]

Several other non-prescription plant-based medications are also used in patients suffering from viral infections and the common cold – either for prevention and/or treatment - and the evidence/issues associated with the most popular of these is outlined below. Nutritional considerations, e.g., vitamin C, zinc, vitamin A, N-acetylcysteine (NAC), dehydroepiandrosterone (DHEA) and high lactoferrin whey protein are not reviewed here.

Echinacea

The Echinacea species - *Echinacea angustifolia, Echinacea pallida* and *Echinacea purpurea* - have a long history of medicinal use for a variety of medical conditions, particularly infections.[38] Commercial echinacea samples and marketed echinacea products may contain one or more of the three echinacea species. Many are also combination products with other active ingredients, e.g., Thuja, zinc, vitamin C and wild indigo.

An obstacle to the performance of definitive studies with Echinacea is the fact that different medicinal preparations have different compositions. The three different species of Echinacea are all being used for medicinal purposes, each with a different phytochemical composition, In addition to the selection of plant species, the composition of the final product may be altered by the part of the plant used, the method of extraction, and even the season in which the plant is harvested.[39] Furthermore, as with any plant, the chemical makeup of echinacea is not consistent throughout the organism. When reviewing studies, it is important to note the difference between the aerial parts (the leaves, stem and flowers) (standardized to echinosides) and root parts (standardized to the alkylamides). Germany's Commission E, an authoritative expert herb panel which guides modern drug laws in Germany,

only recommends *echinacea purpurea* aerial parts and the roots of another species, *echinacea pallida*. They don't approve *angustifolia*. The root has been promoted as containing a more efficacious mixture of active chemicals. However, opinions are divided as to which is the best part of the plant to use.

However, the immunological effects of a wide range of echinacea preparations comprising different species, plant parts and types of extract, have been investigated extensively *in vitro* and *in vivo*.

In vitro experiments with human macrophages[40] found that fresh pressed juice and dried juice from the aerial parts of *E. purpurea* stimulated production of cytokines, including interleukin 1 (IL-1), IL-10, and tumor necrosis factor α (TNFα). Antiviral activity has been described for various different preparations of echinacea in another *in vitro* study.[41] An 'indirect' antiviral effect was documented in experiments involving the addition of glycoprotein-containing fractions obtained from E. purpurea root to mouse spleen cell cultures. Interferon-α and -β produced by the cells were then tested for activity against vesicular stomatitis virus. These glycoprotein-containing fractions were also tested directly against HSV and were reported to reduce the number of plaques by up to 80%. However, overall, raw data are lacking and statistical tests do not appear to have been conducted.

Human trials of echinacea preparations for the prevention of upper respiratory tract infections have typically involved an 8- or 12-week duration of treatment and administration of the study medication for 6-10 days. An *in vivo* study,[42] conducted using a rigorous randomized, double-blind design, assessed the effects of an echinacea product (Nature's Resource, CVS Pharmacy, USA). It showed that differential white cell counts were significantly altered throughout the 8-week study period in the echinacea group compared with the control group. There were no changes in the phagocytic activity of circulating leukocytes, as assessed by their ability to ingest latex particles, in either group during the study.

In a meta-analysis of 14 studies[43] evaluating the effect of echinacea on the incidence and duration of the common cold, echinacea decreased the odds of developing the common cold by 58% and the duration of a cold by 1.4 days.

In fact, several clinical trials of echinacea preparations have reported effects superior to those of placebo in the prevention and treatment of URIs.[44-52] However, evidence of efficacy is not definitive with several studies reporting no effect vs. placebo.[53-55] Furthermore, marketed and studied medicinal products contain different species (*E. purpurea, E. angustifolia, E. pallida*), different organs (roots and herbs) and different preparations (extracts and expressed juice), their chemical composition is very different and they have studied different patient groups making them hard to compare.

Echinacea appears to be well-tolerated. Based on limited safety data - mainly from short-term clinical trials of echinacea preparations for the prevention and treatment of URIs - the main safety issues are the possibility of allergic reactions. Concern has been expressed about the use of echinacea by patients with progressive systemic diseases, such as tuberculosis, leukemia, collagen disorders, multiple sclerosis and other autoimmune diseases but this warning is based on theoretical considerations rather than human data.[56]

Excessive use of echinacea should be avoided in view of the lack of toxicity data. The potential for echinacea preparations to interact with conventional medicines should be considered.

Overall, there is insufficient evidence to recommend any specific echinacea products, or to advise on optimal dose and treatment duration. Further well-designed clinical trials using well-defined, standardized preparations are necessary in order to establish efficacy.

Panax quinquefolium (North American ginseng)

The root of *Panax quinquefolium* (North American ginseng) has been shown in controlled trials to reduce the incidence, duration, number and severity of colds and flu, and their symptoms, in both ill and healthy individuals.[25,57-61]

A randomized, double-blind, placebo-controlled study at the onset of the influenza season evaluated 323 healthy adults (ages 18-65 years) with a history of at least two colds the previous year. Those in the treatment group received two 200mg capsules daily of a standardized extract of *P. quinquefolium* containing 80% poly-furanosyl-pyranosyl-saccharides or placebo twice daily for four months. In patients taking the ginseng extract, the mean number of reported colds was reduced by 9.2% and the risk of developing a cold was reduced by 12.8% compared to the placebo group. In addition, the ginseng group reported a 31% lower symptom score (severity) and 34.5% fewer symptom days (duration) than the placebo group.[59]

In a second study using a proprietary extract containing highly concentrated poly-furanosyl-pyranosyl- saccharides from the *P. quinquefolium* root,[43] community-dwelling elderly adults were given 200mg capsules of the extract or placebo twice daily for four months. One month into the study, all participants received an influenza vaccination. Despite no differences between the two groups in the first two months, during the last two months, 32% of subjects taking the *P. quinquefolium* reported an upper respiratory tract infection compared to 62% in the placebo group. In addition, the treatment group reported average symptom duration of 5.6 days compared to 12.6 days in the placebo group.[60]

In fact, a review of four trials[59-61] involving almost 500 participants showed *P. quinquefolius* to be effective in the prevention of common colds in healthy adults in terms of reducing the frequency and the number of common colds vs. placebo, and reducing the duration of the common cold vs. placebo.[58]

Its safety and tolerability in the treatment of pediatric upper respiratory tract infection has also been confirmed and its efficacy in this patient group will be reviewed.[62]

Oscillococcinum

Oscillococcinum is manufactured from wild duck heart and liver. It is one of the most widely used and popular homeopathic medicines in France and Russia. A systematic review of seven studies with a total number of 2,265 patients on Oscillococcinum determined whether Oscillococcinum or similar medicines were more effective than placebo in the prevention of influenza and influenza-like syndromes.[63] The authors concluded that current evidence does not support a preventive effect of Oscillococcinum-like homeopathic medicines in preventing influenza and influenza-like syndromes.

In a review of four placebo-controlled studies to assess the evidence for the effectiveness of complementary and alternative therapies for preventing or treating influenza or influenza-like illness, including avian influenza,[64] the authors concluded that, although some encouraging results have been reported for Oscillococcinum, the findings are of limited value.

Pelargonium reniforme/sidoides

Pelargonium is used in upper respiratory tract infections, e.g., acute bronchitis in adults and children, and sinusitis in adults.[65,66] A Cochrane review noted that *P. sidoides* may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults, but doubt exists. Reliable data on treatment for other respiratory infections were not identified.[67]

Aconitum

Aconitum, known as aconite, monkshood, wolfsbane, leopard's bane, women's bane, Devil's helmet or blue rocket, has long been used in the traditional medicine of Asia. Aconite is a genus of over 250 species of flowering plants belonging to the buttercup family (Ranunculaceae).

Studies have suggested some anti-oxidant, anti-inflammatory and immunological/immunomodulatory effects of Aconitum.[68-71] However, issues with toxicity are well-recognized.[72]

Engystol®: a different approach

There is scope for improvement in the management of viral infections and colds, particularly in light of the increasing resistance to mainstream antivirals, as well as their risks vs. benefits.

The aim of treatment with Engystol® is to activate and support the body's endogenous defense mechanisms, i.e., to strengthen the natural immune response in cases of viral invasion, resulting in milder symptoms[4,5] and shorter recovery times.[2,3,5] It also has the potential to protect against subsequent infections.[3] Taken either preventively or at the first signs of a cold, Engystol® may prevent the development of acute symptoms.

Engystol® has a good record of studies and publications in patients of all ages. Numerous studies with Engystol® demonstrate its excellent efficacy and tolerability, and the antiviral treatment and preventive benefits of Engystol® in cases of viral infection and other pulmonary conditions with and without fever, such as bronchitis/asthma, RSV, upper respiratory tract infections, flu, etc.[1-5]

Studies have shown that it is safe and well-tolerated, and can be used safely with other medications. Engystol® has been shown to be as effective as paracetamol but with a faster recovery time.[2]

3 Composition

Both formulations of Engystol® contain two main active ingredients which are listed below, including the characteristics of the ingredients.[6,7]

Constituent	Characteristics[73]	Oral tablets (per 1)	Injectable solution/ drinkable ampoule (1.1ml)
Vincetoxicum hirundinaria (swallowwort)	Stimulation of the body's own defenses with vascular and sympathetic action, e.g. in feverish viral diseases, such as influenza, mumps, etc.	*Vincetoxicum hirundinaria* D6, 75mg *Vincetoxicum hirundinaria* D10, 75mg *Vincetoxicum hirundinaria* D30, 75mg	*Vincetoxicum hirundinaria* D6, 6.6µl *Vincetoxicum hirundinaria* D10, 6.6µl *Vincetoxicum hirundinaria* D30, 6.6µl
Sulfur (sulphur)	Reactant in all chronic diseases, e.g. acute and chronic inflammation of the respiratory organs, catarrh of the upper respiratory tract, dyspnea, bronchial asthma, throbbing headache.	Sulfur D4, 37.5mg Sulfur D10, 37.5mg	Sulfur D4, 3.3µl Sulfur D10, 3.3µl

Carrier substances:

Oral tablets – 300mg lactose, 1.5mg magnesium stearate

Injectable solution/drinkable ampoule – 0.9% saline solution

4 Mechanism of action

The exact mechanism of action of Engystol® is still under investigation. However, the immunostimulating effects of Engystol® have been substantiated in several studies:

A. Proposed contribution of Engystol® on acute inflammation during viral infection.

i. Increased phagocytic activity and migration

- Immune system cells, e.g., granulocytes, perform phagocytosis as part of the innate (non-specific) immune system activity, trapping harmful materials (e.g., viruses) when they enter the body and destroying them so that they cannot cause damage. The innate immune system is the body's first line of defense against invading organisms. A substance that increases phagocytic activity will, therefore, give the body an increased chance of fighting the invading organism.
- An *in vitro* study has shown that Engystol® stimulates the phagocytic activity of human granulocytes by up to 33.5% above control cultures. In this study, the increase in phagocytosis occurred rapidly. However, the study did not permit a statement to be made concerning whether Engystol® exerted its effects directly by stimulating phagocytizing leukocytes, or indirectly by means of the stimulation of T-cell sub-populations, or via a release of certain mediators.[8]
- Another *in vitro* test has shown that Engystol® led to an increase in phagocytic activity of between 20-40% (depending on dilution; undiluted, 1:10 or 1:100) in three different immunological tests: the granulocyte test, the carbon clearance test and the granulocyte bioluminescence test.[9]
- Increased phagocytic activity was also evident in a clinical study in infants with RSV infection (see page 25).[3]
- In a clinical setting, after treatment with Engystol®, granulocytes displayed decreased activity judged by reduced nitroblue tetrazolium staining (NBT). These finding were supported by decreased superoxide generation in these granulocytes. In addition, an increase in granulocyte migration was evident (see page 28).[4]
- Recent data on whole blood cultures confirmed that Engystol® stimulates superoxide anion generation by neutrophils and cytokine(s) production by T-lymphocytes. The authors concluded that Engystol® stimulates the secretion of lymphokine(s) with inhibiting action on the superoxide anion generation of neutrophils that prevail over the direct stimulating effect, confirming and extending the immunostimulatory ability of Engystol®.[74]
- Other studies have confirmed the effects of Engystol® on increasing granulocyte, phagocyte and neutrophil activity when given pre-operatively in 61 patients with neoplastic disease (breast and abdominal cavity carcinoma), as well as stimulation by Engystol® of the anti-influenzal humoral response.[11,12]

Furthermore, Engystol® was shown to stimulate type 1 IFN release [see box] in different cell systems (Figure 1). In a virus-susceptible epithelial cell line, Engystol® showed a 56%-increase in IFN release at a 1:4 dilution compared to control; in human peripheral blood mononuclear cells (PBMCs) – cells of the immune system - up to 4-fold increase in IFN-α production was observed at a 1:4 dilution at day 5 of incubation In the ELISA. These findings suggest that the antiviral activity of Engystol® may be mediated via modulation of the antiviral type 1 IFN host response. The authors noted *"Since Engystol® showed efficacy against a broad panel of structurally different viruses such as RNA and DNA viruses – enveloped and non-enveloped -, it seems likely that Engystol®... also modulate host defense mechanisms."*[13]

Engystol® stimulates type 1 IFN[13]

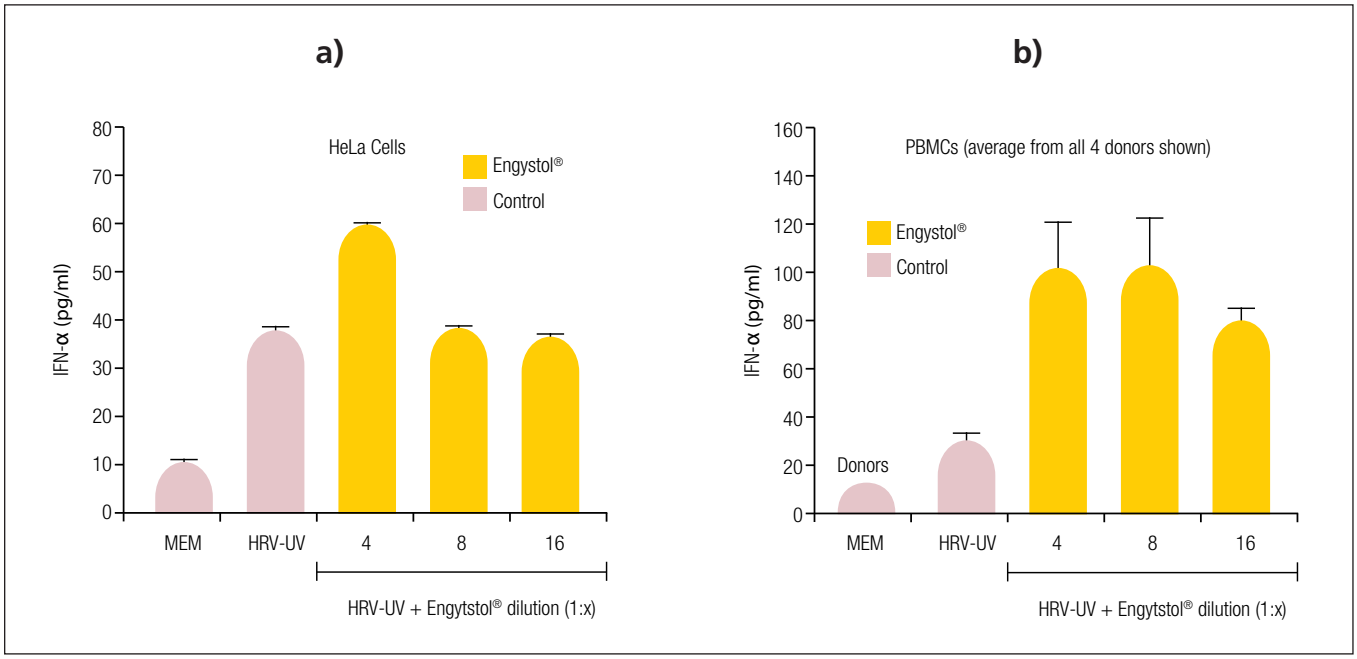

Figure 1. *In vitro* type 1 IFN production following Engystol® incubation[13]

Effect of Engystol® on type 1 IFN production in HRV-UV infected HeLa (a) and HSV-UV-co-stimulated PBMCs (b) was determined using IFN-α specific ELISA 5 days after incubation. In figure (a), the data represents mean values ± SD (n=3). For the PBMC setting (b), four different donors were used for each treatment group; a mean for all four is shown.

HRV-UV=UV-inactivated HRV-14
MEM=cultivation medium with Hanks' buffered saline solution containing 2% fetal calf serum
HeLa = virus-susceptible cell lines; PBMCs = human peripheral blood mononuclear cells

ii. Increased proliferation (increased IFN-γ production)

- Interferon-γ [see next page] is produced by several varieties of cells, such as helper T-cells, cytotoxic T-cells and natural killer cells. An increase in interferon-γ production indicates, among other roles, activation of the immune system. Production is induced by specific contact with antigens or through unspecific stimulation by substances that may be of biological or chemical origin.[10]
- Another *in vitro* study[10] demonstrated that Engystol® significantly increased the expression of interferon-γ producing T-lymphocytes ($p<0.001$) (Figure 2) indicating "*that the active ingredients in the agent have a quite high stimulating activity*" according to the study authors. Whilst the exact mechanism behind the observed effects of Engystol® remains to be elucidated, a therapy that improves interferon-γ production in response to stimuli might be expected to confer benefits to patients at risk of infection or exposed to infectious agents.

Engystol® stimulates the phagocytic activity of human granulocytes by up to 33.5% above control cultures.

There are two types of interferons (IFNs): type I or 'viral' IFNs (IFN-α, IFN-β and IFN-ω) and type II IFN (IFN-γ). Type 1 IFN production plays an important role in antiviral response and involves a large family of multifunctional immunoregulatory proteins. The synthesis of type I IFN is triggered by viral infection acting on IFN-regulatory factors, whilst type II IFN is induced by mitogenic or antigenic stimuli.[13]

Engystol significantly increases the expression of interferon-γ producing T-lymphocytes vs. a control solution[10]

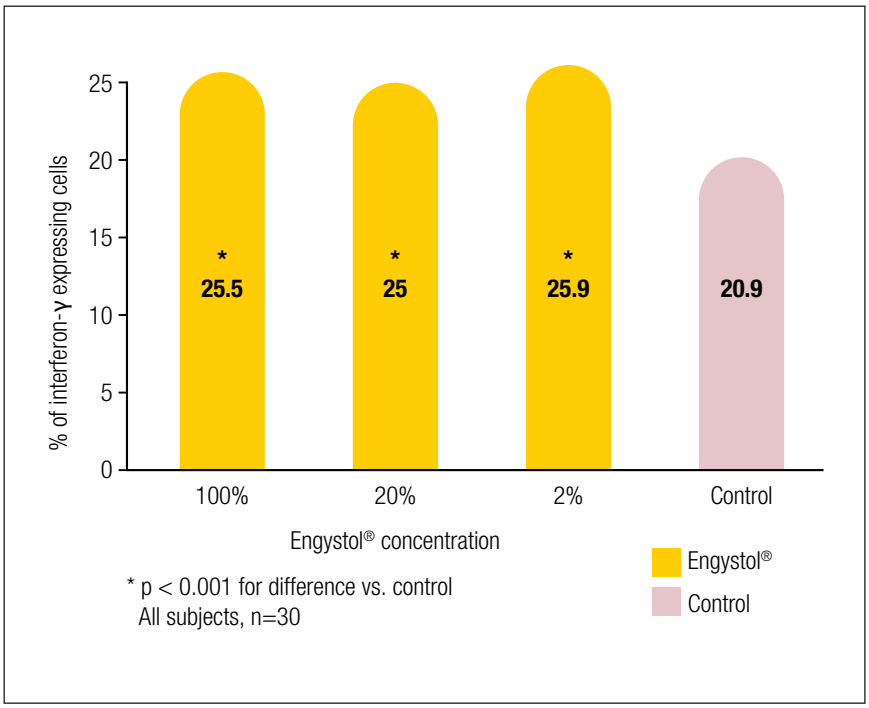

Figure 2. Percentage of T-lymphocytes expressing interferon-γ after treatment with different dilutions of Engystol® or with control (NaCl solution)[10]

iii. Additional antiviral activity

- Furthermore, the Enbergs paper also suggested that Engystol® may interact directly with virus particles and reduce infectivity independent of its possible effects on the immune system.[10]
- Further data suggest that Engystol® may influence virus-specific components necessary for viral replication, but without a direct interaction with viral surface proteins. The authors noted *"It seems highly likely that the observed effects are the result of a real antiviral effect of Engystol®."*[14]
- In another study (a pilot),[75] conducted in a clinical setting in patients who suffered frequent infections of the respiratory tract (n=20), there were significant increases in T-lymphocytes (carriers of cellular immunity) and T-helper cells after six months of treatment with Engystol®, and there was an increase in phagocytosis*. The authors suggested that the increase in total T-lymphocytes resulting from Engystol® treatment indicates stimulation of cellular defense against infection and the increase in phagocytosis should be *"regarded as an important macrophage resistance factor."*[75]

Note: Engystol® is often used as an immunostimulating adjuvant in combination with other cold and flu remedies. It does not alter body temperature and so antipyretic agents may still be required.

… the increase in total T-lymphocytes [resulting from Engystol® treatment]… indicates stimulation of cellular defense against infections…"

Engystol® may interact directly with virus particles and reduce infectivity independent of its possible effects on the immune system.

IFN-γ plays a major immunomodulatory role and is a key mediator of virus-specific cellular immunity.[13]

B. Proposed contribution of Engystol® ingredients on acute inflammation during viral infection

Examination of the effects of the individual components of Engystol® (sulfur and *Vincetoxicum hirundinaria*) may help to further elucidate its mode of action.

i. Sulfur

Sulfur is the sixth most abundant macromineral in breast milk and the third most abundant mineral based on percentage of total body weight. The sulfur-containing amino acids are methionine, cysteine, cystine, homocysteine, homocystine, and taurine.[76] Methionine, cysteine, homocysteine and taurine are the 4 common sulfur-containing amino acids. Of these, the first two are incorporated into proteins.[77]

Methylsulfonylmethane (MSM), a volatile component in the sulfur cycle, is another source of sulfur found in the human diet.[76] MSM may be effective for the treatment of allergy, pain syndromes, athletic injuries, and bladder disorders. Other sulfur compounds, e.g., SAMe, dimethylsulfoxide (DMSO), taurine, glucosamine or chondroitin sulfate, and reduced glutathione may also have clinical applications in the treatment of a number of conditions such as depression, fibromyalgia, arthritis, interstitial cystitis, athletic injuries, congestive heart failure, diabetes, cancer and AIDS.[76]

Three major products of sulfur amino acids - glutathione (GSH), homocysteine (Hcy), and taurine (Tau) - influence mainly inflammatory aspects of the immune response *in vitro* and *in vivo* at high concentrations.[78]

Sulfur has shown evidence of mucolytic and plastic effects on epithelial cells by altering plasma membrane cystein and disulphide bond formation.[79-82]

Sulfur also has a potential role in affecting the arachidonic pathway by modulation of COX-2 activity and modulation of adenylate kinase pathway (also inhibiting cytokine production) (pro-inflammatory activities).[83,84]

Sulfur... low toxicological profiles of... sulfur compounds, combined with promising therapeutic effects.[76]

ii. Vincetoxicum hirundinaria

Constituents of *Vincetoxicum hirundinaria* have also shown modulatory abilities towards the arachidonic cascade[85,86] and also potential mucolytic effects.[87]

Constituents of *Vincetoxicum hirundinaria* may also exhibit pain modulatory effects acting via the GABA(A)-benzodiazepine receptor.[88]

Examination of the effects of the individual components of Engystol® may further elucidate its mechanism of action.

Summary – the actions of Engystol® on the immune system

- Increases phagocytic activity of human granulocytes by up to 40%[8,9]
- Increases interferon-γ production by T-lymphocytes[10]
- Stimulates type 1 IFN release in different cell systems[13]
- Hypothetical activation of natural killer cells and cytotoxic T-cells[10]
- Stimulates the secretion of lymphokine(s) with inhibiting action on the superoxide anion generation of neutrophils[74]
- Elimination of viral infected cells and tumor cells[11,12]
- Examination of the effects of the individual components of Engystol® (sulfur and *Vincetoxicum hirundinaria*) may help to further elucidate its mode of action.

5 Antiviral activity of Engystol®

Many respiratory viruses, most commonly influenza, respiratory syncytial virus (RSV) and rhinovirus, are capable of causing respiratory disease, either by their direct effects or by exacerbating underlying conditions. Several pharmaceutical antiviral substances exist but they are associated with side effects and there is still a need for antiviral substances with good efficacy and tolerability, and low toxicity.[14]

Basic *in vitro* research has revealed the activity of Engystol® against numerous respiratory viruses, such as influenza (flu) A virus, adenovirus type 5, Herpes Simplex Virus type 1 (HSV 1), human rhinovirus B serotype 14 (HRV-14) and Respiratory Syncytial Virus (RSV).[13,14] In addition, in a double-blind, placebo-controlled trial for the prophylaxis of flu (influenza) and the common cold, Engystol® has shown itself to be able to shorten the time of infection and reduce antibody titers against influenza A.[5]

Basic *in vitro* research has revealed the activity of Engystol® against numerous respiratory viruses.

Such antiviral activity has never been revealed with either paracetamol or alpha-adrenergic receptor activating drugs, i.e., drugs commonly given for colds and flu which cause vasoconstriction.[89-92]

In terms of activity against the influenza virus, a randomized, placebo-controlled, double-blind trial in 102 healthy males showed that Engystol ® can achieve favorable results in the prophylaxis of uncomplicated viral illnesses of the upper respiratory tract, which are unresponsive to specific therapeutic measures. The duration and severity of symptoms was considerably lower in the Engystol® group compared with the placebo group.[5]

The duration and severity of symptoms was considerably lower in the Engystol® group compared with the placebo group

In an *in vitro* study,[14] Engystol® showed a dose dependent antiviral activity against the DNA viruses, adenovirus type 5 (73% reduction) and Herpes Simplex Virus type 1 (HSV 1) (80% reduction). In addition, an antiviral effect was observed against the RNA viruses, Respiratory Syncytial Virus (RSV) (37% reduction) (Figures 3 and 4) and human rhinovirus (HRV) (20% reduction). Furthermore, no cytotoxic effects or other toxic effects were observed with Engystol® at the doses examined. This antiviral activity was independent of the activation of the cellular interferon system suggesting, according to the authors, that *"the observed effects are a result of a real antiviral effect of Engystol®."*[14] We assume that Engystol® is virostatic and not virucidal.

However, further work is needed to establish an explanation for the effects at the molecular level, and to assess the relevance of the *in vitro* results in this study to determine how they translate into the benefits observed with Engystol in clinical practice.[14]

Engystol® inhibits activity of the viruses, Respiratory Syncytial Virus (RSV) and adenovirus type 5[14]

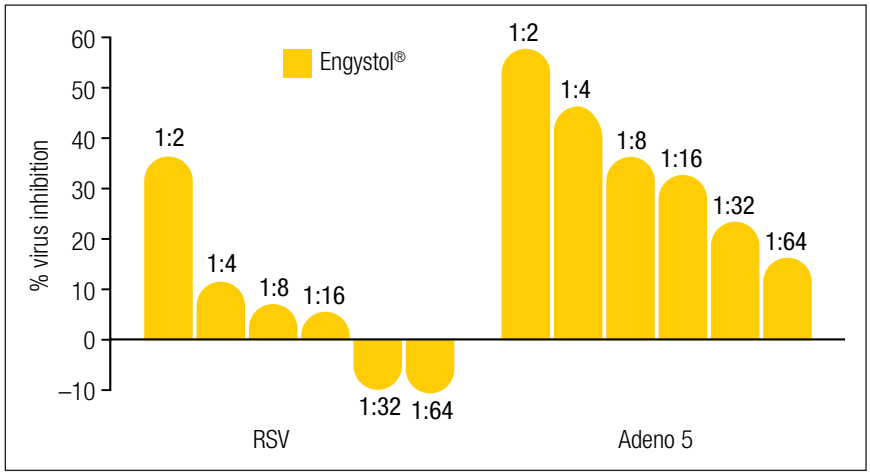

Figure 3. RSV and adenovirus type 5 inhibition with Engystol®[14]

Percentage inhibition of viral activity of different dilutions of Engystol® tested on various RNA and DNA viruses. Inhibition was based on plaque-reduction assay for RSV and $TCID_{50}$ values for adenovirus type 5 (adenovirus 5) were calculated as a percentage of the equivalent value from control cell cultures not exposed to Engystol®. Mean of four values (two repetitions of two separate experiments) with standard deviations.

Engystol® inhibits activity of the virus, Herpes Simplex Virus type 1 (HSV 1)[14]

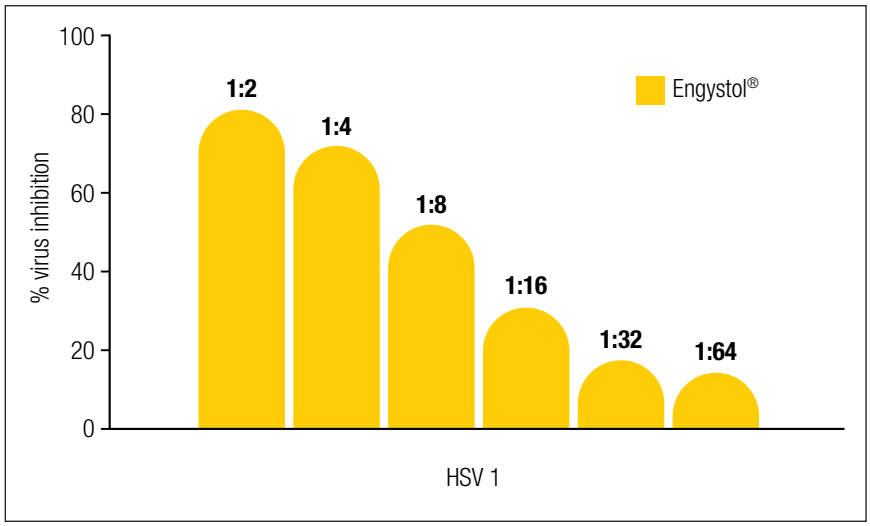

Figure 4. HSV 1 inhibition with Engystol®[14]

Percentage inhibition of viral activity of different dilutions of Engystol® tested on Herpes Simplex Virus type 1 (HSV 1). Inhibition was based on viral protein-specific enzyme-linked immunoabsorbent assay (ELISA) and was calculated as a percentage of the equivalent value from control cell cultures not exposed to Engystol®. Mean of four values (two repetitions of two separate experiments) with standard deviations.

In a further recent *in vitro* study,[13] Engystol® was again shown to display antiviral activity (in both RNA and DNA viruses) in the prophylactic and therapeutic setting. Engystol® inhibited the replication of a variety of respiratory viruses (influenza A virus, human rhinovirus B serotype 14 (HRV-14), HSV 1 and adenovirus type 5) (Figure 5).

Engystol® inhibits activity of the viruses, Influenza A, human rhinovirus B serotype 14 (HRV-14), Herpes Simplex Virus type 1 (HSV 1) and adenovirus type 5[13]

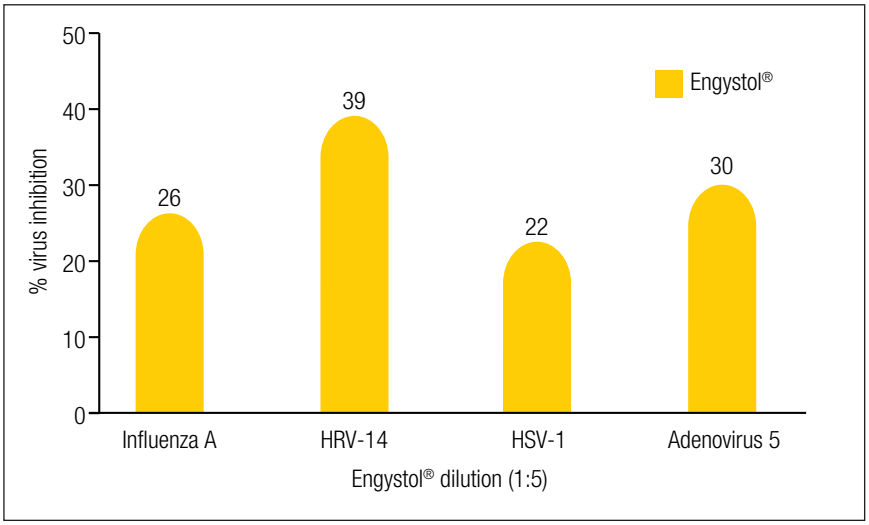

Figure 5. Antiviral effect of Engystol® against four viruses[13]

Inhibitory effect of Engystol® on Influenza A, HRV-14, Adenovirus 5 and HSV-1 and were determined using plaque reduction assay and virus-specific ELISA for adenovirus type 5, respectively ('therapeutic approach'). Data are shown as percentage of inhibition compared to the untreated control (100% inhibition, n=4).

Summary - antiviral activity of Engystol®

- Basic *in vitro* research has revealed the activity of Engystol® against numerous respiratory viruses, such as influenza (flu) A virus, adenovirus type 5, Herpes Simplex Virus type 1 (HSV 1), human rhinovirus B serotype 14 (HRV-14) and Respiratory Syncytial Virus (RSV).[13,14]

6 The evidence base for Engystol® - clinical efficacy and tolerability

Several clinical trials of Engystol® oral tablets and Engystol® injectable solution/drinkable ampoules have demonstrated its excellent efficacy and tolerability, and its treatment and preventive benefits in cases of infection and other pulmonary conditions, with and without fever, such as bronchitis/asthma, RSV, upper respiratory tract infections, flu, etc.[1-5]

The clinical evidence base for Engystol® is detailed in the following pages.

Therapeutic effect

A complex homeopathic preparation for the symptomatic treatment of upper respiratory infections associated with the common cold: an observational study

Reference: Schmiedel V *et al.*, Explore 2006;2:109-114.

Objective

- To compare the effects of Engystol® with those of conventional therapies on upper respiratory symptoms of the common cold in a setting closely related to everyday clinical practice.

Study design

- A non-randomized, observational study; treatment period of two weeks.
- n=397 patients with upper respiratory tract symptoms of the common cold.
- Patients received Engystol® tablets (n=175) or popular over-the-counter (OTC) treatments (n=222, antipyretic/analgesic/anti-inflammatory) for the common cold
  - Engystol® tablets were usually given three times daily (69.6%); this dosage was not fixed
  - Control group used paracetamol (42%), aspirin (16%), metamizol (18%) and ibuprofen (12%).
- Patients receiving Engystol® were permitted to take other short-term medications, but long-term use of analgesics, antibiotics and anti-inflammatory agents was not permitted.
- In patients with a diagnosis of rhinitis, pharyngitis, laryngitis or bronchitis, changes in symptoms related to these diagnoses were also monitored.
- The effects of treatment were evaluated on the variables; fatigue, sensation of illness, chill/tremor, aching joints, overall severity of illness, sum of all clinical variables, temperature, and time to symptomatic improvement.
  - Tolerability was assessed through monitoring adverse events.

Results

- Both treatments provided significant symptomatic relief (-7.9 for Engystol® vs. -7.2 for control for the sum of all clinical variables); for most variables, there were no statistically significant differences between the two groups:
  - The results for Engystol® were comparable to those of conventional therapy, such as paracetamol.
- Significantly more patients ($p<0.05$) using Engystol® reported improvement within 3 days (77.1% vs. 61.7% for the control group) (Figure 6).

Significantly more patients (p<0.05) using Engystol® reported improvement within 3 days (77.1% vs. 61.7% for the control group)

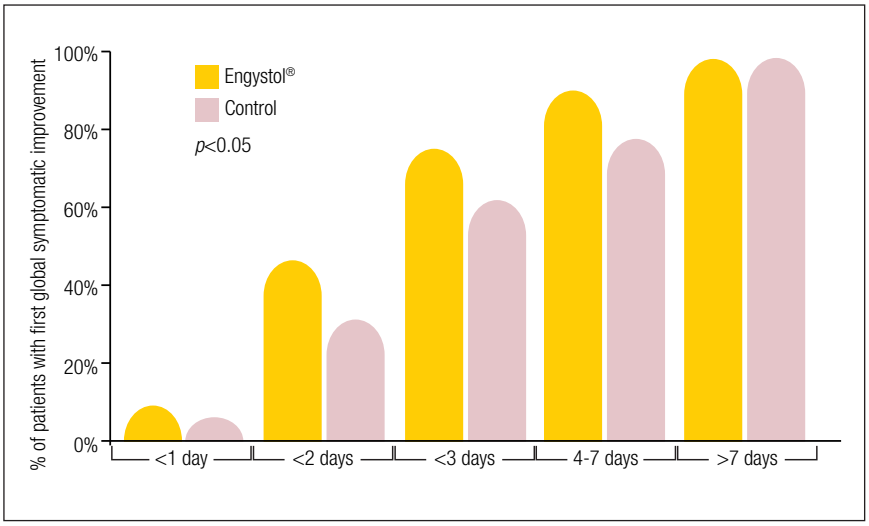

Figure 6. Time to first improvement in global symptoms in Engystol® and control group

- No adverse events were reported in any of the treatment groups:
  - 89.2% of patients reported 'very good' overall tolerability with Engystol® compared to control therapies (81.2%).
  - Almost 100% of patients reported 'very good' or 'good' compliance with Engystol® and with control therapies.

Conclusions

- Engystol® is an ideal component of an integrated symptomatic therapy for the common cold.
- Engystol®'s efficacy is comparable to conventional therapy.
- Engystol® leads to faster improvement in symptoms than conventional therapy.

The effect of a homeopathic preparation on the clinical condition of patients with corticosteroid-dependent bronchial asthma

Reference: Matusiewicz R. *Biomedical Therapy* 1997;XV(3):70-74.

Objective

- To determine less harmful methods in the treatment of patients with corticosteroid-dependent bronchial asthma, and the effects of Engystol® on certain immunological parameters.

Study design

- A randomized, double-blind, placebo-controlled study.
- n=40 corticosteroid-dependent asthma patients, aged 24-48 years.
- Inclusion criteria: all patients had taken triamcinolone 4 to 8mg/24 hr for at least 5 years; FEV_1 (forced expiration volume in the first second) exceeded the normal expected value by 50%; PEFR (peak expiratory flow rate) below 80%.
- 20 patients received one ampoule of Engystol® subcutaneously every 5 to 7 days; 20 patients received placebo; treatment period of six months.
  - In addition, all patients received methyloxanthine preparations to liquefy mucus; tetracyclines were administered if exacerbation of symptoms.
- Clinical parameters measured for each patient included PEFR, FVC (forced vital capacity), FEV_1 and granulocyte function.

Results

- Statistically significant increases in mean PEFR, FVC and FEV_1 values for patients treated with Engystol® from 200 to 330ml, 2.2 to 3.5l and 1.7 to 2.4l, respectively ($p<0.01$) vs. decreases from 210 to 190ml, 2.3 to 2.2l and 1.9 to 1.8l, respectively ($p<0.01$) in placebo group (Figures 7,8 and 9).

Engystol® significantly increased the mean PEFR over six months whereas there was no change with placebo

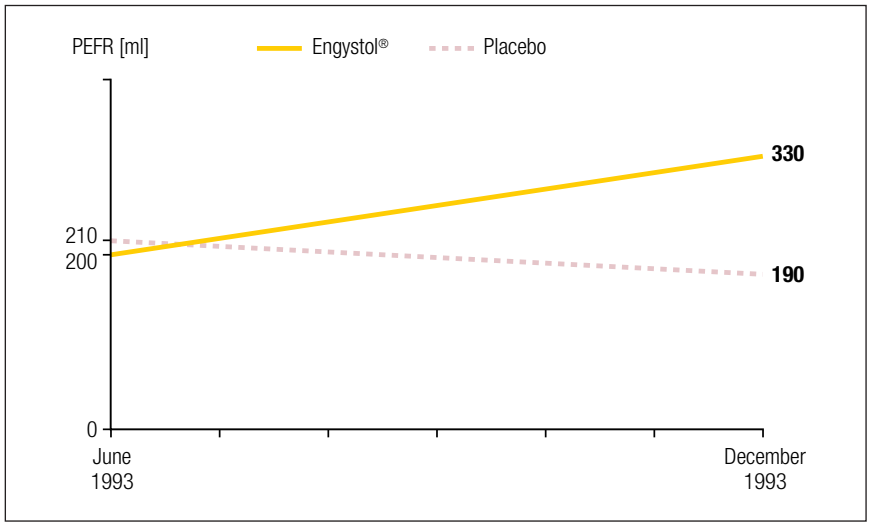

Figure 7. Mean PEFR values Engystol® vs. placebo

Engystol® significantly increased the mean FVC over six months whereas there was no change with placebo

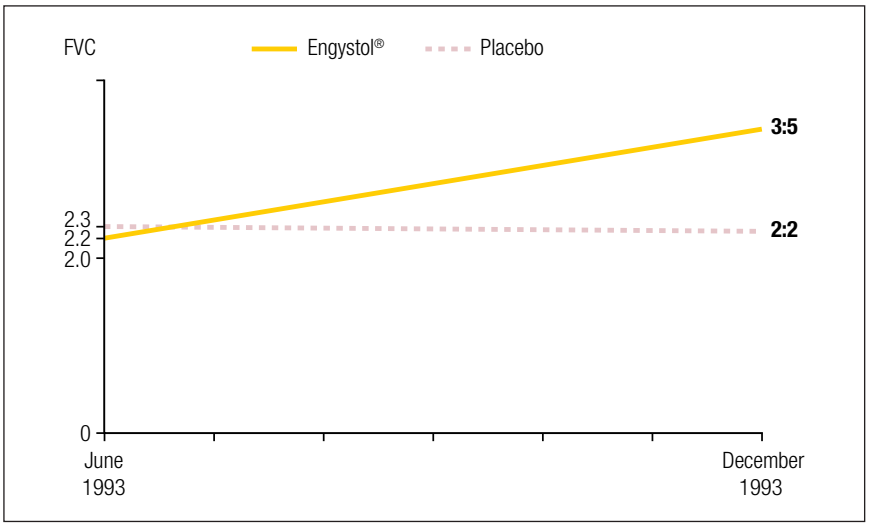

Figure 8. Mean FVC values Engystol® vs. placebo

Engystol® significantly increased the mean FEV_1 over six months whereas there was no change with placebo

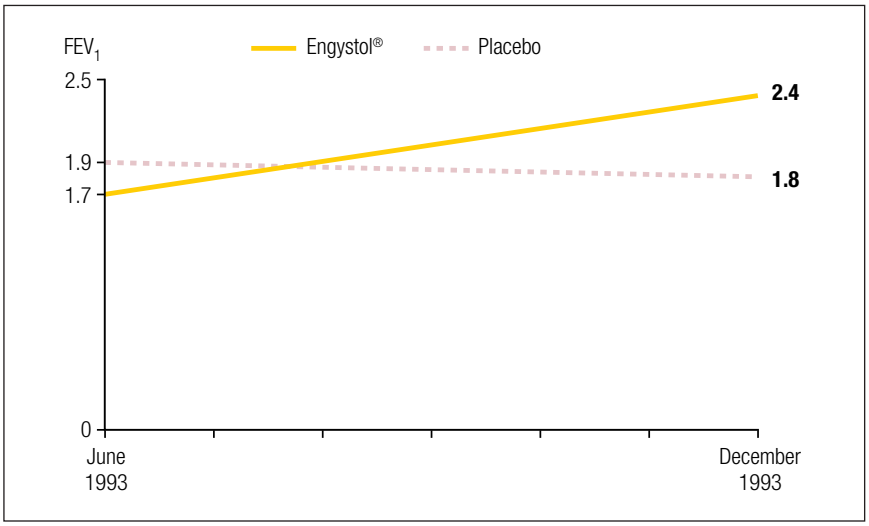

Figure 9. Mean FEV_1 values Engystol® vs. placebo

- A decrease from 6.0-3.0mg/day in corticosteroid dosage was possible in patients treated with Engystol®:
  - In the placebo group, corticosteroid dosage required was 5.0-7.0mg/day.

Conclusions

- Engystol® is an effective and safe medication in the treatment of corticosteroid-dependent bronchial asthma.
- Its administration enables a significant reduction in the required dose of corticosteroids.

RSV infections in infants: therapy with a homeopathic preparation

Reference: Torbicka E *et al. Biomedical Therapy* 1998;XVI(4):256-260.

Objective

- To assess the effect of Engystol® as an adjunct therapy in infants with Respiratory Syncytial Virus (RSV) infections.

Study design

- Double-blind, placebo-controlled study.
- n=128 infants hospitalized for RSV infections; median age 5.1±4.2 months.
- The infants were randomly divided into two groups;
  - 66 received Engystol® (0.5ml) intramuscularly daily during the first week of hospitalization, then every other day during the second week, in addition to standard therapy
  - 62 received standard therapy plus placebo
  - Infants treated with Engystol® in the hospital continued the treatment in tablet form and were given either Engystol® or placebo twice daily.
- Each child's general condition was evaluated as 'good', 'fair' or 'serious'.
- Regression of symptoms was recorded after 5, 10 and 15 days of treatment on a 5-point rating scale (Symptom Improvement Score (SIS)).
- Infants were re-examined at two and six months after discharge.

Results

- Initial examination in the hospital showed:
  - 65% of the infants suffering from RSV infections were in a 'fair' condition
  - 5% were in a 'serious' condition.
- By the fifth day of treatment, faster regression of symptoms was noted in the Engystol® group compared to the control group (SIS 2.4±1.3 vs. 3.0±1.6)
  - On days 10 and 15, the SIS in the Engystol® group was also less than that of the control group (p=0.058) (Figure 10)

By the fifth day of treatment, there was a faster regression of symptoms in the Engystol® group compared to the control group (SIS 2.4±1.3 vs. 3.0±1.6) which was sustained at days 10 and 15

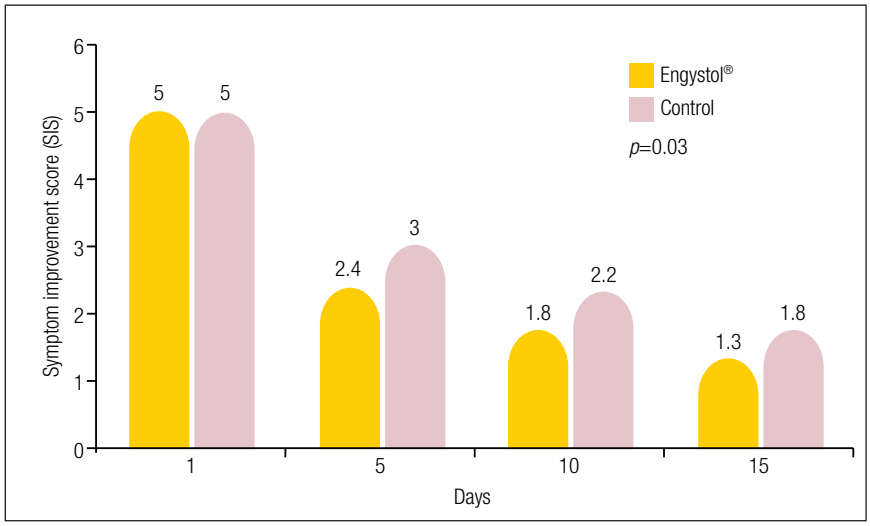

Figure 10. Symptom improvement in Engystol® vs. control group

- After two weeks of treatment, there was a significant increase in phagocytic activity in the Engystol® group compared with baseline (p=0.008)
  - NBT (nitroblue tetrazolium) value (measure of phagocytic activity) increased from 6.5±5.8% to 11.6±8.5% (p=0.002) (Figure 11)
- No adverse effects on liver and kidney function were observed.

After 15 days, Engystol® significantly increased phagocytic activity whereas there was no change in the control group

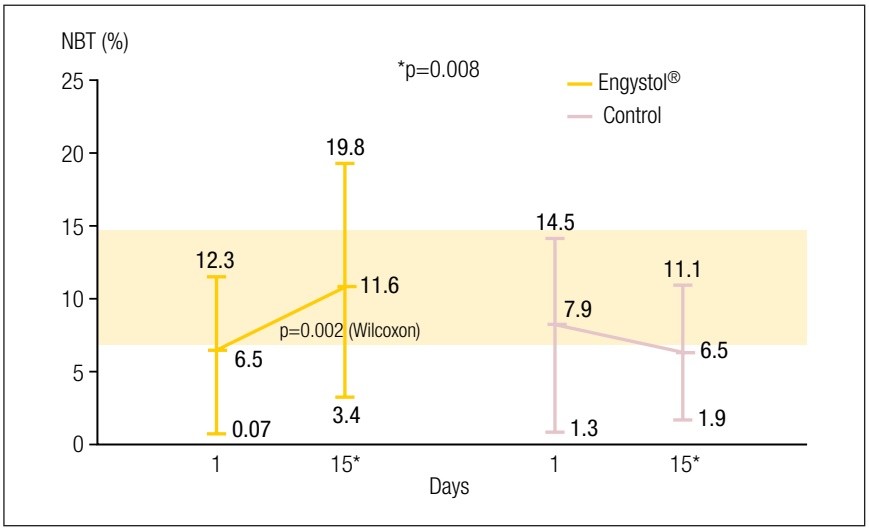

Figure 11. NBT test (phagocytic activity measure) at the start and at day 15 for Engystol® vs. control group

- Six months after discharge, the Engystol® group contracted significantly fewer respiratory infections than those in the placebo group: 45% with Engystol® vs. 91% in the control group (p<0.0025) (Figure 12).

Significantly fewer children had contracted infections at six months follow-up with Engystol® vs. placebo

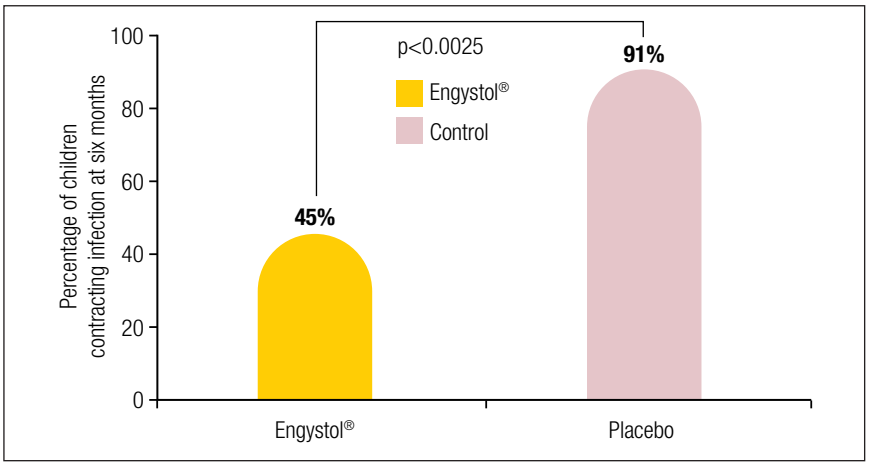

Figure 12. Percentage of children who had contracted infections at six months follow-up

Conclusions

- Engystol® is effective as an adjunctive therapy for RSV infection in infants, both in accelerating symptom resolution during acute infection, and in protecting patients from subsequent respiratory infections.

Homeopathic treatment of infections of various origins: a prospective study

Reference: Herzberger G. *Biomedical Therapy* 1997;XV(4):123-127.

Objective

- To study therapeutic use, efficacy and tolerability of Engystol® in an unselected patient population.

Study design

- Prospective study, in which data on therapeutic use, as well as efficacy and tolerability to Engystol®, were systematically recorded in 1,479 patients (aged <11 to >60 years), treated by 154 physicians from three European countries.
- No criteria were established for inclusion/exclusion from the study.
- The dosage of Engystol®, the duration of treatment and the choice of whether or not to prescribe supplemental therapies was left to participating physicians.
- Primary usage indications: flu, feverish infections, and prophylactic administration to increase endogenous defenses:
  - Additional usage indications: acute and chronic diseases of the upper respiratory tract.
- Results were evaluated according to the following scale:
  - 'Very good' = complete freedom from symptoms
  - 'Good' = clear improvement
  - 'Satisfactory' = slight improvement
  - 'No success' = symptoms remained the same
  - 'Worse' = symptoms worsened.
- Similarly, tolerance to Engystol® was assessed as 'excellent', 'good', 'moderate' and 'poor'.

Results

- Improvement in symptoms was noted within 1-4 days in half the cases.
- Overall evaluation of therapy showed that either 'complete freedom from symptoms' or 'clear improvement in symptoms' was achieved in 9 out of 10 patients (90%)
  - The treatment was unsuccessful in 4% of patients (Table 1).
- Comparison between the patients treated with and without supplemental therapy showed that 'good' and 'very good' results were obtained even when Engystol® was administered as a monotherapy (Table 1).

Patients treated with and without supplemental therapy showed 'good' and 'very good' results in around 90% of cases, even when Engystol® was administered as a monotherapy

	Results of treatment					
Treatment group	**Very Good**	**Good**	**Satisfactory**	**No success**	**Worse**	**No result reported**
Total Engystol® (n=1479)	46.2	42.5	7.0	3.7	0.5	0.1
Patients receiving Engystol® plus supplemental pharmaceutical and/ or physical therapies (n=870)	44.0	44.0	7.4	3.9	0.5	0.2
Patients receiving Engystol® without supplemental therapy (n=609)	49.2	40.4	6.6	3.3	0.5	-

Table 1. Overall results of treatment within different treatment groups (%)

- In almost all diagnostic groups, 'very good' and 'good' therapeutic results were obtained in over 80% of patients (Table 2)

Patients treated with Engystol® rated it as 'very good' or 'good in over 80% of cases, whatever the diagnosis

	Results of treatment					
Usage indications	**Very Good**	**Good**	**Satisfactory**	**No success**	**Worse**	**No result reported**
Feverish infections (n=958)	47.5	44.0	4.8	3.0	0.5	0.2
Flu (n=486)	55.2	36.6	6.4	1.6	0.2	-
Prophylactically, to activate endogenous defense system (n=411)	33.8	51.2	8.0	6.8	-	0.2
Other indications (n=235)	34.5	43.4	13.2	7.2	1.3	0.4

Table 2. Overall results of treatment within different diagnostic groups (%)

- Tolerance to Engystol® was rated 'excellent' to 'good' by the participating physician in 97% of patients.

Conclusions

- Engystol® was therapeutically effective both as a monotherapy and in combination with other forms of therapy.
- The authors concluded *"The results of overall evaluation of the therapy show that either complete freedom from symptoms or clear improvement in symptoms was achieved in 9 out of 10 cases,"* i.e., in all age groups studied.
- No negative effects were observed when Engystol® was used in combination with conventional medicines.
- This study demonstrated the efficacy and tolerability of Engystol® in a wide range of viral infections.

Preventive effect

A combination injection preparation as a prophylactic for flu and common colds

Reference: Heilmann A. *Biological Therapy* 1994;XII(4):249-253.

Objective

- To verify the prophylactic effectiveness of Engystol® injection to reduce the frequency of influenza (flu), infections and common colds compared to a control group.

Study design

- Randomized, placebo-controlled, double-blind trial.
- n=102 healthy males (soldiers), aged 20-48 years, randomized to either Engystol® or control.
- Subjects received twice weekly 1.1ml of Engystol® ampoules intravenously or isotonic saline solution as control; a series of six injections were given over three weeks.
  - An observation period of eight weeks followed this injection phase.
- Laboratory tests were regularly conducted during the injection and observation phase: total leukocyte and lymphocyte count, lymphocyte sub-populations, and the antibody titer for influenza A and B.

Results

- Of the 102 test subjects, a total of 21 became ill: 11 in the Engystol® group; 10 in the placebo group.
  - Engystol® had no influence on the frequency of the flu or the common cold.
- The average length of time between the last injection and the appearance of flu or a cold was 34 days in the Engystol® group and 19 days in the placebo group (Figure 13).

Engystol® almost doubles the number of days until the appearance of flu or a cold vs. placebo

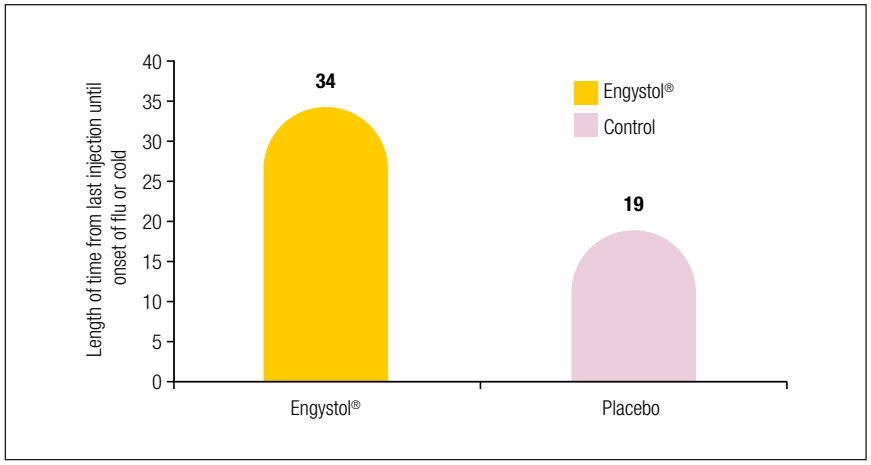

Figure 13. Length of time from last injection until onset of flu or cold

- The average length of illness was 11 days in the Engystol® group and 16 days in the placebo group (Figure 14).

Engystol® considerably reduced the number of day's sick leave from flu or a cold vs. placebo

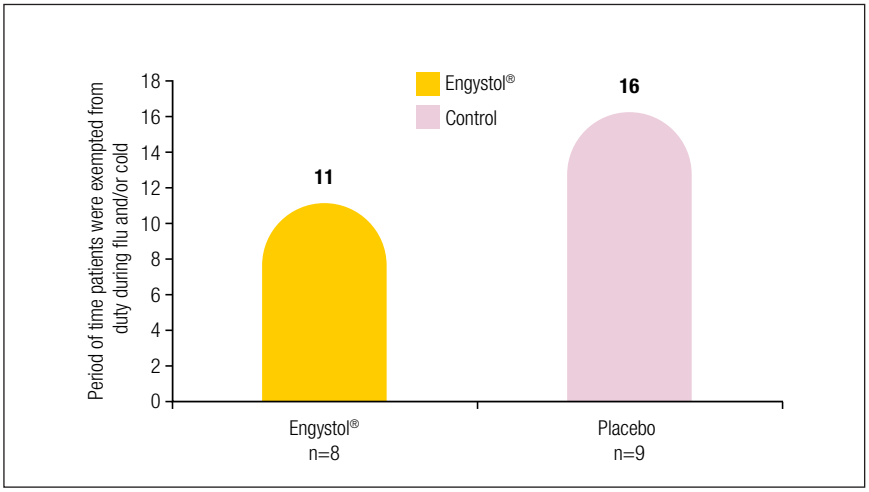

Figure 14. Period of time the various test persons (soldiers) were exempted from duty outdoors during flu and/or cold

- The severity of symptoms was less in the Engystol® group with 11 compared to 16 symptom characteristics for the placebo group.
- The increase in the antibody titer for influenza A was less in the Engystol® group than in the placebo group.
- There was no difference in blood count parameters in both Engystol® and placebo groups.

Conclusions

- Engystol® can achieve favorable results in the prophylaxis of uncomplicated viral illnesses of the upper respiratory tract, which are unresponsive to specific therapeutic measures.
- The duration and severity of symptoms was considerably lower in the Engystol® group compared with the placebo group.

7 Clinical safety

Clinical studies in adults

Safety

In a non-randomized, 2-week, observational study in 397 patients to compare the effects of Engystol® with those of conventional therapies on upper respiratory symptoms of the common cold in a setting closely related to everyday clinical practice,[2] no adverse events were reported in any of the treatment groups.

In a randomized, double-blind, placebo-controlled study in 40 corticosteroid-dependent asthma patients (aged 24-48 years), a decrease from 6.0-3.0mg/day in corticosteroid dosage was possible in patients treated with Engystol®.[4] In comparison, in the placebo group, corticosteroid dosage required was 5.0-7.0mg/day. Engystol® administration, therefore, enables a significant reduction in the required dose of corticosteroids.

In a prospective study reviewing the homeopathic treatment of infections of various origins (primary usage indications: flu, feverish infections, and prophylactic administration to increase endogenous defenses: additional usage indications: acute and chronic diseases of the upper respiratory tract) in an unselected patient population,[1] data were systematically recorded in 1,479 patients, treated by 154 physicians from three European countries, no negative effects were observed when Engystol® was used in combination with conventional medicines.

No negative effects were observed when Engystol® was used in combination with conventional medicines.

Tolerability

In a non-randomized, 2-week, observational study in 397 patients to compare the effects of Engystol® with those of conventional therapies on upper respiratory symptoms of the common cold in a setting closely related to everyday clinical practice,[2] 89.2% of patients reported 'very good' overall tolerability with Engystol® compared to control therapies (81.2%), and almost 100% of patients reported 'very good' or 'good' compliance with Engystol® and with control therapies.

Engystol is better tolerated than conventional therapies.

In a prospective study reviewing the homeopathic treatment of infections of various origins (primary usage indications: flu, feverish infections, and prophylactic administration to increase endogenous defenses: additional usage indications: acute and chronic diseases of the upper respiratory tract) in an unselected patient population,[1] data were systematically recorded in 1,479 patients, treated by 154 physicians from three European countries. Tolerance to Engystol® was rated 'excellent' to 'good' by the participating physician in 97% of patients. This study demonstrated the tolerability of Engystol® in a wide range of viral infections.

Engystol® administration, therefore, enables a significant reduction in the required dose of corticosteroids.

Safety in children

In a double-blind, placebo-controlled study in 128 infants hospitalized for RSV infections (median age 5.1±4.2 months), no adverse effects on liver and kidney function were observed subjects who received Engystol®.[3]

Side effects: ***Tablets, Solution for injection:*** allergic (hypersensitivity) reactions (e.g. skin allergies, redness/swelling at the injection site) may occur in very rare cases (i.e. affects less than 1 in 10,000 users).

Interaction with other medicaments and other forms of interaction: ***Tablets, Solution for injection:*** No interactions have been reported, and none are expected due to the homeopathic dilutions.

Special warnings and special precautions for use: ***Tablets:*** patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Contraindications: ***Tablets, Solution for injection:*** Known allergy (hypersensitivity) to one or more of the ingredients.

Pregnancy and lactation: ***Tablets, Solution for injection:*** For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicament are not known to be toxic during pregnancy and lactation. No adverse effects have so far been reported.

Overdose: ***Tablets, Solution for injection:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions.

8 Use in clinical practice

Place in therapy

For patients

Engystol® is used to activate the body's non-specific (innate) immune system, particularly in the case of influenza like illnesses and various viral diseases.

For healthcare professionals

Consider using Engystol® in a prophylactic and therapeutic way in:

- Patients who are susceptible to, or who have, a viral infection, such as a cold or flu
- Patients with pre-existing medical conditions,[1] or those over 60 years of age,[1] who might be more susceptible to viral infections, e.g., in winter[1]
- Primarily healthy younger children who might be susceptible to viral infections, e.g., RSV, in the winter season
- The entire family with viral infections.

Engystol® formulations and dosing recommendations

Engystol® is available in a variety of formulations for flexibility of use and to maximize patient convenience and compliance. It can be obtained in:

- Oral tablets
- Injectable solution/drinkable ampoule.

Medication names, indications and formulas may vary from country to country; package inserts provide country-specific information.

Engystol® is used to activate the non-specific immune system, particularly in influenza-like infections and viral diseases in general.

Each year, over half a million patients are treated with Engystol® worldwide.

Dosage

Oral tablets		**Solution for injection (i.m., s.c., i.d., i.v.)**	
Unless otherwise prescribed:		*Unless otherwise prescribed:*	
Standard dosage:		Standard dosage:	
Adults: 1 tablet 3x daily.		**Adults:** 1 ampoule 1 to 3x weekly.	
Pediatric:		**Pediatric:**	
Below 2 yrs.:	1 tablet 1x daily.	2–5 yrs.:	½ ampoule 1 to 3x weekly.
2–5 yrs.:	1 tablet 1–2x daily.	6–11 yrs.:	⅔ ampoule 1 to 3x weekly.
6–11 yrs.:	1 tablet 2x daily.	12–18 yrs.:	1 ampoule 1 to 3x weekly.
12–18 yrs.:	1 tablet 3x daily.		
Acute or Initial Dosage:		Acute or Initial Dosage:	
Adults: 1 tablet every ½ to 1 hr., up to 12x daily, and then continue with standard dosage.		**Adults:** 1 ampoule daily, and then continue with standard dosage.	
Pediatric:		**Pediatric:**	
Below 2 yrs.:	1 tablet every 1 to 2 hrs., up to 4x daily, and then continue with standard dosage.	2–5 yrs.:	½ ampoule daily, and then continue with standard dosage.
2–5 yrs.:	1 tablet every 1 to 2 hrs., up to 6x daily, and then continue with standard dosage.	6–11 yrs.:	⅔ ampoule daily, and then continue with standard dosage.
6–11 yrs.:	1 tablet every 1 to 2 hrs., up to 8x daily, and then continue with standard dosage.	12–18 yrs.:	1 ampoule daily, and then continue with standard dosage.
12–18 yrs.:	1 tablet every ½ to 1 hr., up to 12x daily, and then continue with standard dosage.		

Engystol® is available in two formulations to maximize convenience and flexibility of use.

With both dosage forms, the level of symptomatic improvement will be the same after four days of treatment.

For prevention therapy, the general dosage should be administered in cycles of one week on and one week off. Continue this regime of cycles for a total of 4 weeks. Wait 1 month before starting again.

Pharmaceutical particulars

Storage

Products should not be frozen or exposed to excessive heat. See packaging instructions for specific storage recommendations of each Engystol® formulation.

Ingredients

Engystol® oral tablets

Composition: 1 tablet contains:

- *Vincetoxicum hirundinaria* D6,
  Vincetoxicum hirundinaria D10,
  Vincetoxicum hirundinaria D30 - 75mg each
- Sulfur D4, Sulfur D10 – 37.5mg each.

Engystol® injectable solution/drinkable ampoule

Composition: 1.1ml ampoule contains:

- *Vincetoxicum hirundinaria* D6,
  Vincetoxicum hirundinaria D10,
  Vincetoxicum hirundinaria D30 6.6µl each
- Sulfur D4, Sulfur D10 3.3µl each.

Packaging

Engystol® oral tablets

Pack sizes: Packs containing 50 and 250 tablets.

Engystol® injectable solution/drinkable ampoule

Pack sizes: Packs containing 5, 10, 50 and 100 ampoules of 1.1ml.

9 Summary

The benefits of Engystol®:

- Scientifically demonstrated and clinically proven safety and efficacy; a good record of studies and publications in patients of all ages
- May be used for both prevention and treatment of viral infections
- Stimulates the specific and non-specific immune system (immunostimulator) ➡ strengthens the immune system
- Can be used safely with other medications
- As effective as paracetamol in common cold and flu-like illnesses but with a faster recovery time
- Safe for pregnant women or nursing mothers, as well as the entire family
- Very rarely reported side effects, no relevant contraindications and no known interactions
- Very well-tolerated
- Suitable for long-term treatment
- May be combined with other natural or conventional immunostimulating therapies.

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11 Appendix

Engystol®: Tablets • Solution for injection

Compositions: ***Tablets:*** 1 tablet contains: *Vincetoxicum hirundinaria* D6, *Vincetoxicum hirundinaria* D10, *Vincetoxicum hirundinaria* D30 - 75mg each, Sulfur D4, Sulfur D10 – 37.5mg each. ***Solution for injection:*** 1.1ml ampoule contains: *Vincetoxicum hirundinaria* D6, *Vincetoxicum hirundinaria* D10, *Vincetoxicum hirundinaria* D30 6.6µl each, Sulfur D4, Sulfur D10 3.3µl each.

Indications: ***Tablets, Solution for injection:*** To activate the non-specific immune system, particularly in influenza-like infections and viral diseases in general.

Contraindications: ***Tablets, Solution for injection:*** Known allergy (hypersensitivity) to one or more of the ingredients.

Side effects: ***Tablets, Solution for injection:*** Allergic (hypersensitivity) reactions (e.g. Skin allergies, redness/swelling at the injection site) may occur in very rare cases (i.e. Affects less than 1 in 10,000 users).

Interaction with other medicaments and other forms of interaction: ***Tablets, Solution for injection:*** No interactions have been reported, and none are expected due to the homeopathic dilutions.

Special warnings and special precautions for use: ***Tablets:*** patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ***Solution for injection:*** None.

Dosage: ***Tablets:*** *Unless otherwise prescribed:*

Standard dosage:

Adults:

1 tablet 3x daily.

Pediatric:

Below 2 yrs.: 1 tablet 1x daily.

2–5 yrs.: 1 tablet 1–2x daily.

6–11 yrs.: 1 tablet 2x daily.

12–18 yrs.: 1 tablet 3x daily.

Acute or Initial Dosage:

Adults:

1 tablet every ½ to 1 hr., up to 12x daily, and then continue with standard dosage.

Pediatric:

Below 2 yrs.: 1 tablet every 1 to 2 hrs., up to 4x daily, and then continue with standard dosage.

2–5 yrs.: 1 tablet every 1 to 2 hrs., up to 6x daily, and then continue with standard dosage.

6–11 yrs.: 1 tablet every 1 to 2 hrs., up to 8x daily, and then continue with standard dosage.

12–18 yrs.: 1 tablet every ½ to 1 hr., up to 12x daily, and then continue with standard dosage.

Method of Administration:

Preferably allow the tablet to dissolve in the mouth, and then swallow.

Solution for injection (i.m., s.c., i.d., i.v.): *Unless otherwise prescribed:*

Standard dosage:

Adults:

1 ampoule 1 to 3x weekly.

Pediatric:

2–5 yrs.: ½ ampoule 1 to 3x weekly.

6–11 yrs.: ⅔ ampoule 1 to 3x weekly.

12–18 yrs.: 1 ampoule 1 to 3x weekly.

Acute or Initial Dosage:

Adults:

1 ampoule daily, and then continue with standard dosage.

Pediatric:

2–5 yrs.: ½ ampoule daily, and then continue with standard dosage.

6–11 yrs.: ⅔ ampoule daily, and then continue with standard dosage.

12–18 yrs.: 1 ampoule daily, and then continue with standard dosage.

Method of Administration:

Solution for injection may be administered by the s.c., i.d., i.m. or i.v. route.

Package sizes: *Tablets:* Packs containing 50 and 250 tablets. ***Solution for injection:*** Packs containing 5, 10, 50 and 100 ampoules of 1.1ml.

Pregnancy and lactation: *Tablets, Solution for injection:* For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicament are not known to be toxic during pregnancy and lactation. No adverse effects have so far been reported.

Overdose: *Tablets, Solution for injection:* No cases of overdose have been reported, and none are expected due to the homeopathic dilutions.

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