Kaloba® (EPs® 7630)
PELARGONIUM SIDOIDES
For Relieving the Symptoms of Upper Respiratory Tract Infections Including the Common Cold
PRODUCT MONOGRAPH

From Nature. For Health.
The Medicines and Healthcare Products Regulatory Agency (MHRA) granted Dr Willmar Schwabe & Co. KG a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Kaloba® (EPs®7630) Oral Solution (Traditional Herbal Registration Number THR 05332/0003) on 26th March 2008. This product is available without a prescription and can be bought from pharmacies and other outlets.

Further registration approvals for the Kaloba® (EPs®7630) range, all containing the Pelargonium extract EPs® 7630, have been obtained. Kaloba® (EPs®7630) film-coated tablets received approval on 31st March 2009, and Kaloba® (EPs®7630) syrup on 11th June 2010.

The active ingredient of the product Kaloba® (EPs®7630) comes from the roots of the plant Pelargonium sidoides DC (Pelargonium). Kaloba® (EPs®7630) is a traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including the common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only.

This registration is based exclusively upon longstanding use of the extract from the roots of the plant and not upon data generated from clinical trials. This is because there is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product works.

However, there is a large body of published clinical and pre-clinical evidence relating to Pelargonium sidoides DC (Pelargonium) that forms the basis of this monograph, which should be read in conjunction with the current Summary of Product Characteristics. Most of the available published clinical trials have been conducted with Kaloba® (EPs®7630) extract.
1. INTRODUCTION TO SCHWABE PHARMA

Leading the World in Herbal Medicine Self-Care

For more than 140 years, the Dr Willmar Schwabe group of companies has been committed to improving people’s health and wellbeing. We do so by proving through research and development, that plant based medicines offer a safe, efficacious alternative to conventional medicines.

Schwabe Pharma (UK) Ltd produces a range of registered traditional herbal remedies (THRs) used to relieve or prevent the symptoms of common minor ailments including coughs & colds, stress, low mood, muscle and joint pain, digestive disorders, menopause, migraine and premenstrual syndrome. We are leading the way in registering herbal medicines approved for both quality and safety by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Dr Willmar Schwabe Pharmaceuticals is the leading manufacturer of herbal medicines worldwide and is committed to four key values:

1. **Innovation** - we take people’s needs seriously and research them with passion and commitment, every day, every month, every year.

2. **Reliability** - it’s in our nature. For more than 140 years, the family owned company has been dedicated to providing innovative traditional herbal medicines across the globe.

3. **Responsibility** - we are committed to environmental protection and the conservation of our natural resources. Our cultivated plants on managed farms assist in the preservation of natural habitats and protect native plants from further decimation and potential extinction.

4. **Quality** - we control the whole process from harvesting the plants to the production of the finished herbal medicines and we ensure that only high quality plant materials are used for the production of these unique products. On our plantations, the raw materials for our products are grown under controlled conditions, following Good Agricultural and Collective Practice (GACP) guidelines.

Our special extracts are prepared using modern pharmaceutical technology using unique extraction processes to guarantee a concentrated and high quality end product. All manufacturing stages, from raw plant material testing to final release of the product are carried out to international requirements of the Good Manufacturing Practice (GMP) guidelines.

At Schwabe Pharma we share a common vision: “From Nature. For Health”.

2. REGULATION AND QUALITY OF HERBAL MEDICINES

2.1 Quality of Herbal Starting Material

It is important that consumers are able to choose to purchase herbal medicines as part of their self-care programme, that are of a consistently high quality from batch to batch. This consistent quality standard can only be achieved if the herbs used in the herbal medicine meet certain quality standards. These quality standards for the herbal starting material are described in reference texts which we call pharmacopoeial monographs. These herbal monographs describe in detail the European quality standards which must be met, ranging from all components allowable in the herb to the consistent amount of certain marker compounds characteristic to a particular herb that must be present.

Reliable and reproducible quality can only be achieved where the herbal starting material complies with these herbal monograph standards.

2.2 Growing and Harvesting Herbs – and Protecting the Environment

Controlled cultivation on managed farms of medicinal herbs will clearly lead to a more reliable quality than herbs that have been collected and harvested in the wild. In addition, controlled cultivation helps to ensure that consumer demand for a herb does not put survival of the herb at risk. Therefore, great efforts are taken to support the controlled cultivation of herbs worldwide. For example, Dr Willmar Schwabe owns and manages controlled cultivation of *Pelargonium sidoides* in South Africa, *Rhodiola rosea* in Canada and *Ginkgo biloba* in France and China.

Although controlled cultivation has many advantages over wild collection of herbs, there are some circumstances where only wild collection is possible. It is essential that wild collection is managed with great care in order to protect the herb from possible extinction.

A European Guideline entitled “Good Agricultural and Collective Practice” (GACP) has been adopted throughout the EU and this Guideline describes a set of quality standards which must be adopted in growing and collecting all herbs for the manufacture of traditional herbal registered products. This European Guideline is very important in helping to protect vulnerable plant species from extinction through exploitation and market demands.

N.B. Unlicensed herbal medicines and herbal food supplements, often known as "botanicals", do not have to comply with this Guideline.
2.3 EU Herbal Monographs – Quality Signposting

The quality of herbs used in manufacture of traditional herbal medicines are characterised by the following parameters:

- A clear botanical and scientific definition
- Identification of the herb
- Purity
- Content

A clear botanical definition comprises the Latin and scientific names of the plant and the part of the plant used. The identity and authentication of a herb is usually based on the macroscopic (visual) and microscopic features. Additional tests, such as thin-layer chromatography fingerprint analysis are often required as well. These allow for identification on the basis of compounds always found in a particular herb.

Other tests are often included in the monograph to ensure that the herb meets acceptable standards. For example, moisture content of the dried herb is often stipulated, as moisture can affect the stability of some of the active compounds found in a particular herb. Microbiological standards are also an important part of a monograph, in order to ensure that the herb is safe to use.

Heavy metals such as lead, mercury, cadmium and arsenic can accumulate in some plants, and heavy metal levels are therefore strictly controlled in herbal monographs.

Herbal monographs usually stipulate levels of specific marker compounds that are characteristic of that particular herb. For example, the herb Feverfew contains parthenolide; Chaste Tree or Agnus Castus contains casticin; and Milk Thistle contains silymarins. The levels of these marker compounds, both in the harvested herb, and the finished tablet or capsule must be achieved, otherwise the herb or finished tablet or capsule cannot be sold and marketed.

Achieving the high quality necessary to achieve a herbal registration requires competent scientific and technical skills. The herbal starting materials right through to the manufacture of the finished tablet or capsule must comply with rigorous manufacturing standards that are described in Good Manufacturing Practice Guidelines (GMP). These Guidelines are positively regulated in the UK by the Medicines and Healthcare Products Regulatory Agency who have GMP Inspectors who visit manufacturers regularly to check manufacturing compliance.

This type of positive regulation and Inspection does not take place with either unlicensed herbal medicines or herbal food supplement (“botanical”) type products, and is essential in giving patients and healthcare professionals assurance about the quality of traditional herbal registered medicines.

2.4 The Difference between “traditional use” and “clinical evidence”

Conventional licensed medicines in the UK are always assessed for quality, safety and efficacy by the Medicines and Healthcare Products Regulatory Agency (MHRA). Efficacy is assessed by MHRA clinical assessors based on at least two pivotal clinical trials and many related clinical trials that must comply with the European Clinical Trials Directive. It will often cost several million pounds to complete just one clinical trial as part of licensing a conventional medicine.

The fragmented nature of the herbal products market, with many companies having an annual turnover of less than the cost of a high quality clinical trial, has led to the introduction of the European Traditional Herbal Medicinal Products Directive.

This Directive requires that in order to obtain a registered herbal medicine approval, the company must demonstrate that the herb has been used for 30 years at the dosage in the herbal product that is being registered, for the required indication. At least 15 years of the 30 year period, must have been in an EU country and only indications that are for self-limiting, over-the-counter, minor ailments are acceptable. So clinical efficacy, as for conventional medicines, is not assessed – only traditional usage over a 30 year period.

Key Questions about the Traditional Herbal Medicinal Products Directive

Does “Traditional use” mean anything in evidence terms?

Yes. It is unlikely that sustained use of a herb for a particular indication would have survived over a 30 year period unless the users had experienced benefit. It is for this reason that traditional use for many people is a powerful reason for trying a herb to relieve a particular ailment or complaint. Indeed, some herbs have been used in some ethnic cultures for many hundreds of years, and have been passed down from generation to generation.

Do any traditional herbal registered products have clinical evidence of benefit?

Yes. Some products, including Pelargonium, do have clinical evidence that a particular herb is of benefit in a specific herbal registered product, but this evidence has NOT been assessed by the MHRA as part of the approval process. Schwanke Pharma has a heritage of carrying out clinical trials as part of a programme of developing a robust evidence base for herbal medicines both in the UK and in many countries throughout the world. This programme will continue, but does not form part of the assessment process for registering herbal medicines.

Are traditional herbal registered products of the same quality as conventional medicines?

Yes. The quality requirements for registered herbal products are strictly controlled and the same high standards of manufacture are required as for conventional medicines.
The manufacturing standards are strictly enforced through a rolling two year MHRA Inspection programme of the manufacturing facility.

N.B. Herbal food supplements ("botanicals") and unlicensed herbal medicine manufacturing procedures are not regulated in this way.

Many conventional medicines have information leaflets with the medicine. What is the situation with traditional herbal registered products?

The situation is identical. All traditional herbal registered products have an MHRA approved patient information leaflet which describes useful information for the patient, including when and how to take the product, and any contra-indications on when the product should not be taken – such as pregnancy or breast-feeding.

N.B. Herbal food supplements ("botanicals") and unlicensed herbal medicines do NOT have information leaflets that have been approved as described above.

3. INTRODUCTION TO ACUTE UPPER RESPIRATORY TRACT INFECTIONS

Acute upper respiratory tract infections (URTIs) are the most common diseases treated in general and paediatric primary care practice and affect all age groups, particularly during the winter months. During a cold or flu epidemic, they can account for up to 50% of all GP consultations. GP consultations for colds and flu alone cost between 600 and 800 million pounds every year. This is a significant challenge for GPs working in primary care, both clinically and in terms of managing patient expectations, because the majority of infections are virus-mediated.

Acute upper respiratory tract infections are diseases which are generally self-limiting in nature. However, if left untreated, there is a risk that the clinical course of the symptoms may be considerably prolonged. This can lead to extended time off work or away from school, which often causes difficulties for families in an increasingly challenging and demanding work environment. Complications can occur in children, the elderly and vulnerable groups such as diabetics or asthmatics. These vulnerable patients are at particular risk of developing bronchitis, with an increased likelihood of developing an acute, serious infection such as, for example, pneumonia.

In conclusion, it should be emphasised that even respiratory tract infections which appear harmless at first sight should be treated, particularly in vulnerable patients.

3.1 Pathophysiology of Upper Respiratory Tract Infections

A disrupted immune balance is the basis of any infection. The immune system can no longer protect the body from an increased pathogenic burden. This is primarily the case with particularly aggressive viruses that are unknown to the immune system, particularly in patients in vulnerable groups or where the immune system is already affected by stress, anxiety or other debilitating diseases.

The nasal cavity/pharynx is generally the starting point for an upper respiratory tract infection. This is where rhinopharyngitis, which is characterised by the initial symptoms of sore throat, rhinitis (runny nose) and lethargy, actually develops.

Pathogen ascendance subsequently triggers sinitis whilst pathogen descendance causes tonsillitis, laryngitis and frequently acute tracheobronchitis. This also explains why acute bronchitis is virtually always associated with other symptoms caused by the inflammatory processes in the nasal cavities and pharynx (Figure 1).

The onset of infection with reference to interaction with epithelial cells is completed in three stages:

1. Adhesion – pre-requisite for infection
2. Internalisation – pathogen proliferation and reservoir for recurrence
3. Paracellular translocation – spread of infection in the deep tissues

Internalised and paracellularly translocated pathogens in the deeper cell layers can often not be reached by substances with a direct, antimicrobial effect. Thus it is even more important to protect the mucosal cells and to activate the non-specific immune system, especially the natural killer cells, which are the first line of defence.
Viruses are by far the most important group of pathogens associated with URTIs, accounting for 90 – 95% of upper respiratory tract infections (Table 1). Conversely, primary bacterial pathogens are only seldom detected in acute sinusitis.

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Table 1: Overview of pathogens involved in acute tracheobronchitis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Significance</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus (types 1-7, 12)</td>
<td>+++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Coxsackie virus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other enteroviruses</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Influenza virus A and B</td>
<td>+++</td>
<td>+ to ++++</td>
</tr>
<tr>
<td>Influenza virus C</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Parainfluenza virus 1,2</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Parainfluenza virus 3</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>RSV (respiratory-syncytial virus)</td>
<td>+++</td>
<td>+ to +++</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>+++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Tonsillitis causality is less clearly defined. Although simple catarrhal, mostly viral-induced tonsillitis can occur; a streptococcal sore throat that in general has to be treated with antibiotics, can occur as well. The treatment of acute tonsillitis therefore falls into the medical domain, although the risk of developing post-streptococcal complications in countries with a good standard of hygiene is extremely low. The post-streptococcal risk described in many textbooks is most probably a “phantom risk” in Germany.

The current incidence of this particular risk was quantified by Adam in a 2001 study. Even in 1980, only one case of rheumatic fever occurred during the working life of 12 general practitioners. Based on this minimal risk, the authors concluded that immediate antibiotic treatment should not be recommended. However, it is generally accepted that patients presenting with acute symptomatic streptococcus-induced infection should receive antimicrobial therapy. However, this treatment is still effective when started (with a delay of up to 9 days). According to Adam, this means that treatment can be delayed until laboratory test results of a throat swab have been received and an appropriate antibiotic can then be prescribed for the pathogen spectrum identified through the swab result.

3.2 Current Treatments and Related Problems

Although 9 out of 10 upper respiratory tract infections are caused by viruses, antibiotics are prescribed in over 80% of cases. However, clinical and scientific evidence to support the use of antibiotics in upper respiratory tract infections is poor, as detailed below:

**Antibiotics in the treatment of Non-A-Streptococcal Pharyngitis**

A meta-analysis of 27 studies involving 2,835 patients conducted by the Cochrane Collaboration (2006) led to the conclusion that antibiotic therapy in this indication only shortens symptoms by 16 hours and that most patients do not benefit at all from this form of treatment.

**Antibiotics in the treatment of laryngitis**

The Cochrane Review (2007) authored by Reveiz et al. of 206 adult patients did not show a clinically significant benefit. The authors concluded that antibiotics in the management of acute laryngitis did not improve symptoms and should therefore not to be recommended as a first-line treatment for acute laryngitis.

**Antibiotics in the treatment of otitis media (inflammation of the middle ear)**

Similarly, a meta-analysis was carried out by the Cochrane Collaboration (2003). The examination of 8 studies involving a total of 2,287 children led Glasziou et al. to the conclusion that the prescribing of antibiotics in the treatment of otitis media is only slightly beneficial to children and should be carefully evaluated in view of the side effects, particularly since otitis media is a clinical condition that spontaneously heals in most cases.

**Antibiotics in the treatment of colds and acute purulent rhinitis**

In a Cochrane Review of six studies with a total of 1,147 patients, Arroll and Kenealy (2005) concluded that there is inadequate evidence regarding the use of antibiotics in this indication and that the routine administration of these substances cannot be recommended.
Antibiotics in the treatment of acute sinusitis

A Cochrane Review by Williams et al. (2003) (meta-analysis of 49 studies involving a total of 13,660 patients) revealed that there is only very limited evidence regarding the beneficial use of antibiotics and that doctors should consider carefully the limited therapeutic effect against the existing potential for side effects 14.

Antibiotics in the treatment of acute bronchitis

In the Cochrane meta-analysis (2004) of 9 studies involving a total of 750 adults and children, the authors concluded that antibiotics only have a minimal benefit in the treatment of acute bronchitis. The use of antibiotics should be weighed against the broad spectrum of side effects. In addition, the significant risk of antibiotic resistance development, and the high cost of this therapy should also be taken into consideration 15.

Antibiotics in the management of acute bronchiolitis

Bronchiolitis is a serious and often life-threatening disease of the lower respiratory tract that mainly affects babies. The disease is caused by the RSV (Respiratory Syncytial Virus). A Cochrane analysis (2007) did not reveal any significant difference between placebo and antibiotics when considering the primary end points of disease duration and death.

In conclusion, antibiotic therapy was only statistically significant and clinically relevant in relation to increased frequency of side effects, especially allergic exanthema, gastrointestinal disorders and fungal infections.

It should be noted that almost 8 out of 10 children will be treated at least once with antibiotics between the 2nd and 4th year of their life. The average duration of treatment is 17.6 days/child/year 17.

The uncontrolled administration of antibiotics in children is of particular concern, particularly as asthma is 2.5 times more prevalent in 7 year-old children given antibiotics at an early age compared to their untreated peers. Moreover, allergies are twice as prevalent in this same patient category 18.

3.3 Problems of Antibiotic Resistance

Another side effect of antibiotic treatment is bacterial (antibiotic) resistance, which has become a major international problem.

Bronzwaer (2002) highlighted the correlation between the frequency of the use of antibiotics and the proportion of resistant bacterial strains in the overall European population 19. This study showed that the number of prescribed daily doses of antibiotics is positively correlated with the occurrence of bacterial resistance in different Member States (Figure 2).
In practical terms, this means that an antibiotic administered at the beginning of the infectious season in the Autumn can trigger resistance which is sustained throughout the winter months through to Spring.

As a result of increasing antimicrobial resistance, a switch to so-called reserve antibiotics or to combination therapies with a significant synergistic potential is increasingly required. This treatment regimen not only generates enormous budgetary health service costs, but also means that a significant number of pathogens lose their sensitivity to antibiotics.

The outcome of the above is that every year, 50,000 people in Europe die from antibiotic resistant infections that can no longer be treated adequately with existing antibiotics.

Antiviral agents in the treatment of respiratory tract infections?

Neuraminidase inhibitors, such as oseltamivir (Tamiflu), which are authorised for use in the management of influenza mediated infections, are not a therapeutic alternative in the treatment of all upper respiratory tract infections. The benefits of using neuraminidase inhibitors to treat what are mainly self-limiting infections are far outweighed by the risk of increasing viral resistance, along with significant budgetary costs to already overstretched health services. The extent of resistance development already exceeds previous expectations. In 2005 and 2001, up to 18% of children and up to 4% of adults, respectively, were already experiencing oseltamivir-resistant influenza type viral infections. Bacterial and viral resistance cannot be considered merely as a governmental or global problem. Particular attention should be paid to the fact that resistant pathogens are rapidly transmitted between people and can pose a threat to young children and/or vulnerable groups such as pregnant or elderly relatives.

Medically supervised watchful waiting is not a recommended option either: Altina (2001) reported that 50% of all untreated patients presenting with acute bronchitis still coughed on observation day 21, 25% on observation day 30 and 2 – 5% even after 6 months. The most serious acute complication is pneumonia, which mainly affects young children due to their incompletely developed immune system, and immunocompromised subjects such as the elderly or diabetic patients. The mortality rate of community acquired pneumonia in Germany is currently estimated at approximately 11%.

The risk of developing a chronic disease condition is of both individual and economic significance. One in three patients presenting with acute bronchitis that is inadequately treated will develop chronic bronchitis, which accounts for 5% of all deaths.

4. KALOBA® (EPs®7630) – QUALITY INFORMATION

4.1 Introduction

The active drug substance contained in Kaloba® (EPs®7630) is a patented dry root extract of the herb Pelargonium sidoides DC. The extract is known by the name EPs®7630 and it has a herb-extract ratio of 1:8-10. The extract solvent is 11% (v/v) ethanol. Schwabe Pharma (UK) Ltd distributes three different preparations: Kaloba® (EPs®7630) oral drops, Kaloba® (EPs®7630) tablets and Kaloba® (EPs®7630) syrup. The three preparations all contain the Pelargonium patented extract EPs®7630 but in different dosage forms. For a full list of excipients refer to Section 7.

For centuries, medicine men of South African tribes have used decoctions obtained from Pelargonium sidoides to cure various infections including tuberculosis. The Zulu word for the plant is “Umckaloabo” and it means “bad cough” indicating its use in traditional Zulu medicine.

In 1897, the Englishman Major Charles H. Stevens, who was suffering from pulmonary tuberculosis, travelled to South Africa where he was cured with this traditional medicine after 4 months of treatment. He introduced this herbal remedy into the UK under the name of “Stevens’ Consumption Cure”.

The identity of the root drug contained in Stevens Consumption Cure, Pelargonium sidoides, a South African plant belonging to the Pelargonium genus, Geraniaceae family, was first identified in Germany in 1972. As time went by, modern medical research-discovered many of the numerous mechanisms of action of this unique plant extract.
The plant grows to a height of 20 – 80 cm, has greyish green leaves and purple flowers (Figure 4). The roots of *Pelargonium sidoides* provide the raw material used in the manufacture of the extract EPs®7630, which is the active constituent of the Kaloba® (EPs®7630) brand. Rhizomes and roots that are aged from 2 – 4 years contain the optimal amount of effective substances. Nowadays, *Pelargonium sidoides* is grown on specialised managed farms using ecological and sustainable cultivation methods. These methods ensure that wild habitats remain intact addressing sustainability of the species. Occasionally, the raw material is collected in the wild with special permits from the authorities. The whole process through from ground cultivation, seeding, harvesting and collection is carried out in compliance with European Guidelines on Good Agricultural and Collective Practice (GACP).

This sustainable approach is an essential element to the growing and harvesting of all herbal extracts that are used in the manufacture of licensed herbal medicines. The manufacture of the extract to GACP Guidelines, as well as ensuring sustainability of the species, gives valuable employment to a significant number of farm workers in what is a relatively poor area of Southern Africa. The starting material is not treated with fumigants. The dried herb is tested macroscopically, microscopically and using TLC (thin layer chromatography) for identity according to the European Pharmacopoeia (Ph. Eur.). Purity testing is carried out for pesticide residues, heavy metals, aflatoxins and microbial contamination. When all these tests comply with the Ph. Eur. the dried herbal material is then processed to EPs® 7630 extract using specialised patented techniques. All the stages of manufacture follow strict Good Manufacturing Practice (GMP) and Good Agricultural and Collective Practice (GACP) Guidelines from starting material to the finished product to ensure ongoing sustainability and consistent reproducible quality of the finished product.

Kaloba® (EPs®7630) is approved in the UK as a traditional herbal medicinal product to relieve the symptoms of upper respiratory tract infections including the common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only.

### 4.2 Qualitative and Quantitative Information

The drug substance, EPs®7630 extract is a complex mixture of constituents. The pharmaceutically active substance in Kaloba® (EPs®7630), contains characteristic groups of substances, namely:

- Polyphenols (total phenols, 40%)
- Proteins (10%)
- Purines (2%)
- Minerals (12%)
- Saccharides (12%)
- 7-hydroxycoumarin derivatives, in lower concentrations

The polyphenols mainly comprise the monomeric flavan-3-ols catechin and gallocatechin. All 7-hydroxycoumarin derivatives including umckalin (7-hydroxy-5,6-dimethoxycoumarin), which is found in the largest quantity and is typical of this plant species, significantly differ in terms of chemical structure from the known anticoagulant coumarins. Some of the substances contained in *Pelargonium sidoides* have not yet been identified – a typical feature of phytopharmaceuticals (Figure 5).

Tests carried out with the individual chemical compounds compared to the whole extract show that only the whole extract possesses an optimal, therapeutic effect. The isolated individual compounds displayed very weak effects, if, indeed, any.
5. PHARMACOLOGY

5.1 Mode of Action

Kaloba® (EPs®7630) has a multi-faceted mode of action. The following mechanisms of action for Kaloba® (EPs®7630) have been found to be relevant in the treatment of respiratory tract infections:

1. Antiviral and cytoprotective properties
   - Modulation of the production of interferons, pro-inflammatory cytokines and defensins
   - Anti-oxidant properties
   - Inhibition of leukocyte elastase

2. Antibacterial properties
   - Increased adhesion of bacteria to dead epithelial cells of the respiratory tract mucosa
   - Inhibition of adhesion of bacteria to living epithelial cells in the respiratory tract mucosa
   - Stimulation of phagocytosis and chemotaxis

3. Secretomotory properties
   - Stimulation of the ciliary beat frequency of the respiratory ciliated epithelium

4. Inhibition of “sickness behaviour”

These modes of action are involved in every stage of respiratory tract infections, as shown in Figure 6, and are described separately in the following.

5.1.1 Antiviral and cytoprotective properties

The cytoprotective effect of Kaloba® (EPs®7630) and the various compounds contained in the extract against virus-induced cell destruction was confirmed in the following model: Fibroblasts were incubated with macrophage residues (interferon induction by control substance / EPs®7630) and infected with the encephalomyocarditis virus (EMCV).

The survival capacity of the cells increased with greater concentrations of EPs®7630 up to twice that recorded in the control group incubated only with the test compounds i.e. the whole extract and not individual compounds was responsible for the cell-protective effect (Figure 7).

Figure 6: Pathogenesis of respiratory tract infections and mechanisms of action of Kaloba® (EPs®7630).

Figure 7: Increase in cell vitality with Kaloba® (EPs®7630)
Kaloba® (EPs®7630) also increases the release of antimicrobial peptides, the so-called defensins, from neutrophilic granulocytes. Defensins were initially discovered in plants, which, unlike mammals, have no specific immune system, and which have successfully defended themselves for millions of years against attack from microorganisms. In humans, defensins have been detected on the surface of CD4 cells in the skin. These are said to play an essential role in the defence against pathogens. Current research is focusing on discovering the underlying mechanism.

The antiviral effect of Kaloba® (EPs®7630) is principally derived from the modulation of the non-specific immune system.

Increase in interferon synthesis

Kaloba® (EPs®7630) triggers stimulation of interferon (INF)-β production (Figure 8). This is particularly relevant because the type 1 interferon INF-β not only protects cells against virus-mediated destruction, but also has a direct antiviral effect and activates natural killer cells. The latter play an important role in the initial stages of infection as immune cells of the first line of defence.

A study carried out with EPs®7630 on human cell cultures using the viral dsRNA analogue polyI:polyC confirms this effect.

Moreover, Kaloba® (EPs®7630) induces the other type-1-interferons, IFN-α and INF-γ, which also possess cytoprotective properties.

Improvement of phagocyte function

Increased phagocytosis and the intracellular destruction of microorganisms (intracellular killing) is another pharmacological property of Kaloba® (EPs®7630) in preventing the progress of infection. A significant improvement in the function of human phagocytes in peripheral blood was detected in corresponding flow-cytometry assays using Candida albicans as the target organism.

In addition to phagocytosis per se, the formation of reactive oxygen species – the so-called oxidative bursts that damage the phagocytosed (internalized) pathogens directly - is decisive for the activity of these immune cells.

At clinically relevant concentrations, Kaloba® (EPs®7630) increased both the active phagocyte count (p < 0.002) as well as the proportion of burst-active phagocytes (p < 0.001) (Figures 9 and 10).

The convergence of the four groups at the end of the test series is due to the fact that all pathogens are phagocytosed at this point.
5.1.2 Antibacterial properties

The direct bacteriostatic effect of Kaloba® (EPs®7630) is inferior to that of conventional antibiotics.35

However, it is interesting to note that in a study carried out with multiresistant strains of Staphylococcus aureus (MRSA), the susceptibility of these strains to Kaloba® (EPs®7630), was comparatively favourable when compared to the non-resistant reference strain, St. aureus ATCC 25923.36

The indirect antibacterial effects are more important.

Kaloba® (EPs®7630) inhibits the adhesion of bacteria to healthy mucosal cells and thus counteracts a key mechanism in the pathogenesis of bacterial respiratory tract infections.

The effect of EPs®7630 on the adhesion of bacteria to 90% vital human HEp-2 cells, a cell line of the larynx, was investigated in an in vitro study by means of flow cytometry. A-streptococci (Streptococcus pyogenes) were used as the test organism. Clinically relevant concentrations ranging from 0 to 30 μg EPs®7630 led to a significant reduction in the adhesion of A-streptococci to these cells by up to 46% (p < 0.001) (Figure 12).37
This reduction in adhesion was confirmed by fluorescence microscopy (Figure 13a/b). In the same adhesion test, the identical test procedure was carried out using 90% dead epithelial cells of the oral mucosa. This test showed that streptococcal adhesion to these dead cells increased 7-fold with Kaloba® (EPs®7630) (p < 0.001). Pathogenic organisms can therefore be trapped and eliminated in this way. The result was confirmed in additional tests.

The internalisation of bacteria in the host cells plays a decisive role in the development of recurrent infections because internalised bacteria evade the immune system’s defence mechanisms. The intracellular proliferation of micro-organisms remaining after the initial infection results in a renewed bout of infection.

The effect of extract EPs® 7630 on the penetration of pathogens into HEp-2 cells was therefore investigated.

The result of this study showed a significant reduction in internalisation at test times 60, 120 and 180 minutes (Figure 14)37.

5.1.3 Secretomotory properties

The recovery or stimulation of mucociliary clearance is a decisive factor in the defence against respiratory tract infections. Kaloba® (EPs®7630) stimulates this mechanism, as shown in an in vitro study with human nasal epithelial cells. EPs® 7630 increased the ciliary beat frequency in a dose-dependent manner by 23% and 33% at 30 μg/ml and 100 μg/ml, respectively (Figure 15)38.
5.1.4 Inhibition of “sickness behaviour”

Infections are frequently accompanied by non-specific changes in behaviour and both physical and mental symptoms (weakness, fatigue, lack of interest and drive, anorexia, social isolation, poor concentration, sleep disorders, anxiety, depression, etc.), which are mediated by the effect of pro-inflammatory cytokines (e.g. IL-1β, TNF-α and IL-6) on the central nervous system.

The effect of Kaloba® (EPs® 7630) on sickness behaviour triggered by lipopolysaccharide (LPS) injection was tested in mice using a highly sensitive model to detect behavioural changes – the light/dark box. Laboratory animals given EPs® 7630 after LPS administration remained substantially longer in the dark section of the box than those animals in the control group.

Kaloba® (EPs® 7630) inhibited the LPS-mediated behavioural changes in a significant, dose-dependent manner (Figure 16). This test result means that the positive effect on sickness behaviour could play a crucial role in the therapeutic effects of Kaloba® (EPs® 7630).39

5.2 Clinical Information

5.2.1 Clinical Studies

Clinical studies of acute bronchitis in adults

Two placebo-controlled, double-blind studies were pivotal for an identical product to gain a marketing authorization for the indication “acute bronchitis” in Germany. The most important results of these studies are summarised below.

The Bronchitis Severity Score (BSS), the expression of symptom severity and thus of the disease-mediated impact, was used, amongst others, to assess efficacy. This score is calculated from the sum of the key symptoms – cough, expectoration, rales, chest pain on coughing and dyspnoea, as evaluated by the investigating physician on a scale of 0 (not present) to 4 (very severe).
Secondary outcome criteria included remission of the individual symptoms, time to onset of action, patient compliance, tolerability, evaluation of therapeutic success by doctor and patient using the Integrative Medicine Outcomes Scale (IMOS) and parameters recorded in patient diaries such as intensity of symptoms, general wellbeing and health-related quality of life.

**Study 1**

**Study of acute bronchitis in adults**

<table>
<thead>
<tr>
<th>Author</th>
<th>Chuchalin et al. 2005⁴⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, prospective, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs® 7630 (Kaloba®) vs. placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>124</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>7 days</td>
</tr>
<tr>
<td>Dosage</td>
<td>3 x 30 drops/day, optional 500 mg paracetamol p.o. when body temperature rises to &gt; 38.5°C</td>
</tr>
<tr>
<td>Target criteria</td>
<td>Proof of superiority of the active drug confirmed by a change in the BSS</td>
</tr>
</tbody>
</table>

**Results**

An improvement in BSS of 7.2 (active drug) vs. 4.9 (placebo) (p < 0.0001) was recorded on day 7. More rapid recovery of ability to work (84.4% vs. 45.0% on day 7)

**Tolerability**

98.4% of patients and 96.7% of doctors assessed the tolerability of Kaloba® (EPs®7630) as “very good” or “good”
Study 2

Study of acute bronchitis in adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Matthys &amp; Heger, 2007⁴¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, prospective, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs® 7630 (Kaloba®) vs. placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>217</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>7 days</td>
</tr>
<tr>
<td>Dosage</td>
<td>3 x 30 drops/day, optional 500 mg paracetamol p.o. when body temperature rises to ≥ 38.5°C</td>
</tr>
<tr>
<td>Target criteria</td>
<td>Proof of superiority of the active drug confirmed by a change in the BSS</td>
</tr>
<tr>
<td>Results</td>
<td>An improvement in BSS of 7.6 (active drug) vs. 5.3 (placebo) (p &lt; 0.0001) was recorded on day 7</td>
</tr>
<tr>
<td>Tolerability</td>
<td>No serious adverse events same tolerability as placebo</td>
</tr>
</tbody>
</table>

Study 3

Study of acute bronchitis in adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Matthys et al. 2003⁴²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs® 7630 (Kaloba®) vs. placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>468</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>7 days</td>
</tr>
<tr>
<td>Dosage</td>
<td>3 x 30 drops/day, optional paracetamol tablets (500 mg) when body temperature rises to ≥ 39°C</td>
</tr>
<tr>
<td>Target criteria</td>
<td>Proof of superiority of the active drug over placebo</td>
</tr>
<tr>
<td>Results</td>
<td>Change of BSS on day 7, decrease in BSS of 5.9 ± 2.9 (active drug) vs. 3.2 ± 4.1 (placebo) (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Tolerability</td>
<td>96.1% of patients assessed the tolerability of EPs® 7630 as “very good” or “good”</td>
</tr>
</tbody>
</table>

Figure 18a: Improvement in bronchitis symptoms with Kaloba® (EPs®7630) (p=0.0001)(p<0.0001)

Figure 18b: Improvement in individual symptoms of bronchitis with Kaloba® (EPs®7630)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EPs® 7630</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>52</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Rales</td>
<td>88</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Weakness/fatigue</td>
<td>80</td>
<td>47</td>
<td>33</td>
</tr>
<tr>
<td>Expectoration</td>
<td>68</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>80</td>
<td>56</td>
<td>24</td>
</tr>
<tr>
<td>Headache</td>
<td>88</td>
<td>68</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>88</td>
<td>77</td>
<td>11</td>
</tr>
<tr>
<td>Chest pain</td>
<td>93</td>
<td>86</td>
<td>7</td>
</tr>
<tr>
<td>Fever</td>
<td>98</td>
<td>91</td>
<td>7</td>
</tr>
<tr>
<td>Joint pain</td>
<td>93</td>
<td>88</td>
<td>5</td>
</tr>
</tbody>
</table>
Clinical studies in acute bronchitis in children

Two placebo-controlled studies involving 200 and 220 patients were carried out to assess the treatment of acute bronchitis in children and adolescents. The design and results of these studies correlate with the studies described earlier that were carried out in adults.

Study I

Study of acute bronchitis in children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Kamin, 2007(^{43})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, prospective, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs(^{®}) 7630 (Kaloba(^{®})) vs. placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>200 children between 1 and 18 years of age</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>7 days</td>
</tr>
</tbody>
</table>
| Dosage | Patients between 1 and 6 years of age: 3 x 10 drops/day  
Patients > 6 to 12 years of age: 3 x 20 drops/day  
Patients > 12 to 18 years of age: 3 x 30 drops/day |
| Target criteria | Proof of superiority of the active drug confirmed by a change in the BSS |
| Results | An improvement in BSS of 3.4 (active drug) vs. 1.2 (placebo) (\(p < 0.001\)) was recorded on day 7 |

**Figure 19a:** Improvement in bronchitis symptoms with Kaloba\(^{®}\) (EPs\(^{®}\)7630)

**Figure 19b:** Reduction of inability to work with Kaloba\(^{®}\) (EPs\(^{®}\)7630) on day 7

**Figure 20:** Investigator’s assessment of the efficacy of Kaloba\(^{®}\) (EPs\(^{®}\)7630)
Study 2

Study of acute bronchitis in children and adolescents

- **Author:** Kamin, 2007
- **Study design:** Multicentre, prospective, randomised, double-blind, placebo-controlled study
- **Investigational medicinal product:** EPs® 7630 (Kaloba®) vs. placebo
- **Number of patients:** 220 children between 1 and 18 years of age
- **Duration of treatment:** 7 days
- **Dosage:**
  - Patients between 1 and 6 years of age: 3 x 10 drops/day
  - Patients > 6 to 12 years of age: 3 x 20 drops/day
  - Patients > 12 to 18 years of age: 3 x 30 drops/day
- **Target criteria:** Proof of superiority of the active drug confirmed by a change in the BSS
- **Results:** An improvement in BSS of 4.4 (active drug) vs. 2.9 (placebo) (p < 0.001) was recorded on day 7.
**Study 3**

**Study of acute bronchitis in children and adults**

<table>
<thead>
<tr>
<th>Author</th>
<th>Matthys, et al. 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, prospective, open observational study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs® 7630 (Kaloba®)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>2099 patients aged 0-93; 127 patients &gt; 6 – 12 years; 241 patients ≤ 6 years</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>14 days</td>
</tr>
</tbody>
</table>
| Dosage | Adults and children > 12 years of age: 3 x 30 drops/day  
Children > 6-12 years of age: 3 x 20 drops/day  
Children 6 years of age or less: 3 x 10 drops/day |
| Target criteria | Change of BSS |
| Results | In all patients: The BSS decreased from 7.1 ± 2.9 at baseline to 1.0 ± 1.9 at the last visit  
Subgroup analysis: For children (patients < 18 years, n = 498): The BSS decreased from 6.3 ± 2.8 to 0.9 ± 1.8 at the last visit  
Subgroup of infants (patients < 3 years, n = 78): The BSS decreased from 5.2 ± 2.5 to 1.2 ± 2.1 at the last visit |
| Tolerability | The tolerability of EPs® 7630 was very good  
Adverse events occurred in only 1.2% of the patients, none of the events was serious |

![Figure 23: BSS changes during the study period in children and infants](image1)

![Figure 24: Remission rates from baseline to last observation for bronchitis specific symptoms in all patients (n = 2099)](image2)
Additional studies

Acute sinusitis

The efficacy of Kaloba® (EPs®7630) in the management of acute sinusitis was confirmed in the following controlled double-blind study.

The primary test criterion was the Sinusitis Severity Score (SSS), which comprised the total score of the following symptoms: headache, pain in the upper jaw region, percussion pressure on bending forward, pressure or pain on bending forward, blocked nose, purulent nasal secretion and purulent discharge in the median nasal passage. These symptoms were assessed on the scale of 0 (not present) to 4 (very severe). The maximum cumulative score was therefore 24.

X-rays of paranasal sinuses were taken at the beginning and end of the study in order to confirm the diagnosis.

Study 1

<table>
<thead>
<tr>
<th>Study of acute Sinusitis maxillaris in adults</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
<td>Bachert et al. 2009&lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Multicentre, prospective, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td><strong>Investigational medicinal product</strong></td>
<td>EPs® 7630 (Kaloba®) vs placebo</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>103</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>21 days</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>3x60 drops per day</td>
</tr>
<tr>
<td><strong>Target criteria</strong></td>
<td>Proof of superiority of the active drug confirmed by a change in the SSS</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>An improvement in the SSS of 5.4 (active drug) vs. 2.5 (placebo) (p&lt;0.0001) was recorded at the end of the double blind phase (day 21)</td>
</tr>
</tbody>
</table>

![Graph showing changes in the Sinusitis Severity Score (SSS) ITT analysis (n = 103)](image)

**Figure 25a: Improvement in sinusitis symptoms with Kaloba® (EPs®7630)**

![Bar chart showing % patients who improved / were symptom-free](image)

**Figure 25b: Improvement in individual symptoms of sinusitis with Kaloba® (EPs®7630)**
Study 2

Study of acute non-group A beta-haemolytic streptococcal (GABHS) tonsillopharyngitis in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Bereznoy et al. 2003[6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs® 7630(Kaloba®) vs placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>143 children between 6 and 10 years of age</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6 days</td>
</tr>
<tr>
<td>Dosage</td>
<td>3x20 drops per day (Paracetamol suppositories (500mg) when body temperature rises to &gt;38.5°C (day 0 to day 4))</td>
</tr>
<tr>
<td>Target criteria</td>
<td>Proof of superiority of the active drug confirmed by a change in the TSS</td>
</tr>
<tr>
<td>Results</td>
<td>Decrease in TSS of 7.1 ± 2.1 (active drug) vs. 2.5 ± 3.6 (placebo) (p&lt;0.0001) was recorded on day 4</td>
</tr>
<tr>
<td>Tolerability</td>
<td>97.2% of patients and 97.3% of doctors assessed the tolerability of EPs® 7630 as ‘very good’ or ‘good’</td>
</tr>
</tbody>
</table>

Decrease of the Tonsillopharyngitis Severity Score (TSS) ITT analysis (n = 143)

Figure 26a: Improvement in individual symptoms of tonsillopharyngitis with Kaloba® (EPs® 7630)

Figure 26b: Remission rates for tonsillitis specific symptoms
Study 3

Study of common cold in adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Lizogub et al. 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, prospective, randomised, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>EPs®7630 (Kaloba®) vs. placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>103</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>10 days</td>
</tr>
<tr>
<td>Dosage</td>
<td>3 × 30 drops/day</td>
</tr>
<tr>
<td>Target criteria</td>
<td>Proof of superiority of the active drug over placebo</td>
</tr>
<tr>
<td>Results</td>
<td>Change in Cold Intensity Score (CIS), after 5 days the CIS decreased by 10.4 ± 3.0 in the EPs®7630 and by 5.6 ± 4.3 in the placebo group</td>
</tr>
<tr>
<td>Tolerability</td>
<td>On day 5, more than 9 out of 10 patients assessed the tolerability of EPs®7630 as “very good” or “good”, no adverse events were reported</td>
</tr>
</tbody>
</table>

5.2.2 Pre-Clinical Studies

There are some more recent studies that have been carried out in order to investigate further potential actions and indications for Kaloba® (EPs®7630). The two studies below give details on the anti-viral effect of EPs®7630 on the Herpes virus and the influenza virus strain H1N1.

Study 1

Efficacy of an aqueous Pelargonium sidoides EPs® 7630 extract against herpes virus


Abstract

The compounds of an aqueous root extract of the African medicinal plant *Pelargonium sidoides* were analysed by LC-MS spectroscopy and antiviral effect of this extract against herpes simplex virus was examined in cell culture. Besides predominant coumarins, simple phenolic structures as well as flavonoid and catechin derivatives were identified as major constituents in the Pelargonium extract. The inhibitory activity of this extract against herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) was tested in vitro on RC-37 cells using a plaque reduction assay and exhibited high antiviral activity against both herpes viruses in viral suspension tests.
The 50% inhibitory concentration (IC50) of the aqueous *Pelargonium sidoides* extract for herpes simplex virus plaque formation was determined at 0.00006% and 0.000005% for HSV-1 and HSV-2, respectively. At maximum non-cytotoxic concentrations of the extract, plaque formation was significantly reduced by more than 99.9% for HSV-1 and HSV-2 and a clear concentration-dependent antiviral activity against HSV could be demonstrated for this extract. In order to determine the mode of antiviral action, the extract was added at different times to the cells or viruses during the infection cycle. Both herpes viruses were significantly inhibited when pretreated with the plant extract or when the extract was added during the absorption phase, whereas aciclovir demonstrated antiviral activity only intracellularly during replication of HSV. These results indicate that *Pelargonium sidoides* extract affected the virus before penetration into the host cell and reveals a different mode of action when compared to the classical drug aciclovir. Hence this extract is capable of exerting an antiviral effect on herpes simplex virus and might be suitable for topical therapeutic use as an antiviral drug both in labial and genital herpes infections.

**Figure 28:** Antiviral effect of *Pelargonium sidoides* extract against HSV-1. Dose-response experiments were repeated independently 3 times and data presented are the average of 4 experiments. Details of experiment: Cells were pre-treated with *Pelargonium sidoides* extract prior to virus infection (pretreatment cells), viruses were pretreated prior to infection (pretreatment virus), the *Pelargonium sidoides* extract was added during the absorption period (adsorption) or after penetration of the viruses into cells (replication).

**Abstract**

A prodelphinidin-rich extract from *Pelargonium sidoides* DC, EPs®7630 (Kaloba®), which is licensed to treat respiratory tract infections such as acute bronchitis, was investigated for its antiviral effects. EPs®7630 showed dose-dependent anti-influenza activity at non-toxic concentrations against pandemic H1N1, oseltamivir-sensitive and - resistant seasonal H1N1, seasonal H3N2 and the laboratory H1N1 strain A/PuertoRico/8/34, while it had no antiviral activity against adenovirus or measles virus.

The extract inhibited an early step of influenza infection and impaired viral hemagglutination as well as neuraminidase activity. However, EPs®7630 did not exhibit a direct virucidal effect, as virus preincubation (unlike cell preincubation) with the extract did not influence infectivity. Importantly, EPs®7630 showed no propensity to resistance development in vitro. Analysis of EPs®7630 constituents revealed that prodelphinidins represent the active principle.

**Study 2**

EPs®7630 (Kaloba® (EPs®7630)), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity in vitro and in vivo.\(^{49}\)


**Figure 29:** Antiviral activity of *Pelargonium sidoides* extract against HSV-2. Data presented are mean of 4 experiments.
5.3 General Safety Information on Kaloba® (EPs®7630)

The favourable clinical safety profile of Kaloba® (EPs®7630) is corroborated by toxicological investigations. All standard tests such as cytotoxicity, acute and chronic toxicity in rats and dogs, genotoxicity studies (Ames test, chromosome aberration test and micronucleus test) as well as tests for carcinogenic potential, local tolerability, immunotoxicity and reproduction toxicity yielded no significant results.

5.3.1 Coumarins in Kaloba® (EPs®7630) and Their Effects on the Hepatobiliary System

Coumarins represent a large group of compounds for which hepatotoxic potential has been reported. It is known that some compounds in the large group of coumarin derivatives may have hepatotoxic effects. However, these substances differ structurally from the 7-hydroxycoumarins that are present in EPs®7630 (Kaloba®).

There is no reference in the scientific literature to hepatotoxic effects with 7-hydroxycoumarins. On the contrary, the metabolism of coumarin compounds via 7-hydroxylation is viewed as a detoxification mechanism and there is evidence that 7-hydroxycoumarins (such as, for instance, 4-methylumbiliferone) may even have hepatoprotective effects.

Products containing 4-methylumbiliferone have been available since the 1990s in both the USA and Europe as food supplements to improve liver function. They have also been used in part as medicinal products owing to their spasmylocytic and choleric effects. As expected, hepatotoxic effects were not observed in acute or chronic toxicity studies in dogs and rats following oral administration of up to 3000 mg/kg of EPs®7630. This is confirmed in studies carried out on human hepatocytes and hepatoma cells.

Figure 30a and b: Anti-influenza activity of EPs®7630 in mice. Infection of 10 mice per group with 4 MLD50 or 1 MLD50 of A/Puerto Rico/8/34, treatment with EPs®7630 or water by inhalation 3 times a day for 10 days. Numbers represent surviving animals from a group of 10. Influence of EPs®7630 treatment on virus lung titers. Lungs were removed on the day when less than 75% bodyweight was reached or on day 14 for surviving mice. Homogenisation and titration on MDCK cells. MLD50, half maximal mouse lethal dose.
The species-specific metabolism of this substance group plays a crucial role in determining whether or not coumarins develop any toxic effects. Highly toxic epoxides are formed as metabolites in rats, for instance, but do not occur in humans54.

Human primary hepatocytes (with normal and reduced CYP2A6-activity) were incubated with the coumarin derivative umckalin (10 and 100 μm), which is contained in EPs®7630 (Kaloba®). After up to four hours’ incubation, two metabolites were detected in addition to the intact starting substance, namely glucuronide and sulphate conjugates of umckalin55.

5.3.2 Coumarins in EPs® 7630(Kaloba®) and Their Effects on Blood Coagulation

In contrast to the well documented anticoagulant 4-hydroxycoumarins, the structurally different coumarins contained in EPs®7630 (Kaloba®) do not cause inhibition of vitamin-K-dependent synthesis of coagulation factors in the liver (Figure 31)56. High-dose studies in rats carried out over 14 days with 10, 75 or 500 mg/kg EPs®7630 revealed no change in thrombin time, partial thrombin time and thromboplastin time. No potentiation of the anticoagulant effect was observed following concomitant administration of 0.05 mg/kg warfarin. The results suggest that neither direct effects on haemostasis nor haemostatic effects due to interaction with anti-coagulants are likely during treatment with Kaloba® (EPs®7630) (Figure 32)56.

5.3.3 Drug Interactions

Interactions with other medicinal products are generally not expected as EPs®7630 (Kaloba®) does not affect liver metabolism except for a clinically irrelevant inhibition of CYP2C9. An effect on other tested cytochrome-P450 isoenzymes has not been observed at relevant concentrations. This includes CYP3A4, which is responsible for the metabolism of many pharmacologically active substances57. Similarly, no induction of cytochrome-P450-isoenzymes has been observed in human hepatocytes58.

These results are supported by findings in an interaction study conducted by Roots et al., who did not observe any relevant differences for the primary target criterion, AUC (Area Under the Curve) of penicillin V with and without concomitant administration of EPs®7630 (Kaloba®). The double-blind, randomised study was conducted in 2004 with Kaloba® and penicillin V (3 x 30 drops EPs®7630 (Kaloba®) vs. 3 x 1.2 mega Isocillin® p.o.) for 7 days59.

5.3.4 Tolerability

Approximately 304 million daily doses of Kaloba® (EPs®7630) were sold between 1994 and 2006, predominantly in Germany. The incidence of side effects is extremely low and equates to 0.53 per million defined daily doses (defined daily doses – DDD). This means that only one in 189,000 patients will experience a side effect during an average treatment period of 10 days. The rate of side effects is 0.27 per million DDD for hypersensitivity reactions (especially redness and pruritus), 0.13 for gastrointestinal disorders (such as stomach pain, heartburn, nausea or diarrhoea) and 0.05 for gingival haemorrhaging and nose bleeds.
There is insufficient experience to date with regard to the use of Kaloba® (EPs®7630) during pregnancy and lactation. For this reason, Kaloba® (EPs®7630) should not be administered during pregnancy and lactation without seeking medical advice.

Auto-immune diseases
Kaloba® (EPs®7630) has an immuno-modulating effect rather than an immuno-stimulating effect and it therefore boosts the immune system only in the event of infection. Consequently, there are no contra-indications on the use of Kaloba in patients with auto-immune diseases, although there have been no studies carried out to date in this patient group. Significantly, Kaloba can be used by asthmatics unlike Echinacea, which is contra-indicated for use in both asthmatics and patients suffering from auto-immune diseases.

Children under 6 years of age
Kaloba® (EPs®7630) is not approved in the UK for use in children under 6 years of age. However in Germany it is indicated from 1 year due to very good tolerability and proven efficacy. Kaloba® (EPs®7630) oral drops and syrup are indicated from 6 years onwards, and Kaloba® (EPs®7630) tablets from 12 years in the UK.

Alcoholics
Herbal remedies in liquid form such as Kaloba® (EPs®7630) Oral Solution, frequently contain alcohol. This is used as an extraction agent, natural stabilising agent and absorption-enhancing agent. The natural blood alcohol level in humans is 0.003%. This is only slightly changed by the intake of a small quantity of alcohol such as that contained in Kaloba® (EPs®7630) Oral Drops because these small quantities are metabolised very quickly after ingestion. Many foodstuffs consumed in normal quantities contain as much as or even more alcohol than that contained in a daily dose of Kaloba® (EPs®7630). Similarly, there is no risk to children. A glass of apple juice (0.2l) contains more than three times as much pure alcohol (0.76ml) than the maximum paediatric dose of 60 drops Kaloba® (EPs®7630). Regardless of this, the medicinal product can be administered in a small glass or warm tea or juice. A large proportion of the alcohol evaporates and the taste is also lost.

Drug interactions
No interactions with other medicinal products have been reported to date. However, in view of the theoretical effect of Kaloba® (EPs®7630) on coagulation parameters, enhancement of the effects of anticoagulant drugs such as phenprocoumon and warfarin (e.g. Marevan®) cannot be excluded when these are administered concomitantly with Kaloba® (EPs®7630).

Special patient groups and questions
Diabetics
Kaloba® (EPs®7630) oral drops, tablets and syrup are suitable for diabetics. The amount of sugar absorbed in the daily dose is clinically insignificant and need not be taken into account in any daily sugar intake calculation.

Coeliac disease
Kaloba® (EPs®7630) does not contain gluten and can be administered to patients with gluten-sensitive coeliac disease.

Pregnancy/lactation
There is insufficient experience to date with regard to the use of Kaloba® (EPs®7630) during pregnancy and lactation. For this reason, Kaloba® (EPs®7630) should not be administered during pregnancy and lactation without seeking medical advice.

Auto-immune diseases
Kaloba® (EPs®7630) has an immuno-modulating effect rather than an immuno-stimulating effect and it therefore boosts the immune system only in the event of infection. Consequently, there are no contra-indications on the use of Kaloba in patients with auto-immune diseases, although there have been no studies carried out to date in this patient group. Significantly, Kaloba can be used by asthmatics unlike Echinacea, which is contra-indicated for use in both asthmatics and patients suffering from auto-immune diseases.

Children under 6 years of age
Kaloba® (EPs®7630) is not approved in the UK for use in children under 6 years of age. However in Germany it is indicated from 1 year due to very good tolerability and proven efficacy. Kaloba® (EPs®7630) oral drops and syrup are indicated from 6 years onwards, and Kaloba® (EPs®7630) tablets from 12 years in the UK.

Alcoholics
Herbal remedies in liquid form such as Kaloba® (EPs®7630) Oral Solution, frequently contain alcohol. This is used as an extraction agent, natural stabilising agent and absorption-enhancing agent. The natural blood alcohol level in humans is 0.003%. This is only slightly changed by the intake of a small quantity of alcohol such as that contained in Kaloba® (EPs®7630) Oral Drops because these small quantities are metabolised very quickly after ingestion. Many foodstuffs consumed in normal quantities contain as much as or even more alcohol than that contained in a daily dose of Kaloba® (EPs®7630). Similarly, there is no risk to children. A glass of apple juice (0.2l) contains more than three times as much pure alcohol (0.76ml) than the maximum paediatric dose of 60 drops Kaloba® (EPs®7630). Regardless of this, the medicinal product can be administered in a small glass or warm tea or juice. A large proportion of the alcohol evaporates and the taste is also lost.

Drug interactions
No interactions with other medicinal products have been reported to date. However, in view of the theoretical effect of Kaloba® (EPs®7630) on coagulation parameters, enhancement of the effects of anticoagulant drugs such as phenprocoumon and warfarin (e.g. Marevan®) cannot be excluded when these are administered concomitantly with Kaloba® (EPs®7630).

Special patient groups and questions
Diabetics
Kaloba® (EPs®7630) oral drops, tablets and syrup are suitable for diabetics. The amount of sugar absorbed in the daily dose is clinically insignificant and need not be taken into account in any daily sugar intake calculation.

Coeliac disease
Kaloba® (EPs®7630) does not contain gluten and can be administered to patients with gluten-sensitive coeliac disease.
7. CORE SUMMARY OF PRODUCT CHARACTERISTICS

7.1 Kaloba® (EPs®7630) oral drops

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
10 g (= 9.75 mL) of oral solution contains 8.0 g extract from the roots of Pelargonium sidoides DC (1 : 8 - 10) (EPs® 7630).
Extraction solvent: 11% ethanol (w/w).

1 ml (approximately 20 drops) of Kaloba Oral Drops, solution contains 120 mg ethanol (alcohol) equivalent to 2.4 ml beer or 1.0 ml of wine.

CLINICAL PARTICULARS

Therapeutic indications

Traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only.

Posology and method of administration

Adults and adolescents over the age of 12:
Take 30 drops three times per day.

Children aged between 6-12 years:
Take 20 drops three times per day.

The necessary amount of drops may be taken directly from a spoon or, if preferred, can be mixed with half a glass of water and the contents of the entire glass should be drunk straightaway. The dose should be taken in the morning, at midday and in the evening.

20 drops is equivalent to approximately 1ml
30 drops is equivalent to approximately 1.5ml.

Duration of application

After relief of symptoms, continuation of treatment for further 2 – 3 days is recommended in order to prevent a relapse, however treatment duration should not exceed 2 weeks.

Contraindications

Kaloba is not to be used in the following cases:
• hypersensitivity to the active substance or to the excipient,
• increased tendency to bleeding and application of coagulation-inhibiting drugs,
• severe hepatic and renal diseases, as no adequate data are available in these areas,
• pregnancy and lactation
• children < 6 years.

Special warnings and precautions for use

In the package leaflet, the patient is advised to consult a doctor immediately if his or her condition does not improve within one week, in case of fever lasting for several days or in case of shortness of breath or bloody sputum.

Kaloba oral solution contains 12 vol % ethanol (alcohol).
This corresponds to:
• 180 mg alcohol equivalent to 3.6 ml beer or 1.5 ml wine per adults’ single dose (30 drops)
• 120 mg alcohol equivalent to 2.4 ml beer or 1.0 ml wine per children’s single dose (20 drops).

Harmful for those suffering from alcoholism. To be taken into account in children and high-risk groups such as patients with liver disease, or epilepsy.

Interaction with other medicinal products and other forms of interaction

Drug interactions have not been reported to date.

However, due to the potential influence of Kaloba on coagulation parameters, the possibility that this product enhances the effect of coagulation-inhibiting drugs such as warfarin in cases of simultaneous intake cannot be excluded.

Pregnancy and lactation

This product should not be used in women who are pregnant or breast-feeding, as there are no data available for these patient groups.

Effects on ability to drive and use machines

Kaloba has no or negligible influence on the ability to drive and use machines.
Undesirable effects

The evaluation of adverse reactions is based on the following information on frequency:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>more than 1 out of 10 treated persons</td>
</tr>
<tr>
<td>Common:</td>
<td>more than 1 out of 100 treated persons</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>more than 1 out of 1000 treated persons</td>
</tr>
<tr>
<td>Rare:</td>
<td>more than 1 out of 10 000 treated persons</td>
</tr>
<tr>
<td>Very rare:</td>
<td>1 or less out of 10 000 treated persons including single cases</td>
</tr>
</tbody>
</table>

Gastro-intestinal complaints such as stomach pain, heartburn, nausea or diarrhoea may occur uncommonly (≥ 1/1,000 to < 1/100) during treatment with Kaloba.

In rare cases (≥1/10,000 to ≤ 1/1,000), mild bleeding from the gingiva or nose may occur. Furthermore, hypersensitivity reactions (e.g. exanthema, urtica, prurius of skin and mucous membranes) have been described in rare cases. Such reactions may already occur at the first intake of the pharmaceutical product.

In very rare cases (≤ 1/10,000), serious hypersensitivity reactions with swelling of the face, dyspnea and drop of blood pressure may occur.

In single cases, signs indicating disturbances of liver function have been reported after intake of Kaloba; the causal relationship between this effect and the application of the product has not been demonstrated.

Overdose

The effects of overdose are unknown.

Although there are no data on cases of overdose, overdose is likely to increase side effects. Thus, treatment should be symptomatic and as clinically indicated.

PHARMACEUTICAL PARTICULARS

List of excipients

Glycerol 85%
Ethanol

7.2 Kaloba® (EPs®7630) tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 20 mg of extract (as dry extract) from the roots of Pelargonium sidoides DC (1 : 8 - 10) (EPs®7630)
Extraction solvent 11% ethanol (w/w).

CLINICAL PARTICULARS

Therapeutic indications

Traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including the common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only.

Posology and method of administration

Adults and adolescents over 12 years of age:
Take 1 tablet three times daily (morning, midday, evening).

Tablets should be swallowed whole with a little water. The tablets should not be chewed.

The use in children under 12 years of age is not recommended (see section 4.4 “Special warnings and precautions for use”).

Duration of use:

After relief of symptoms, continuation of treatment is recommended for a further 2 – 3 days in order to prevent a relapse. However, treatment duration should not exceed 2 weeks.

If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Contraindications

Kaloba is not to be used in the following cases:
• hypersensitivity to the active substance or to any of the excipients,
• increased tendency to bleeding,
• patients using coagulation-inhibiting drugs,
• severe hepatic and renal diseases, due to lack of adequate data.
Special warnings and special precautions for use

In the patient information leaflet, the patient is advised to consult a doctor immediately if his or her condition does not improve within one week, in case of fever lasting for several days or in case of shortness of breath or blood in the sputum.

One film-coated tablet contains 20 mg lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

On theoretical grounds Kaloba should not be used where there is a likelihood of increased tendency to bleeding or use of coagulation-inhibiting drugs.

Kaloba should not be used in case of severe hepatic and renal diseases, due to lack of adequate data.

This formulation is not suitable for children under 12 years of age.

Interaction with other medicinal products and other forms of interaction

Drug interactions have not been reported to date.

However, due to the potential effect of Kaloba on coagulation parameters, this product may enhance the effect of coagulation-inhibiting drugs such as warfarin and should not be taken concomitantly with these drugs.

Pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

Undesirable effects

The evaluation of adverse reactions is based on the following information on frequency:

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Gastro-intestinal complaints such as stomach pain, heartburn, nausea or diarrhoea may occur uncommonly (≥1/1,000 to < 1/100) during treatment with Kaloba.

In rare cases (≥1/10,000 to ≤1/1,000), mild bleeding from the gums or nose may occur. Furthermore, hypersensitivity reactions (e.g. exanthema, urticaria, pruritus of skin and mucous membranes) have been described in rare cases. Such reactions may occur after the first intake of the product.

In very rare cases (≤1/10,000), serious hypersensitivity reactions with swelling of the face, dyspnoea and drop in blood pressure may occur.

In single cases, signs indicating disturbances of liver function have been reported after intake of Kaloba; the causal relationship between this effect and the use of the product has not been demonstrated.

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

Overdose

The effects of overdose are unknown.

Although there are no data on cases of overdose, overdose is likely to increase side-effects. Thus, treatment should be symptomatic and as clinically indicated.

PHARMACEUTICAL PARTICULARS

List of excipients

Extract:
Maltodextrin
Children aged between 6-12 years:
Take 5 ml of the syrup three times per day.
Syrup is to be taken in the morning, midday and evening.

The use in children under 6 years of age is not recommended (see section 4.4 “Special warnings and precautions for use.”)

Duration of use
After relief of symptoms, continuation of treatment is recommended for a further 2 – 3 days in order to prevent a relapse. However, treatment duration should not exceed 2 weeks.

If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Contraindications
• hypersensitivity to the active substance or to any of the excipients
• increased tendency to bleeding
• patients using coagulation-inhibiting drugs
• evere hepatic and renal diseases due to lack of adequate data

Special warnings and special precautions for use
In the patient information leaflet, the patient is advised to consult a doctor immediately if his or her condition does not improve within one week, in case of fever lasting for several days or in case of shortness of breath or blood in the sputum.

On theoretical grounds Kaloba should not be used where there is a likelihood of increased tendency to bleeding or use of coagulation-inhibiting drugs.

Kaloba should not be used in case of severe hepatic and renal diseases, due to lack of adequate data.

The use of this product in children or adolescents under 6 years of age is not recommended because data are not sufficient and medical advice should be sought.

Interaction with other medicinal products and other forms of interaction
Drug interactions have not been reported to date.

However, due to the potential effect of Kaloba on coagulation parameters, this product may enhance the effect of coagulation-inhibiting drugs such as warfarin and should not be taken concomitantly with these drugs.
Pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data use during pregnancy and lactation is not recommended.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects

The evaluation of adverse reactions is based on the following information on frequency:

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Gastro-intestinal complaints such as stomach pain, heartburn, nausea or diarrhoea may occur uncommonly (≥1/1000 to <1/100) during treatment with Kaloba.

In rare cases (≥1/10,000 to ≤1/1000) mild bleeding from the gums or nose may occur. Furthermore, hypersensitivity reactions (e.g. exanthema, urticaria, pruritus of skin and mucous membranes) have been described in rare cases. Such reactions may occur after the first intake of the product.

In very rare cases (≤1/10,000) serious hypersensitivity reaction with swelling of the face, dyspnoea and drop in blood pressure may occur.

In single cases, signs indicating disturbances of liver function have been reported after the intake of Kaloba; the causal relationship between this effect and the use of the product has not been demonstrated.

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

Overdose

The effects of overdose are unknown.

Although there are no data on cases of overdose, overdose is likely to increase side-effects. Thus, treatment should be symptomatic and as clinically indicated.

PHARMACEUTICAL PARTICULARS

List of excipients

Extract: Maltodextrin

Syrup:
Xylitol
Glycerol 85%
Citric acid anhydrous
Potassium sorbate
Xanthan gum
Purified water
8. REFERENCES

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56. Koch, K. and Biber, A. Treatment of rats with the Pelargonium sidoides extract EPs® 7630 has no effect on blood coagulation parameters or on the pharmacokinetics of warfarin, Phytomedicine 2007; 14 (Suppl. VI): 40–45.

57. Dr. Willmar Schwabe Arzneimittel Karlsruhe, Präklinische Forschung, 2005: Cerep Study No. 9588.


MHRA Registration Number: THR 05332/0003
AVAILABLE AS:
- Kaloba (EPs®7630) Oral solution

MHRA Registration Number: THR 05332/0005
AVAILABLE AS:
- Kaloba (EPs®7630) film-coated tablets
- Higher Nature Pelargonium Cold Relief film-coated tablets
- Healthspan Pelargonium Cold Relief film-coated tablets

MHRA Registration Number: THR 05332/0006
AVAILABLE AS:
- Kaloba (EPs®7630) Syrup

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Part of the Taking Herbal Medicines Seriously series.