Myrtol standardized
A Clinical Documentation
The Author
Dr. med. Thomas Wittig was born in 1958.
He is an accredited specialist in general medicine
and author of several medical books.
Member of the "Deutsche Atemwegsliga",
Member of the board of the "International Society of Mucociliary Clearance e.V. (ISMCC)"
Thomas Wittig

Myrtol standardized
A Clinical Documentation

Ergebnisse Verlag
Scanning electron microscope
of a normal finding in the respiratory tract,
with kind permission of Prof. Dr. K. Morgenroth,
Ruhr-University, Bochum (Germany)
ISBN 3-87916-072-4
Contents

Foreword ........................................................................... 9

Introduction: Myrtol standardized ........................................ 11

1 Pharmacodynamics

1.1 Basics of mucociliary clearance

1.1.1 Histology ................................................................. 13
1.1.2 Respiratory secretion ................................................ 15
1.1.3 Physiology of mucociliary clearance ......................... 17
1.1.4 Physiology of cough clearance ................................. 19
1.1.5 Pathophysiology ...................................................... 20

1.2 Mucosecretolysis

1.2.1 Secretolytic effect: phenol red method of determination .......................... 22
1.2.2 M cosecretolytic action ............................................... 23

1.3 Mucolysis

1.3.1 Mucolytic effect: method of determination ................... 24
1.3.2 Mucolytic action ........................................................ 25

1.4 Secretomotor action ........................................................ 26

1.5 Actions on mucociliary clearance and cough clearance

1.5.1 Mucociliary and cough clearance .............................. 27
1.5.2 Mucociliary clearance in comparison with other substances .................. 28
1.5.3 Mucociliary clearance (sequential scintigraphy) ................. 29

1.6 Antioxidative actions

1.6.1 Pathomechanisms of inflammation ............................ 31
1.6.2 Oxidative stress: SIN system ....................................... 33
1.6.3 Oxidative stress: Fenton system .................................. 34
1.6.4 Antioxidative effect (SIN system) ............................... 35
1.6.5 Antioxidative effect (Fenton system) ........................... 36

1.7 Antiinflammatory actions

1.7.1 Pathobiochemistry of inflammation ........................... 37
1.7.2 Leucotrienes .............................................................. 39
1.7.3 Prostaglandins ............................................................ 40
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8 Antimicrobial action</td>
<td>42</td>
</tr>
<tr>
<td>1.9 Bronchospasmolytic effect</td>
<td>44</td>
</tr>
<tr>
<td>1.10 Overall pharmacodynamic profile</td>
<td>45</td>
</tr>
<tr>
<td>2 Pharmacokinetics</td>
<td>46</td>
</tr>
<tr>
<td>2.1 Studies on the bioavailability</td>
<td>47</td>
</tr>
<tr>
<td>2.2 Time courses of the plasma concentrations I</td>
<td>48</td>
</tr>
<tr>
<td>2.3 Time courses of the plasma concentrations II</td>
<td>49</td>
</tr>
<tr>
<td>2.4 Summary</td>
<td>50</td>
</tr>
<tr>
<td>2.5 Distribution (sputum investigations)</td>
<td>51</td>
</tr>
<tr>
<td>3 Indication fields</td>
<td>51</td>
</tr>
<tr>
<td>3.1 Acute Sinusitis</td>
<td>51</td>
</tr>
<tr>
<td>3.1.1 GCP-conforming, randomized, controlled, multicentre study</td>
<td>53</td>
</tr>
<tr>
<td>3.1.1.1 Study design</td>
<td>54</td>
</tr>
<tr>
<td>3.1.1.2 Symptom score</td>
<td>55</td>
</tr>
<tr>
<td>3.1.1.3 Symptom score: Improvements</td>
<td>56</td>
</tr>
<tr>
<td>3.1.1.4 Symptom improvement I</td>
<td>57</td>
</tr>
<tr>
<td>3.1.1.5 Symptom improvement II</td>
<td>58</td>
</tr>
<tr>
<td>3.1.1.6 Symptom improvement III</td>
<td>59</td>
</tr>
<tr>
<td>3.1.1.7 Symptom improvement IV</td>
<td>60</td>
</tr>
<tr>
<td>3.1.1.8 Use of antibiotics, incapacitation</td>
<td>61</td>
</tr>
<tr>
<td>3.1.1.9 Summary</td>
<td>61</td>
</tr>
<tr>
<td>3.1.2 Prospective comparative PMS study</td>
<td>62</td>
</tr>
<tr>
<td>3.1.2.1 Study design</td>
<td>63</td>
</tr>
<tr>
<td>3.1.2.2 Symptom improvement</td>
<td>64</td>
</tr>
<tr>
<td>3.1.2.3 Improvement in ultrasound findings</td>
<td>65</td>
</tr>
<tr>
<td>3.1.3 Open, clinical, single-centre study</td>
<td>66</td>
</tr>
<tr>
<td>3.1.3.1 Study design</td>
<td>67</td>
</tr>
<tr>
<td>3.1.3.2 Symptom improvement</td>
<td>68</td>
</tr>
<tr>
<td>3.1.3.3 Global assessment of efficacy</td>
<td>69</td>
</tr>
<tr>
<td>3.1.4 Post marketing surveillance study in children</td>
<td>70</td>
</tr>
<tr>
<td>3.1.4.1 Study design</td>
<td>71</td>
</tr>
<tr>
<td>3.1.4.2 Freedom from symptoms in children</td>
<td>72</td>
</tr>
<tr>
<td>3.1.4.3 Ease of taking capsules by children</td>
<td>73</td>
</tr>
<tr>
<td>3.1.5 Retrospective post marketing surveillance study in children</td>
<td>74</td>
</tr>
<tr>
<td>3.1.5.1 Study design</td>
<td>75</td>
</tr>
<tr>
<td>3.1.5.2 Freedom from symptoms in children</td>
<td>76</td>
</tr>
</tbody>
</table>

## 1.8 Antimicrobial action

## 1.9 Bronchospasmolytic effect

## 1.10 Overall pharmacodynamic profile

## 2 Pharmacokinetics

### 2.1 Studies on the bioavailability

### 2.2 Time courses of the plasma concentrations I

### 2.3 Time courses of the plasma concentrations II

### 2.4 Summary

### 2.5 Distribution (sputum investigations)

## 3 Indication fields

### Overview

### 3.1 Acute Sinusitis

#### 3.1.1 GCP-conforming, randomized, controlled, multicentre study

##### 3.1.1.1 Study design

##### 3.1.1.2 Symptom score

##### 3.1.1.3 Symptom score: Improvements

##### 3.1.1.4 Symptom improvement I

##### 3.1.1.5 Symptom improvement II

##### 3.1.1.6 Symptom improvement III

##### 3.1.1.7 Symptom improvement IV

##### 3.1.1.8 Use of antibiotics, incapacitation

##### 3.1.1.9 Summary

#### 3.1.2 Prospective comparative PMS study

##### 3.1.2.1 Study design

##### 3.1.2.2 Symptom improvement

##### 3.1.2.3 Improvement in ultrasound findings

#### 3.1.3 Open, clinical, single-centre study

##### 3.1.3.1 Study design

##### 3.1.3.2 Symptom improvement

##### 3.1.3.3 Global assessment of efficacy

#### 3.1.4 Post marketing surveillance study in children

##### 3.1.4.1 Study design

##### 3.1.4.2 Freedom from symptoms in children

##### 3.1.4.3 Ease of taking capsules by children

#### 3.1.5 Retrospective post marketing surveillance study in children

##### 3.1.5.1 Study design

##### 3.1.5.2 Freedom from symptoms in children
# Contents

3.2 Chronic sinusitis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1 Open, clinical, single-centre study</td>
<td></td>
</tr>
<tr>
<td>3.2.1.1 Study design</td>
<td>73</td>
</tr>
<tr>
<td>3.2.1.2 Global assessment of efficacy</td>
<td>74</td>
</tr>
<tr>
<td>3.2.1.3 Improvement in radiographic findings</td>
<td>76</td>
</tr>
<tr>
<td>3.2.2 Retrospective post marketing surveillance study in adults</td>
<td></td>
</tr>
<tr>
<td>3.2.2.1 Study design</td>
<td>77</td>
</tr>
<tr>
<td>3.2.2.2 Freedom from symptoms in adults</td>
<td>78</td>
</tr>
<tr>
<td>3.2.3 Retrospective post marketing surveillance study in children</td>
<td></td>
</tr>
<tr>
<td>3.2.3.1 Study design</td>
<td>79</td>
</tr>
<tr>
<td>3.2.3.2 Freedom from symptoms in children</td>
<td>80</td>
</tr>
</tbody>
</table>

3.3 Acute bronchitis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.1 GCP-conforming, randomized, controlled, multicentre study</td>
<td></td>
</tr>
<tr>
<td>3.3.1.1 Study design</td>
<td>81</td>
</tr>
<tr>
<td>3.3.1.2 Patient status at the start of the study</td>
<td>82</td>
</tr>
<tr>
<td>3.3.1.3 Non-responder rates</td>
<td>83</td>
</tr>
<tr>
<td>3.3.1.4 Non-responder rates after 1 and 2 weeks</td>
<td>84</td>
</tr>
<tr>
<td>3.3.1.5 Responder rates</td>
<td>85</td>
</tr>
<tr>
<td>3.3.1.6 Nocturnal coughing fits</td>
<td>86</td>
</tr>
<tr>
<td>3.3.1.7 Coughing fits during the day</td>
<td>87</td>
</tr>
<tr>
<td>3.3.1.8 Pathological auscultation findings</td>
<td>88</td>
</tr>
<tr>
<td>3.3.1.9 Global assessment of efficacy</td>
<td>89</td>
</tr>
<tr>
<td>3.3.1.10 Global assessment of tolerability</td>
<td>90</td>
</tr>
<tr>
<td>3.3.1.11 Summary</td>
<td>91</td>
</tr>
<tr>
<td>3.3.2 Retrospective post marketing surveillance study in children</td>
<td></td>
</tr>
<tr>
<td>3.3.2.1 Study design</td>
<td>92</td>
</tr>
<tr>
<td>3.3.2.2 Cough in children</td>
<td>93</td>
</tr>
<tr>
<td>3.3.2.3 Global evaluation in children</td>
<td>94</td>
</tr>
</tbody>
</table>

3.4 Chronic bronchitis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.1 GCP-conforming, randomized, controlled, multicentre study</td>
<td></td>
</tr>
<tr>
<td>3.4.1.1 Study design</td>
<td>95</td>
</tr>
<tr>
<td>3.4.1.2 Inclusion criteria</td>
<td>96</td>
</tr>
<tr>
<td>3.4.1.3 Acute exacerbation: definition</td>
<td>97</td>
</tr>
<tr>
<td>3.4.1.4 Exacerbation rates I</td>
<td>98</td>
</tr>
<tr>
<td>3.4.1.5 Exacerbation rates II</td>
<td>99</td>
</tr>
<tr>
<td>3.4.1.6 Exacerbation rates: Effect of centre</td>
<td>100</td>
</tr>
<tr>
<td>3.4.1.7 Antibiotic concomitant therapy</td>
<td>102</td>
</tr>
<tr>
<td>3.4.1.8 Summary</td>
<td>103</td>
</tr>
</tbody>
</table>
3.4.2 Randomized, controlled, single-centre study
   3.4.2.1 Study design ........................................................................ 104
   3.4.2.2 Cough .................................................................................. 105
   3.4.2.3 Dyspnea .............................................................................. 106
3.4.3 Retrospective post marketing surveillance study in children
   3.4.3.1 Study design ........................................................................ 107
   3.4.3.2 Cough in children .................................................................. 108
   3.4.3.3 Global evaluation in children .................................................. 109

4 Conclusion .................................................................................. 110

Acknowledgements ......................................................................... 112
The investigation of the mechanisms by which the airways and lungs are cleaned (mucociliary clearance, cough clearance, clearance by diffusion and macrophages) is methodologically time-consuming and is associated with a broad range for aetiopathogenic interpretation. The drug effects are not always simple to measure objectively in vivo.

To date an insufficient amount of research has been conducted on the pathogenesis as well as on the therapy of many diseases of the upper and lower airways associated with cough and disturbed mucociliary clearance (asthma, acute and chronic forms of bronchitis, cystic fibrosis, ciliary dyskinesia, sinusitis and rhinitis).

This book summarizes the methods for evaluation of mucoactive and antioxidatively acting substances, Myrtol standardized in particular. Oxidative "stress" is regarded as a major pathophysiological factor in many respiratory tract diseases (bronchitis, sinusitis, etc.) and lung diseases (emphysema, fibrosis).

The cellular defence mechanisms of leucocytes and macrophages require a lot of oxygen and result in increased ethylene formation, the detection of which makes it possible to confirm an antioxidative effect in vitro. Myrtol standardized, for example, considerably inhibits the formation of ethylene and leucotriene C4/D4/E4.

Furthermore, antimicrobial effects could be demonstrated in-vitro, as well as antiobstructive effects in the guinea pig model.

Finally, randomized, double-blind and placebo-controlled studies conducted in different sites and clinical conditions (acute and chronic sinusitis in children and adults) also demonstrate symptomatic and radiographic improvements according to the criteria for evidence-based medicine. In acute bronchitis, Myrtol standardized stands out as at least equivalent to administration of antibiotics (cefuroxime) and ambroxol, and markedly superior to placebo. The exacerbation rate and cough symptoms in children with infectious bronchitis can also be subsided significantly by Myrtol standardized. One important factor to note that here the tolerability of Myrtol standardized is comparable to that of placebo.
This clinical documentation is a book to be recommended and is a source of information for everyone involved in the investigation of mucoactive, antioxidative and antiinflammatory substances.

Prof. Dr. med. Heinrich Matthys
Head of the Department of Pneumology emeritus
University of Freiburg
Killianstraße 5
79106 Freiburg
Germany
The pharmacological profile of action of Myrtol standardized can be divided into three main sections: The pharmacodynamic profile of action, the pharmacokinetics and therapeutic use in humans within the claimed indications.

The pharmacodynamic profile of Myrtol standardized is classically characterized by mucosecretolytic properties, but based on extensive clinical research it is today supplemented by what are called its "additional effects". These additional effects include antinflammatory and antioxidative effects. The antioxidative effects are of particular clinical importance, as today these are regarded as the most important mode of action for explaining the efficacy in chronic forms. This interesting aspect of the pharmacodynamics of Myrtol standardized is documented in detail in this book.

Another major field of research was to characterize in-vivo pharmacokinetic properties of Myrtol standardized; this is rare with herbal medicines. Published data on the relative bioavailability of Myrtol standardized are also presented.
As far as the indications "acute and chronic bronchitis and sinusitis" are concerned, it should be stressed that the company G. Pohl-Boskamp GmbH & Co. KG has more than 10 years – i.e., practically with the introduction of GCP guidelines – placed considerable emphasis on investigating the therapeutic use of Gelomyrtol® and Gelomyrtol® forte in clinical studies (randomized, controlled, multicentre studies) which were performed according to the international GCP standard ("Good Clinical Practice") in order to demonstrate the efficacy, safety and tolerability according to the principles of evidence-based medicine. The clinically relevant results are presented in detail in this book.

Myrtol standardized is available as enteric-coated capsules in two dosage forms containing 300 mg Myrtol standardized (trade name in Germany: GeloMyrtol® forte) or 120 mg Myrtol standardized (trade name in Germany: GeloMyrtol®).

The capsules are available in several European and non-European countries for the treatment of inflammatory respiratory tract diseases for many years. In The Netherlands, for example, they are registered as Gelodurat® containing 300 mg Myrtol standardized.
In humans, the mucous membranes of the nose, the paranasal cavities (including the paranasal sinuses, the Eustachian tube and parts of the middle ear), the nasopharynx, the larynx and the lower airways as far as the terminal bronchioles are covered with respiratory epithelium\cite{1, 2}. This respiratory epithelium has the task of protecting the airways against external influences, and its surface is made up of three types of cells; ciliated columnar cells (= ciliated epithelium), brush border cells and goblet cells\cite{3}. These cells sit directly on a basement membrane which separates them from the underlying connective tissue (lamina propria).

Other functionally important parts include the seromucous glands, which play an important role in the formation of the respiratory secretion, and the two-layered secretion itself.

It is believed that the nasal and paranasal cavities contain about 450 cm\(^2\) of respiratory epithelium, and the tracheobronchial tree about 5,000 cm\(^2\) with on average 6 to 8 cilia per µm\(^2\) (10\(^9\) cilia per cm\(^2\))\cite{3}.

The ciliated epithelial cells are the most abundant cells of the respiratory epithelium\cite{2, 4}, and have an estimated life-time of about 4 weeks\cite{5}. The particular characteristic of ciliated epithelial cells is that they possess 50 to 300 cilia (kinocilia) per cell\cite{1, 2}. The cilia are 3 – 8 µm in length and have a diameter of between 0.1 and 0.3 µm\cite{2}.
Interspersed between the ciliated epithelial cells are the brush border cells (not shown above)\textsuperscript{3}, which have 200 – 400 microvilli on their luminal surface and play a major role in the regulation of the ion- and water content of the periciliar fluid and thus in the volume of secretion\textsuperscript{6}.

Goblet cells are modified columnar epithelial cells that synthesize and secret the viscous secretion\textsuperscript{3}.

The seromucous glands are present as tubuloalveolar glands in the lamina propria\textsuperscript{1}. The number of these gland cells in the normal upper airways, in the trachea and in the cartilaginous bronchi is 40 times the number of goblet cells\textsuperscript{7}. 

\begin{flushleft}
\textsuperscript{1} Wittig Th & Huzel B, Mikroskopische Anatomie, Urban & Fischer Verlag 1992
\textsuperscript{2} Deitmer Th, Physiology and Pathology of the Mucociliary System, in: Pfaltz CR (Ed.), Advances in Oto-Rhino-Laryngology, Karger 1989, pp. 4 – 18
\textsuperscript{3} Riechelmann H, Experimentelle und klinische Untersuchungen des mukoziliären Transportsystems der Atemwege, Habilitationsschrift, Universität Ulm 1997, 1 – 125
\textsuperscript{5} Herzon FS, Laryngoscope (1983) 93: 63 – 66
\textsuperscript{7} Kaliner MA et al., Respiratory mucus, in: Kaliner MA & Barnes PJ (Eds.), The airways, Marcel Dekker, Inc., New York, 1988
\end{flushleft}
1 Pharmacodynamics

1.1 Basics of mucociliary clearance

1.1.2 Respiratory secretion

The mucociliary apparatus of the respiratory epithelium, with kind permission of Prof. Dr. H. Behrbohm[7].

The driving force behind the transport of secretion is the metachronous (time shift) cilial beat of the respiratory epithelium[1]. The respiratory epithelium is covered with a layer of secretion about 8–12 µm thick[1]. It is made up of two layers: a low-viscosity basal periciliar liquid (sol phase) and a highly viscous upper layer of mucus (gel phase).

The mucociliary apparatus is a complex system that includes a motor (cilial apparatus), a transmission system (sol phase), a lubricant (surfactant), and a conveyor belt (gel phase)[2].

The cilia beat with an average frequency of 5–15 hertz[2] and an amplitude of 5 µm, resulting in a mucus transport speed in the trachea of 0.3–2 cm/min[3]. The effective forwards stroke with angled cilia lasts about one third of the beat. After this phase, the cilium collapses and then slowly moves backwards. This makes the liquid particles in the low-viscosity sol phase move in a circular motion, which then is presumed to drive the overlying gel phase[4]. In addition, the cilial tips can also during the effective part of the beat penetrate into the high-viscosity gel phase and displace it[1].
Between the sol phase and the gel phase there is an increased amount of surfactant, which presumably has been transported from the lung periphery towards the mouth[5]. This surfactant reduces the viscosity of the periciliar fluid and reduces the friction losses during the cilial beat[2]. As the cilia of neighbouring cells beat metachronously (time shift) in the direction of the pharynx, the result is transport of the superficial mucous layer towards the pharynx[3]. This means that in the nose and the nasal and throat spaces, the cilial beat is directed backwards, in the paranasal cavities it is always directed to the ostia, and in the trachea and bronchi it is directed cranially[6]. These biological cleaning processes are grouped together under the heading "mucociliary clearance".

1 Riechelmann H, Experimentelle und klinische Untersuchungen des mukoziliären Transportsystems der Atemwege, Habilitationsschrift, Universität Ulm 1997, 1 – 125
7 Behrbohm H, Kascchke O, Nawka T (Hrsg.), Endoskopische Diagnostik und Therapie in der HNO, Urban & Fischer 1997
Mucociliary clearance is the main mechanism of clearance for insoluble particles in the airways (appr. down to the 16th bronchial generation)\(^1\). In the case of disorders of the mucociliary clearance, coughing becomes the replacement clearing mechanism\(^1\). The main mechanism for clearing insoluble particles in the periphery is phagocytosis by macrophages\(^1\).

As a rule, the half-life of mucociliary clearance of insoluble particles is of the order of hours to days in the bronchial tree and several hundred days in the alveoli\(^1\).

All the data show that the mucociliary clearance in the lower airways decreases from centrally to peripherally. This is accompanied by a microanatomically detectable reduction in cilia length, the number of ciliated cells in the bronchial epithelium, and the amount of mucus. The rate of mucus transport has been measured to be a maximum of 20 mm/min in the central bronchial system, about 1 mm/min in the smaller airways (diameter 1–2 mm)\(^1, 3\), and between 1 and 10 mm/hour in the nasal cavity and nasal sinuses\(^8\).

In healthy subjects, the mucociliary clearance shows a mild to moderate reduction with age (about parallel with the vital capacity), although there is no sex-related difference\(^1\). The direction of mucociliary transport is independent of body position\(^3\).

The respiratory epithelium is covered with a layer of secretion about 8 to 12 µm in thickness\(^4\). It consists of two layers: a surface high-viscosity gel phase (layer of mucus) with a high proportion of linked glycoproteins, and an underlying low-viscosity periciliar fluid (sol phase)\(^4\). The respiratory mucus is formed mainly by the (submucosal) seromucous glands and the goblet cells (sputum is a mixture of mucus and inflammatory cells, cell components, bacteria and a salivary fraction, and is transported by coughing)\(^2, 5\).

There is evidence that the mucus becomes increasingly inhomogeneous as the bronchial tree subdivides into the periphery, so that eventually it is present rather like ”water-lilies“ and floats on the periciliar fluid\(^1\).

The amount of mucus produced each day in healthy adults is estimated to be 4 to 10 ml\(^1\), although some authors have published estimates of 10 to 600 ml and it is assumed to be the true amount to be 100 ml/24 hours\(^1\). There are no exact details of the physiological amount of secretion formed in the paranasal cavities\(^6\), although a daily mucus production of 20 – 40 ml is generally assumed\(^7, 8\).

The periciliar fluid (sol phase) is regulated by transepithelial water and ion transport\(^5\). The depth of the periciliar sol layer plays a key role in the efficiency of the cilial beat\(^6\). An increase in periciliar fluid results in a decrease in secretion viscoelasticity. If the height of the periciliar fluid exceeds
the length of the cilia, there is a reduction in secretion transport, the cilia can get no longer grip in the layer of mucus and they beat ineffectively\[9,10\], and there is a mechanical uncoupling of the cilia and secretion\[4\]. In addition, the viscoelastic properties of the secretion also determine the secretion transport. If the cilial beat frequency remains unchanged, the secretion transport rate rises with increasing elasticity and decreasing viscosity (flow resistance)\[4\].

---

1. **Pharmacodynamics**

1.1 **Basics of mucociliary clearance**

1.1.3 **Physiology of mucociliary clearance**

---

4. Riechelmann H, Experimentelle und klinische Untersuchungen des mukoziliären Transportsystems der Atemwege, Habilitationsschrift, Universität Ulm 1997, 1 – 125
Clearance by coughing is a second line of defence of the lungs, and takes over clearance of the respiratory tract in the event that the lungs are overloaded or the mucociliary clearance is inadequate\[^1\].

In healthy subjects, coughing is used only for the removal of inhaled or aspirated foreign bodies\[^2\]. The mucus transport is not affected as the layer of mucus is very thin\[^2\].

The average mucus transport speed in the trachea is about 0.3 – 2 cm/min, although the speed (frequency x amplitude) on coughing is about 100 times greater\[^1\].

In order for cough clearance to be effective, the mucus must possess certain properties: These are mucoviscosity, elasticity, and adhesivity. Mucoviscosity (flow resistance) is the most important of these variables that affects cough clearance. The elasticity place a role here in a ”recoil“ effect. A high spinning performance or a low viscosity-to-elasticity ratio inhibit cough clearance, as do also the high adhesivity or surface tension\[^1\]. In addition the secretion must be of a certain thickness so that the forces are able to tear it away from the bronchial wall\[^2\]. It thus appears teleologically rational that in the case of disorders of the mucociliary clearance, hypertrophy and hyperplasia of the goblet cells with increased mucus production develops, as otherwise cough clearance cannot work effectively\[^2\]. Pharmacotherapeutically induced mucosecretolysis accordingly facilitates expectoration.

---

In acute usually virus related bronchitis, there is often paralysis of the ciliary epithelium, sometimes with complete shedding\textsuperscript{[1]}. Usually, the ciliary apparatus recovers within a few days. In the event of shedding, the regrowth usually takes one to two weeks, although in a few cases (especially in mycoplasmas), the regeneration can require many months\textsuperscript{[1, 2]}. Sometimes, regeneration does not occur, and chronic bronchitis results\textsuperscript{[1]}. In chronic bronchitis there is usually a reduction in mucociliary clearance, and the differences between the central and peripheral clearance rate is partly abolished or even reversed\textsuperscript{[1]}. In the sinusitis, we find inflammation of the mucosa within closer, sometimes more complicated anatomical structures\textsuperscript{[3]}. The result of this mucosal inflammation is a disturbance in the equilibrium between the production of secretion in the goblet cells and seromucous glands and the removal of the secretion by the ciliated epithelium. This can result in impairment of the mucociliary clearance\textsuperscript{[3]}. A circulus vitiosus then starts: the closure or constriction of the ostia leads to reduction in ventilation and drainage, which in turn leads to retention of secretion. This causes changes to the composition and pH of the secretion, which has a detrimental effect on the gas metabolism of the mucosa. As a result of this, damage to the ciliary epithelium occurs. At the same time, the li-
The consequences of impaired mucociliary clearance are a raised susceptibility to viral and bacterial inflammations and a raised bacterial colonization of the airways\[5\]. In disturbances of secretion transport, the dwelling time of toxic substances in the airways increases\[6\], and this possibly favours the malignant transformation of the mucosa of the airways\[5,7\].
The principle of this test is based on the determination of the tracheal secretion of phenol red, a colour indicator of mucosal tracheal secretion. Mucosecretolytic substances induce an increase in the tracheal secretion of phenol red in mice\(^1\).

**Method:** Oral administration of 300 mg/kg bodyweight of Myrtol standardized by gavage followed 30 minutes later by intraperitoneal (i.p.) administration of 500 mg/kg of phenol red. After a further 30 minutes, extraction of the trachea and immersion in physiological saline solution. Removal of the trachea after 24 hours, followed by spectrophotometric determination of the phenol red concentration in the solution. The higher the phenol red concentration in the solution, the greater the secretolytic effect.

The percentage difference in the phenol red concentration after oral administration of Myrtol standardized in comparison with the values after administration of a control is a measure of the mucosecretolytic effect of Gelomyrtol® forte.

---

1 Pharmacodynamics

1.2 Mucosecretolysis

1.2.2 Mucosecretolytic action

Investigations on the relations between the active substance dosage and the secretolytic effect are a rarity in mucoactive herbal medicines.

Animal experiments on the dose-response relations are available for Myrtol standardized. The investigations on mice (n = 12 per group) document a dosage-linear secretolytic effect after oral administration of Myrtol standardized.

Under the same methodological animal experimental approach (phenol red method), the secretolytic effect of Myrtol standardized in comparison with pure eucalyptus oil was determined. It was found that the Myrtol standardized group showed a significant increase in secretolysis (+32% vs. controls (= blank value); p < 0.05), and this increase was markedly greater than that achieved with a pure eucalyptus oil preparation (+21% vs. controls; not significant). This also means that Myrtol standardized is superior to a pure eucalyptus oil product with regard to the secretolytic effect.

1 Champeroux P & Maurin A, Centre de Recherches Biologiques (France), Myrtol standardisiert Dokumentation 1996

Method:
Obtaining secretion: Sputum samples were obtained from patients with chronic bronchitis (or cystic fibrosis) by expectoration.

Rheological method:
A sample of about 4 µl of mucus is placed directly into the measurement chamber of the magnetic microrheometer\textsuperscript{[1–3]} and the baseline value of the viscoelasticity is measured. Then, 15 µl of Myrtol standardized is pipetted directly into the sample chamber, and the rheological clearance parameters are measured again. The indices for the mucociliary clearance (MCI) and cough clearance (CCI) are determined according to a formula validated by investigations using the model of the frog palette. More detailed descriptions are contained in the literature below\textsuperscript{[1–3]}.

\begin{enumerate}
\item App EM, Atemw.-Lungenkrkh. (1994) 20: 363 – 371
\item King M, in Braga PC & Allegra, Methods in Bronchial Mucology, Raven Press 1988, pp. 73 – 83
\end{enumerate}
In order to determine the mucolytic effect of Myrtol standardized, sputum samples of patients with bronchial asthma, chronic bronchitis and cystic fibrosis were investigated in vitro. Examination of the sputum samples in comparison with controls showed a marked reduction in the mucus consistency after addition of Myrtol standardized.

Overall, the changes in viscoelasticity with Myrtol standardized of -13.8 %, -10.6 % and -16.0 % for chronic bronchitis, bronchial asthma and cystic fibrosis respectively found relative to baseline in this investigation are comparable to those demonstrated with N-acetylcysteine by the same research group[1, 2].

The Principal Investigator[1] summarizes that the therapeutic efficacy of Myrtol standardized in absolute terms is in the same range as that of N-acetylcysteine. This confirms not just the secreto-lytic and secretomotor effects for Gelomyrtol® forte but also a mucolytic quality.

---

In a study under controlled conditions, the team of Ass. Prof. Dr. H. Lenders of the ENT Department of the University Ulm investigated the pharmacodynamic properties of Gelomyrtol® forte in 12 patients with chronic sinusitis\(^1,2\).

Objective parameters: ciliary beat frequency. Method: curettage of mucosal skin samples, immediate video documentation in a phase-contrast microscope.

Subjective parameters: Saccharin test. Method: dropwise addition of saccharin solution on the head of the lower nasal concha and recording the time until a sweet taste is perceived.

As described earlier, secretomotor effects for Myrtol standardized could be confirmed: Myrtol standardized increased the ciliary beat frequency by a factor of 2 relative to placebo and shortened the transit time in the saccharin test by more than 5 minutes. Placebo showed no changes in this test.

According to literature data, normal values for transit time in the saccharin test show a relatively large range. In most publications, they range from 5 to 20 minutes\(^3,4\), so that the shortening in transit time in the saccharin test described here can be regarded as very definitely substantial.

---

1 Lenders H et al., Suitability of various methods as pharmacodynamic models for the investigation of the efficacy of mucolytic agents on the maxillary sinus, Naunyn-Schmiederberg’s Arch. Pharmacol. (1996) 353 (Suppl.) R151
2 Lenders H, Pharmakodynamische Nachweismethoden zur Wirkung von ätherischen Ölen am oberen Respirationstrakt, in Mees K, Die unspezifische Rhino-Sinusitis, Springer Verlag, 1. edition 1996, 40 – 51
3 Deitmer Th, Physiology and Pathology of the Mucociliary System, in: Pfältz CR (Ed.), Advances in Oto-Rhino-Laryngology, Karger 1989, pp. 4 – 18
The microrheological results of the research team led by Dr. App of the Cystic Fibrosis Centre of the University Freiburg demonstrated, for the first time in objective analyses with standardized analysis, a reduction in the viscoelasticity parameters under treatment with Myrtol standardized in patients with chronic bronchitis, bronchial asthma and cystic fibrosis. The rheological changes resulted in substantial increases in the calculated clearance parameters for mucociliary clearance and cough clearance in comparison with the values of a control for all the investigated patient sputum samples[1].

Accordingly – as presented above – a significant improvement in mucociliary clearance by up to 30 % and in cough clearance by up to 100 % could be observed in cystic fibrosis patients. For cystic fibrosis, improvement in cough clearance is much more important than improvement in mucociliary clearance, as an insufficient cough clearance has been described as a critical underlying pathophysiological factor for the prognosis of this disease[1]. For chronic bronchitis, this situation is similar but less dramatic, although in this chronic condition also, cough clearance must compensate for the impaired mucociliary clearance.

---

In cooperation with the research group of the Cystic Fibrosis Centre of the University Freiburg, the question of the improvement in mucociliary clearance in comparison with other mucosecretolytics was also investigated[1].

To do this, sputum samples of patients with chronic bronchitis were analysed. These microrheological investigations revealed a substantial improvement in the mucociliary clearance under Myrtol standardized, and this improvement was statistically significantly (p < 0.05) greater than that of other mucosecretolytics[1].
1 Pharmacodynamics

1.5 Actions on mucociliary clearance and cough clearance

1.5.3 Mucociliary clearance (sequential scintigraphy)

A research team led by Prof. Dr. Behrbohm and Prof. Dr. Kaschke from Berlin investigated five healthy test subjects using nuclear medicine techniques in order to demonstrate the pharmacodynamically secretolytic actions of Myrtol standardized and thus the effect on the mucociliary apparatus\textsuperscript{[1, 2]}. 

1) Minute 1 - 2, before Gelomyrtol\textsuperscript{®} forte
2) Minute 8 - 9, before Gelomyrtol\textsuperscript{®} forte
3) Minute 1 - 2, after Gelomyrtol\textsuperscript{®} forte
4) Minute 8 - 9, after Gelomyrtol\textsuperscript{®} forte
As part of this investigation, two sequential scintigraphic function investigations were performed with 99m-technetium sulphur colloid as the radiolabelled drug. The first scintigraphic investigation was performed before taking Myrtol standardized, and the second was performed after taking Gelomyrtol® forte at a dosage of 3 x 1 capsule daily for 4 days. The above pictures demonstrate nuclear medical findings of the mucociliary clearance of the maxillary sinus during the first (without Gelomyrtol® forte) and the second (after taking Gelomyrtol® forte) scintigraphic function study. Each picture always superimposes the scintigrams of the specified time interval. Figure 1 shows the sequential scintigram in the first to second minute before taking Gelomyrtol® forte, and shows slow removal of the radiolabelled drug from the base of the maxillary sinus. Figure 2 shows the sequential scintigram in the eighth to ninth minute before administration of Gelomyrtol® forte. After eight minutes the radiolabelled drug is transported away via the lateral maxillary sinus wall. Figure 3 shows the sequential scintigram in the first to second minute after taking Gelomyrtol® forte. In comparison with Figure 1, a more rapid removal of the radiolabelled drug via the secretion route of the lateral and medial wall can be seen here. Figure 4 shows the sequential scintigram of the eighth to ninth minute also after taking Gelomyrtol® forte, and in comparison with Figure 2 shows the markedly more rapid secretion transport via the lateral wall. Also, in the right top, the radiolabelled drug has already passed the ostium, and according to the authors\textsuperscript{[1, 2]} this takes place a full 10 minutes earlier than in the function study without Gelomyrtol® forte.

1 Pharmacodynamics
1.6 Antioxidative actions
1.6.1 Pathomechanisms of inflammation

Many acute and chronic inflammatory airways diseases such as sinusitis and bronchitis are due partly to the formation of a reactive species of oxygen called oxygen radicals, which can effect all types of tissues. Irritant gases such as nitric oxide (NO), airborne particles such as soot or pollen, and infectious agents such as bacteria or viruses can lead to increased formation of radicals in the bronchial system\cite{1, 2, 3}.

Such inflammation reactions are usually largely triggered by activated white blood cells (leucocytes). These activated leucocytes form both superoxide $O_2^-$ and NO. These two radicals react with each other very rapidly to form peroxynitrite, which in turn disintegrates with formation of OH radicals. These aggressive oxidants (= radicals) can damage alveolar structures (= oxidative stress)\cite{1, 2, 3}.

Simulation of this pathophysiological situation in oxidative stress allows reactions to be recreated in vitro (the "SIN system" and the "Fenton System"). These in-vitro model reactions are suitable to estimate the toxicological consequences of oxygen radicals. They already have an established place in environmental medicine, as they have been proven to be a rational supplement to the conventional toxicological investigations on the problems of environmentally burdening compounds (asbestos fibres, soot particles, exhaust gas condensate of OTTO and Diesel engines with and without catalysts, alone or in combination with other air pollutants)\cite{2, 3}. 
Such model reactions also allow pathological situations to be simulated, and the potential (antioxidative) effectiveness of, for example, mucopharmaceuticals to be checked\cite{2, 3}.

1 Pharmacodynamics

1.6 Antioxidative actions

1.6.2 Oxidative stress: SIN system

Oxidative stress plays a leading role in the pathomechanisms of many acute and chronic inflammatory airways diseases. Established in-vitro model reactions which can simulate pathological situations are known from environmental medicine, and these also allow the potential (antioxidative) effectiveness of, for example, mucopharmaceuticals to be checked\cite{1–3}. One of these model reactions is called the "SIN system". The term SIN here stands for the substance 3-morpholinosydnonimine, an NO donor which allows formation of radical superoxide and NO from activated leucocytes to be simulated in vitro. It is known that the oxygen radicals can cleave, for example, alpha-keto-S-methyl-butyric acid, a metabolite of the essential amino acid methionine (=building block for structural proteins such as in cell migration). This is called KMB cleavage. This yields ethylene and other substances, and the ethylene is then able to be detected by gas chromatography. Inhibition of the ethylene formation indicates an antioxidative action of the substance being tested.

---

3 Elstner EF, Der Sauerstoff, Wissenschaftsverlag, 1. edition 1990, 479
Pharmacodynamics

1 Pharmacodynamics
1.6 Antioxidative actions
1.6.3 Oxidative stress: Fenton system

The Fenton system is another in-vitro model reaction that can determine the antioxidative properties of mucopharmaceuticals.

Background: The cells of our body must constantly defend themselves against foreign substances and organisms. The sentries of this protective system are the leucocytes. If a leucocyte comes into contact with, for example, bacteria, then certain enzyme systems in the cell membrane of the immune cell are activated, and these then synthesize large amounts of superoxide, radicals and nitrogen oxides. During this phagocytosis, the leucocyte temporarily consumes a large amount of oxygen. This is required for the oxygen activation and the synthesis of hydrogen peroxide (H₂O₂) and other oxidants (= respiratory burst)[1–3].

Principle: The Fenton reaction describes the radical formation of the OH type by a ferrum-mediated interaction of superoxide and hydrogen peroxide in inflamed tissue, and can be simulated in vitro. The formed hydroxy radicals can be determined indirectly by gas chromatography because of the previously described KMB cleavage with subsequent ethylene production. Here again the inhibition of the ethylene formation is an expression of an antioxidative effect.

3 Elstner EF, Der Sauerstoff, Wissenschaftsverlag, 1. edition 1990, 479
1 Pharmacodynamics
1.6 Antioxidative actions
1.6.4 Antioxidative effect (SIN system)

The investigations of antioxidative effects of Myrtol standardized were conducted under the direction of Prof. Dr. Elstner, Holder of the Chair for Phytopathology at the Technical University of Munich\[1, 2\]. As demonstrated above, Myrtol standardized inhibits ethylene formation in the SIN system by more than half (53 ± 2%) and is markedly stronger than pure 1.8-cineole (21 ± 2%). Myrtol standardized acts in the inflammatory processes by capturing the most aggressive oxygen radicals of the OH type (hydroxy radicals) and choking the leucocyte activation. These reactions are presumably lipophilic interactions with the leucocyte membranes in which the signal transfer is extensively changed so that hyperactivation is prevented. Oxidative cell damage is thus corrected.

Antioxidative effects have for a long time been of particular interest in scientific discussions, as the associated protection against oxidative stress is a central explanation for the efficacy of mucopharmaceuticals in the treatment concept of chronic diseases of the respiratory tract\[3–7\].

---

1 Pharmacodynamics
1.6 Antioxidative actions
1.6.5 Antioxidative effect (Fenton system)

The antioxidative properties of Myrtol standardized have also been checked in the Fenton system\(^1,\,2\).

The Fenton reaction describes radical formation of the OH type by ferrum-mediated interaction of superoxide and hydrogen peroxide in inflamed tissue.

In the Fenton system, Myrtol standardized also inhibits the ethylene formation (82 ± 2% vs. 0.0% in the controls) as an expression of pronounced antioxidative properties and thus confirms the results already presented for the SIN system. Conversely, it can be seen that the antioxidative properties of Myrtol standardized described in the SIN system can be reproduced in another valid system, namely, the Fenton system.

For details of the clinical relevance of antioxidative properties of mucopharmaceuticals, please refer to the previous pages.

---

The morphological substrate of acute and chronic bronchitis as well as bronchial asthma is essentially inflammation of the bronchial mucosa. The development of this inflammation involves numerous mediators, mainly mast cells but also other inflammatory cells such as eosinophils, neutrophils and monocytes.

Mediators are biological effector molecules that react with specific receptors on organs or target cells (such as bronchial mucosa or musculature).

Inflammatory cells such as eosinophils, neutrophils and monocytes contain a wide range of mediates, most of which are lipid mediators. These are formed as metabolites from the membrane phospholipids of the cells concerned\(^1,2\).

Some of the most potent mediators in inflammatory airways diseases (and in particular in asthma) are formed during the metabolism of arachidonic acid to leucotrienes by 5-lipoxygenase. The biological activity of the leucotrienes is based on a mixture of the three cysteinyl leucotrienes LTC\(_4\), LTD\(_4\) and LTE\(_4\)\(^1\).
As part of the pathogenesis of chronic obstructive bronchitis of up to bronchial asthma in severity, the mediators (leucotrienes) released from the inflammatory cells are significant for several cell organs: Their action on the smooth bronchial musculature results in bronchoconstriction, they cause mucosal oedema, stimulate the secretion of mucus by the mucous glands and goblet cells, and at the same time paralyse the mucociliary clearance\(^{[1, 2]}\).

All these mechanisms result in a functional airways obstruction and are involved in many different ways in the pathogenesis of bronchial hyperreactivity.

---

1 Pharmacodynamics
1.7 Antiinflammatory actions
1.7.2 Leucotrienes

In this investigation, a research team led by Prof. Dr. Kietzmann of Hannover investigated the question as to whether Myrtol standardized has any effect on the leucotrienes and thus exhibits antiinflammatory properties[1].

Experimental model: Arachidonic model (mouse ear model according to Opas et al.[2])

Method: Oral administration of Myrtol standardized by gavage, followed 1 hour later by generation of inflammatory ear oedema by topical application of 1 mg of arachidonic acid. Determination of the concentration of leucotrienes C4/D4/E4 in the ear skin.

Result: The oral administration of Myrtol standardized results in a dose-dependent reduction in the leucotriene concentration (LTC4/D4/E4), with the highest dose of 900 mg/kg exerting a statistically significant effect. The pharmacodynamic profile of Myrtol standardized is extended by this information on its antiinflammatory properties.

![Effect on the concentration of leucotrienes](image)

In this investigation, a research group led by Prof. Dr. Kietzmann of Hannover investigated the question as to whether Myrtol standardized has any effect on inflammatory processes induced by TPA on isolated perfused bovine udder and thus shows antiinflammatory actions\[1\].

Experimental model:
Isolated perfused bovine udder\[2, 3\]

Method:
Perfusion of Tyrode solution with (A) Myrtol standardized (12.5 mg/l, dissolved in 1.25 ml of cremophor EL) or (B) cremophor EL alone (= vehicle solution). Measurement of the concentration of prostaglandin E2 (PGE2) in the perfusate. Followed, after half an hour, by infusion of TPA (tetradecanolylphorbol-13-acetate) for the experimental induction of inflammation in the mucosae of the teat cisterns. Simultaneous repeated measurement of the PGE2 concentration for (C) Myrtol standardized + TPA and (D) cremophor EL (= vehicle solution) + TPA.

Result:
The rise in the concentration of prostaglandin E2 was significantly weaker in the udder halves perfused with (C) Myrtol standardized than with (D) cremophor EL (p < 0.05). Comparison of the values of (A) and (C) showed only a minimal rise in the prostaglandin E2 concentration, whereas the comparison of (B) and (D) showed the expected marked rise in PGE2. This marked reduction in the rise in PGE2 induced by an inflammatory stimulus (TPA application) confirms antiinflammatory properties of Myrtol standardized.
Previously the research group led by Prof. Dr. Kietzmann had already been able to impressively demonstrate the reduction in the leucotriene concentration (LTC4/D4/E4) using the arachidonic acid model\cite{1}. In supplementary investigations on basophilic leukaemia cells in rats, it could also be shown that Myrtol standardized inhibits 5-lipoxygenase, another key enzyme in the inflammatory cascade\cite{1}. These inhibitory effects on fundamental key areas of the inflammatory cascade characterize the pronounced antiinflammatory properties of Myrtol standardized.
Most acute infections of the upper and lower respiratory tract are caused by viruses[1]. Disturbances of the mucociliary clearance, especially persistent mucostasis, increases the risk of bacterial colonization of the airways. The aetiologically most important bacteria in acute bronchitis are Streptococcus pneumoniae (pneumococci) and Haemophilus influenzae[1]. In acute episodes of chronic bronchitis (exacerbations), bacteria can be demonstrated in over 80 % of cases, and the dominant organisms are again Streptococcus pneumoniae and Haemophilus influenzae[1,2]. These two pathogens are also the most common in acute non-nosocomial bacterial sinusitis[3]. In Europe, fungally caused forms of bronchitis (primarily Candida albicans, and more rarely also Aspergillus species) play a role only in immunosuppressed patients[4]. Myrtol standardized has been tested in the concentration range from 5 – 0.039 % V/V on the above microbial spectrum[5]. Under these conditions, Myrtol standardized shows dose-dependent inhibition of all the organisms with the exception of Pseudomonas aeruginosa. One note-
worthy finding is that Myrtol standardized showed the most extensive antimicrobial actions against those organisms that are most commonly involved in acute infections diseases of the upper and lower airways.

A research group led by Prof. Dr. E. Stahl-Biskup, University Hamburg, confirmed in in-vitro investigations bacteriostatic properties for Myrtol standardized[6].

Antimicrobial actions can be confirmed for Myrtol standardized, and these are most pronounced with the bacterial pathogens that are most relevant for respiratory tract infections.

1 Pharmacodynamics
1.8 Antimicrobial action

4 Eller JM et al., in: Konietzko N, Bronchitis, Urban & Schwarzenberg 1995
5 Bomblies L & Sonnenschein R, Myrtol standardisiert: Ermittlung der „Minimalen Hemmkonzentration“ (MHK) mit verschiedenen Testkeimen. Labor L+S AG, Myrtol standardisiert Dokumentation 1996
Method: Oral administration of 300 mg/kg Myrtol standardized or control by gavage to guinea pigs, followed after one hour by intravenous administration of increasing doses of histamine (1 µg/kg, 10 µg/kg) and determination of the airways resistance\(^1\).

Result: Myrtol standardized lowers histamine-induced bronchospasm by 33 % relative to controls\(^2, 3\).

Myrtol standardized thus exhibits a preventative bronchospasmolytic effect. It is conceivable that this finding can be interpreted in conjunction with the already demonstrated effect on the leucotriene concentration. A progression-inhibiting effect of Myrtol standardized on the obstructive course of chronic bronchitis can possibly be derived here.

---

1 Champeroux P & Maurin A, Centre de Recherches Biologiques (France), Myrtol standardisiert Dokumentation 1997
The pharmacodynamic profile of mucopharmaceuticals is classically regarded as associated with their mucosecretolytic properties. Whereas chemically defined mucopharmaceuticals can usually be ascribed only one of these three mucosecretolytic effects, Myrtol standardized shows secretolytic as well as mucolytic and secretomotor properties.

In recent years, the company G. Pohl-Boskamp GmbH & Co. KG has intensified its preclinical research in order to characterize the supplementary properties of Myrtol standardized. Emphasis was placed on the recognition of the antiinflammatory component of action, as the mucosal inflammation is acknowledged to be the core defect in acute and chronic airways diseases and thus these components of action are of particular importance for the therapeutic concept. Today, both antiinflammatory and antioxidative properties can be confirmed for Myrtol standardized, and these have been able to be impressively demonstrated in various studies by renowned research groups (Prof. Dr. Kietzmann of Hannover, Prof. Dr. Elstner of Weihenstephan).

In addition, Myrtol standardized has antimicrobial effects including the dose-dependent inhibition of a representative bronchial-related selection of bacteria and fungi. Anti-inflammatory and anti-oxidant properties in vitro complete the pharmacodynamic profile of Myrtol standardized.
2 Pharmacokinetics

2.1 Studies on the bioavailability

Myrtol standardized, the active substance of Gelomyrtol® and Gelomyrtol® forte, is offered in enteric coated capsules, and the active substance is therefore intentionally released in the small intestine. After release from the capsule, Myrtol standardized is very rapidly absorbed locally, and is subsequently excreted by various routes including via the bronchial mucosa.

The relative bioavailability and pharmacokinetic properties of Myrtol standardized were investigated in an open, randomized, cross-over study. As no suitable reference preparation is available in Germany and as the lipophilic substance properties make it impossible to manufacture an aqueous solution without the use of additional solubilizers, the investigation was performed as is normal in such cases with crunched enteric coated capsules (i.e., a rapid release formulation) of Gelomyrtol® or Gelomyrtol® forte as the reference.

A total of 20 healthy male subjects between 19 and 42 years of age were enrolled into the GCP-conforming study. The study medication was administered every morning at 08:00 (fasting) in a cross-over design for all four groups (washout period: 6 days). The patient received a light lunch as the first meal of the day 4 hours after taking the study medication.

---

In an open, randomized, cross-over study in accordance with GCP standards, the relative bioavailability and the pharmacokinetic properties of Myrtol standardized were investigated on 20 healthy subjects\(^1\).

Using the example of 1.8-cineole as a marker substance, it was possible to plot the time courses of the geometric mean plasma concentrations for the crunched and swallowed formulations. The most important parameters for 1.8-cineole are presented in the following table.

The relative bioavailability for 1.8-cineole is 95.6 % for the AUC (90 % confidence interval: 80.5 to 138.9 %).

Using the example of the marker substance 1.8-cineole, it could be shown that the enteric coated formulations resulted in lower peak plasma levels and a later start of release of the active substance (increased lag-time \(t_{\text{lag}}\)). The delayed release of the active substance and the longer time for which plasma concentrations are raised characterize the therapeutic advantage of the enteric coated capsule.

In an open, randomized, cross-over study in accordance with international GCP standards, the relative bioavailability and the pharmacokinetic properties of Myrtol standardized (120 mg and 300 mg capsules) were investigated on 20 healthy subjects\(^1\). The question as to whether approximate dose-proportionality existed was also investigated.

The figure shows the time courses of the plasma concentrations using the example of 1.8-cineole as the marker substance after administration of single doses of 120 mg of Myrtol standardized (Gelomyrtol\(^\text{®}\) swollowed) and 300 mg of Myrtol standardized (Gelomyrtol\(^\text{®}\) forte, swollowed), each adjusted arithmetically to an oral dose of 300 mg of Myrtol standardized.

The two curves match very closely, and this reflects approximate dose-proportionality of the pharmacokinetics for the two capsules with different active substance strengths. In comparison with the larger Gelomyrtol\(^\text{®}\) forte capsules, the smaller Gelomyrtol\(^\text{®}\) capsules show a more rapid initial distribution phase.

---

Investigations on the pharmacokinetics and bioavailability are rare for mucoactive herbal medicines. Myrtol standardized, however, stands out because the results of extensive investigations on the relative bioavailability and pharmacokinetics are available\[1\]. Comparison of a enteric coated capsule (swollowed) with a rapid-release formulation (also a enteric coated capsule but crunched) is an established method for the determination of the relative bioavailability, and is a method that can always be used when intravenous formulations are unavailable.

The investigations presented here have shown that Myrtol standardized is absorbed very rapidly from the small intestine. Supplementary investigations show that the active substance is excreted by various routes including via the bronchial mucosa. Using the example of cineole as a marker substance, it was possible to show that Myrtol standardized is almost 100 % bioavailable relative to the crunched formulation. The formulation as enteric coated capsules results in lower peak plasma levels and a later onset of release. This later onset coupled with the longer lasting plasma levels is a clear therapeutic advantage of the gastric juice resistant form over the crunched form.

This explorative study was performed in cooperation with the Cystic Fibrosis Centre of the University of Freiburg\[1\].

In this study, 11 patients with cystic fibrosis received single doses of 120 mg to 600 mg of Myrtol standardized. Sputum was collected in the period from 0 to 4 hours after administration of the drug, and was subsequently analysed. It was striking and pleasing to find that the three measured biological marker substances of Myrtol standardized could be detected in relatively high concentrations in the sputum.

The detection in the sputum of the biological marker substances 1.8-cineole, d-limonene and α-pinene provides important evidence of the "bioavailability" (distribution) of Myrtol standardized in the target organs, i.e. the lungs.

\[1\] App EM; Scheidel B, Steigerwald K: Analytischer Abschlussbericht Bestimmung von Cineol, Limonen und alpha-Pinen in Sputumproben, Myrtol standardisiert Dokumentation 1997
The indications of Gelomyrtol® and Gelomyrtol® forte are acute and chronic bronchitis and sinusitis. It should be stressed that the firm G. Pohl-Boskamp GmbH & Co. KG has for more than 10 years made these indications the focus of randomized, controlled, multicentre studies that have been planned, performed and reported according to Good Clinical Practice in order to document the efficacy and tolerability according to the principles of evidence-based medicine. The Good Clinical Practice guidelines were first published in 1991[3], and since then have been regularly revised and updated[1, 2]. These guidelines are dominated by two fundamental principals: One is the protection of human rights and hence the wishes of the patient or healthy subject, and the other is the reliability of the data. The guidelines for Good Clinical Practice have been accepted worldwide, and are now de facto the ethical and scientific quality standard of clinical studies internationally[4]. Post marketing surveillance studies are pharmacoepidemiological investigations that are used firstly to monitor drug safety ("pharmacovigilance") and secondly to gain further information on the efficacy of the products[5].
The performance of GCP-conforming clinical studies on children with acute clinical conditions comes up against the limits of feasibility for ethical reasons (declaration of consent of both parents, permissibility of a placebo arm)\(^6\). Where such studies are not performed, pharmacoepidemiological investigations using the personal data of patients are a helpful alternative.
3 Indication fields

3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.1 Study design

Randomized, double-blind, active-controlled and placebo-controlled, multicentre study

331 patients with acute sinusitis

16 ENT specialists, specialists for internal and general medicine in Germany

Gelomyrtol® forte: 4 x 300 mg/day

Essential oil

Placebo

Duration of treatment: 6 ± 2 days

This randomized, double-blind, controlled, multicentre study according to international GCP standard was performed together by 16 ENT specialists, specialists for internal and general medicine in Germany in the period from October 1993 to June 1994[1].

A total of 331 patients were enrolled with symptomatically evident acute sinusitis (40.6 % women, age 16 – 86 years, mean weight: 66.5 kg (women) and 82 kg (men)). They received either Myrtol standardized (n = 110), a different essential oil (n = 110) or placebo (n = 111). All patients received as permitted concomitant medication a xylometazoline nasal spray at standard dosage of 4 x 2 puffs. The duration of treatment was on average 6 ± 2 Tage.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Myrtol standardized</th>
<th>Essential oil b)</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>110</td>
<td>110</td>
<td>111</td>
<td>331</td>
</tr>
<tr>
<td>ITT a)</td>
<td>109</td>
<td>110</td>
<td>111</td>
<td>330</td>
</tr>
<tr>
<td>EAP a)</td>
<td>94</td>
<td>97</td>
<td>100</td>
<td>291</td>
</tr>
</tbody>
</table>

a) ITT (intention to treat): All patients who received at least one dose of study medication. EAP (efficacy analysable patients): All patients who completed the study in accordance with the study protocol. b) Investigational formulation, discarded from further development.

3 Indication fields

3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.2 Symptom score

A total of 331 male and female outpatients who clinically assessed by interrogation by the responsible investigators were showing symptomatically evident acute sinusitis of sufficient severity as determined using a symptom scoring system were enrolled into this GCP-conforming study[1]. This was done using a symptom score in which 9 symptoms or clinical signs were rated according to severity. This symptom score was originally developed by Prof. Dr. Burian of the ENT Department of the University of Vienna for clinical studies in the field of sinusitis and then modified by Prof. Dr. Federspil of the ENT Department of the University Homburg (Saar) for the current study.

Depending on severity, a total score for these 9 parameters could reach 25 points, and those patients with a score of over 10 points on the first day of the study were – regardless of duration of the acute clinical condition but taking account of the other in- and exclusion criteria – enrolled into the study. The duration of the acute clinical condition was 2 days in 65 % of the enrolled patients and between 3 – 6 days in other 28 % of cases.

The primary endpoint of the study was the subjective assessment of the efficacy using this symptom score.

3 Indication fields

3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.3 Symptom score: Improvements

<table>
<thead>
<tr>
<th>Symptom score (ITT)</th>
<th>Myrtol standardized</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline value</td>
<td>17.4 ± 2.8</td>
<td>17.7 ± 2.9</td>
</tr>
<tr>
<td>Δ of symptom score</td>
<td>10.3 ± 4.9</td>
<td>9.0 ± 6.0</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.02</td>
<td>---------</td>
</tr>
</tbody>
</table>

The primary endpoint of this GCP-conforming study was the change in the total symptom score after 6 ± 2 treatment days[1, 2].

The initial total symptom scores in the Myrtol standardized group (17.4) and the placebo group (17.7) were comparable. In the course of treatment over 6 ± 2 days, the symptom score in the Myrtol standardized group improved by 10.3 ± 4.9, and thus differed statistically significantly (p < 0.02) from the placebo group in which the sum score improved by 9.0 ± 6.0 in the same treatment period.

Although the result is statistically significant, the extent of the global treatment effect is relatively small due to an unexpectedly high responder rate in the placebo group. As a result of the fact that the patients must have had severe symptoms of acute sinusitis at the start of the study so as to be considered for inclusion and the fact that this was independent of the duration of the history of the acute complaint (6 days in 93% of patients), it can be seen that the responder rate in the placebo group can also be influenced by the natural course of the disease.

The total symptom score in this clinical trial could in fact also show only a global improvement in clinical condition. Unfortunately, within the period of time which is rational for logistical reasons, the symptom score possesses a certain degree of arbitrariness with regard to the course of the illness in individual patients. In addition to the changes in individual (core) symptoms, the signs of a more rapid reduction in symptoms under Myrtol standardized was without question clinically very important, and was worthy of scientific examination. The patients who received Myrtol standardized actually showed some very interesting findings, and these are examined in detail on the following pages.

2 Roos U, Wulkow R, Wortha HP, Lübbe D et al., A randomised, multi-centered, placebo controlled phase III double blinded study with parallel group comparison to investigate the efficacy of Myrtol standardized capsules (4 x 300 mg oral daily) for patients with acute sinusitis. 92/334. Myrtol standardisiert Dokumentation 1994
3 Indication fields

3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.4 Symptom improvement I

From the symptom score developed by Prof. Dr. Burian of Vienna and modified by Prof. Dr. Federspil, Homburg (Saar), with a total of nine parameters, the above figure presents the example of six parameters[1]. The symptoms "headache", "pain on bending forward" and "tenderness at trigeminus pressure points" are regarded as the leading symptoms/sign of acute sinusitis, and the parameters "volume of secretion", "viscosity of secretion" and "nasal respiration" can be regarded as ancillary.

On investigation of the leading symptoms/sign, it can be seen that the extent of the improvement in symptom score is always greater in the group treated with Myrtol standardized than in the placebo group. The parameter "volume of secretion" did not show a manifest trend to reduction in either groups; this is presumably due to the disease-typical increase in the (viscous) secretion flow or the secretolytic action of Myrtol standardized, so that viewed methodologically, a reduction in the amount of secretion cannot necessarily be expected. On the other hand, there is a clear difference between Myrtol standardized and placebo with regard to viscosity of secretion due to the clear secretolytic effect of Myrtol standardized. The relatively striking change in the symptom "impaired nasal respiration" in the two groups could be explained by the permitted concomitant medication (xylometazoline).

---

1 Roos U, Wulkow R, Wortha HP, Lübke D et al., A randomised, multi-centered, placebo controlled phase III double blinded study with parallel group comparison to investigate the efficacy of Myrtol standardized capsules (4 x 300 mg oral daily) for patients with acute sinusitis. 92/334. Myrtol standardisiert Dokumentation 1994
3 Indication fields

3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.5 Symptom improvement II

Facial pain on bending forward could be regarded as the leading symptom of acute sinusitis. The above figure examines the changes from day 1 before therapy to after 6 ± 2 days of therapy, and shows the individual percentage changes broken down according to the baseline conditions of this important leading symptom\(^1\). Overall, in the subjective assessment of the patients, mild to severe facial pain on bending forward improved in 78% of cases under therapy with Myrtol standardized. It is pleasing that 61% of those patients treated with Myrtol standardized no longer complained of any facial pain on bending forward after just this one week of therapy.

---

1 Roos U, Wulkow R, Wortha HP, Lübke D et al., A randomised, multi-centered, placebo controlled phase III double blinded study with parallel group comparison to investigate the efficacy of Myrtol standardized capsules (4 x 300 mg oral daily) for patients with acute sinusitis. 92/334. Myrtol standardisiert Dokumentation 1994
### 3 Indication fields

#### 3.1 Acute sinusitis

3.1.1 GCP-conforming, randomized, controlled, multicentre study

3.1.1.6 Symptom improvement III

---

**Tenderness at trigeminus pressure points**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>69</td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>74</td>
<td>37</td>
</tr>
<tr>
<td>Severe</td>
<td>27</td>
<td>3</td>
</tr>
</tbody>
</table>

Myrtol standardized group

The tenderness at trigeminus pressure points about which these patients complained is a clinical investigation finding that can be used as a leading symptom for the diagnosis of acute sinusitis.

As for the sign "facial pain on bending forward", it was also observed here that the mild to moderate tenderness improved within the treatment period of 6 ± 2 days in 66% of cases in the group treated with Myrtol standardized\(^1\). The proportion of patients who achieved complete freedom from pain within the treatment period was 56%.

On the basis of the leading symptoms/sign "facial pain on bending forward" and "tenderness at trigeminus pressure points", a substantial improvement during the treatment period can be shown for the group treated with Myrtol standardized.

---

\(^1\) Roos U, Wulkow R, Wortha HP, Lübke D et al., A randomised, multi-centered, placebo controlled phase III double blinded study with parallel group comparison to investigate the efficacy of Myrtol standardized capsules (4 x 300 mg oral daily) for patients with acute sinusitis. 92/334. Myrtol standardisiert Dokumentation 1994
The primary endpoint of this GCP-conforming study was the extent of the improvement in a symptom score in acute sinusitis. The extent of the global symptom improvement in the group treated with Myrtol standardized differed statistically significantly from that in the placebo group\(^1\).

Another analysis investigated the question as to whether the success of therapy in the two different groups progressed at different speeds. This was done using only the data on the leading symptoms/sign "headache", "facial pain on bending forward" and "tenderness at trigeminus pressure points" and dividing the patients into two groups: The first group included all those patients who had been treated for \(\leq 6\) days, and the second group all those patients whose treatment lasted \(> 6\) days. The above figure shows a clinically very relevant result. Evaluation of the success of therapy after fewer than 6 days of therapy reveals an improvement in the score of the leading symptoms/sign which is very much in favour of Myrtol standardized and is an expression of the more rapid and more pronounced recovery in symptoms. This difference is no longer so evident after longer durations of treatment when the natural course of the disease comes into play.

This confirms that using Myrtol standardized allows a more rapid and complete recovery from acute inflammatory sinusitis than it is possible with placebo.

\(^1\) Roos U, Wulkow R, Wortha HP, Lübke D et al., A randomised, multi-centered, placebo controlled phase III double blinded study with parallel group comparison to investigate the efficacy of Myrtol standardized capsules (4 x 300 mg oral daily) for patients with acute sinusitis. 92/334. Myrtol standardisiert Dokumentation 1994
The previously presented results of this study show statistically significant treatment differences in favour of Myrtol standardized, and essentially confirm that treatment with Gelomyrtol® forte in acute sinusitis contributed to a more rapid and more complete recovery than it was possible in the placebo group. These findings are endorsed by additional indirect signs that were also determined as part of this clinical study. The need for follow-up antibiotic therapy in the group treated with Myrtol standardized was almost half than that of the placebo group. This finding was also reflected in the analysis of the incapacitation at the end of the clinical phase, and here again the percentage of patients unable to work was reduced by half in the group treated with Myrtol standardized relative to the placebo group. To put it another way, the patients in the group treated with Myrtol standardized were more likely to be able to return to work than those in the placebo group by a factor of 2.

Both these findings are indirect indications of the more rapid and more complete recovery that can be achieved in sinusitis with Myrtol standardized rather than placebo.

---

This randomized, double-blind, placebo-controlled, multicentre study according to international GCP standards enrolled 311 patients with symptomatically evident acute sinusitis\[1\]. The primary endpoint of this study was the extent of the improvement in the total symptom score in acute sinusitis. The extent of the global symptom improvement in the group treated with Myrtol standardized differed statistically significantly from that in the placebo group.

Entirely in agreement with justified patient expectations (including those of the treating physicians), superiority of Gelomyrtol® forte over placebo with regard to the leading symptoms/sign of acute sinusitis such as headache, facial pain on bending forward and tenderness at trigeminal pressure points was demonstrated by evidence of a more rapid and greater recovery in symptoms/signs. This clinically relevant aspect in the treatment of acute sinusitis is supported by indirect results such as the lower need of follow-up antibiotics and a lower degree of incapacitation in favour of Gelomyrtol® forte.

---

3 Indication fields

3.1 Acute sinusitis

3.1.2 Prospective comparative PMS study

3.1.2.1 Study design

Prospective comparative post marketing surveillance study (PMS-study)

569 patients with acute rhinosinusitis

96 ENT specialists (49 %), specialists for internal and general medicine in Germany

Gelomyrtol® forte (n = 284; 156 women, 128 men)

Herbal medicine (n = 285; 168 women, 117 men)

Duration of treatment: Gelomyrtol® forte 14.9 days (median)

Herbal medicine 15.4 days (median)

In a prospective comparative post marketing surveillance study, a total of 569 patients (324 women, 245 men) with acute rhinosinusitis were treated by 96 ENT specialists (49 %) and primary care physicians[1]. Patients in two approximately equally sized groups received either Gelomyrtol® forte or a secretolytic herbal medicine for a duration of treatment of just over two weeks. The prescribed daily dosages in each treatment arm were essentially those recommended by the manufacturer.

As part of a supplementary questionnaire completed by the investigators participating in this study, one of the particular reasons they stated for their choice to use Gelomyrtol® forte was its good efficacy in all forms of inflammatory respiratory tract diseases, and it was also generally preferred in severe clinical conditions. By contrast, the comparison preparation was used in mild acute conditions of the upper airways.

---

1 Wittig T, Gelomyrtol® forte im Vergleich zu einem pflanzlichen Sekretolytikum bei akuter Rhinosinusitis: Eine prospektive vergleichende Anwendungsbeobachtung, Myrtol standardisiert Dokumentation 1998
3 Indication fields

3.1 Acute sinusitis

3.1.2 Prospective comparative PMS study

3.1.2.2 Symptom improvement

A total of 569 outpatients with acute rhinosinusitis were treated in this post marketing surveillance study. The patients received either Gelomyrtol® forte or a secretolytic herbal medicine for a duration of treatment of about 2 weeks[1].

On comparison of the clinical courses in the two treatment groups, it is evident that the rhinosinusitis can be expected to wear off and the patient to recover within the treatment period. This treatment period appears to correspond to the natural course of the illness, so that therapeutic differences are no longer evident after 2 weeks. Using the examples of the clinical signs such as sinus percussion pain and trigeminus tenderness, it can be seen that there is a tendency for the symptoms to wear off more pronounced and more rapidly under Gelomyrtol® forte than under the secretolytic herbal medicine. This difference is particularly evident at the checks performed after about one week of treatment.

Referred to the total number of enrolled patients, the quality characteristics were rated as "good" or "very good" in the global evaluation of the efficacy in 95 % of cases for Gelomyrtol® forte and in 83 % of cases for the secretolytic herbal medicine. The global assessment by the participating investigators did not differ substantially from that of the patients.

The need for antibiotics were slightly lower in the group treated with Gelomyrtol® forte (19.0 %) than in the comparison group (23.9 %). The duration of antibiotic treatment in both treatment groups was about one week. On closer analysis of the prescribed antibiotics, it is evident that tetracyclines and macrolide antibiotics were prescribed most frequently.

---

1 Wittig T, Gelomyrtol® forte im Vergleich zu einem pflanzlichen Sekretolytikum bei akuter Rhinosinusitis: Eine prospektive vergleichende Anwendungsbeobachtung, Myrtol standardisiert Dokumentation 1998
A total of 569 outpatients with acute rhinosinusitis were treated with either Gelomyrtol® forte or a secretolytic herbal medicine for a treatment period of about two weeks in a prospective comparative PMS-study\(^1\). About half (49 %) of the patients participating in this study were under the care of an ENT specialist.

As part of the clinical monitoring by the ENT specialist it was intended that an optional ultrasound assessment of the clinical condition should be performed, and this was actually performed with a significant proportion of these patients. The presence or absence of back wall echoes, being the ultrasound correlate of mucosal swelling in maxillary sinusitis, was specifically recorded as part of the ultrasound assessment.

The back wall echo recorded as part of the ultrasound assessment also showed a markedly more rapid normalization of the findings under Gelomyrtol® forte than under the secretolytic herbal medicine. This finding matches the more rapid and complete reduction in symptoms shown previously using the examples of individual clinical investigation findings.

\(^1\) Wittig T, Gelomyrtol® forte im Vergleich zu einem pflanzlichen Sekretolytikum bei akuter Rhinosinusitis: Eine prospektive vergleichende Anwendungsbeobachtung, Myrtol standardisiert Dokumentation 1998
3 Indication fields

3.1 Acute sinusitis

3.1.3 Open, clinical, single-centre study

3.1.3.1 Study design

- **Open, clinical, single-centre study**
- **13 patients with acute sinusitis**
- **ENT Department of the Army Hospital in Hamburg**
  (Senior Physician: Dr. Klaus Simm)
- **Gelomyrtol® forte: 4 x 300 mg/day**
- **Duration of treatment: 10 days**

This open, clinical, single-centre study was conducted between April 1986 and September 1987 in the ENT Department of the Army Hospital in Hamburg (Senior Physician: Dr. Klaus Simm)[1]. A total of 13 patients (12 men and 1 woman) between 20 and 44 years of age with acute, radiographically and in most cases also endoscopically confirmed sinusitis whose symptoms had already lasted an average of 7 days (median) were enrolled.

To confirm the diagnosis, all the patients underwent radiographic assessment of the sinuses (maxillary and frontal sinus) at the start of treatment, and in 11 of 13 cases endoscopic sinuscopy was also performed.

A total of 10 of 13 patients had no record of seasonal allergy.

Exclusion criteria included an antibiotic indication at the start of treatment or previous treatment with antibiotics or mucosecretolytics.

---

3 Indication fields

3.1 Acute sinusitis

3.1.3 Open, clinical, single-centre study

3.1.3.2 Symptom improvement

A total of 13 patients with acute, radiographically and in most cases also endoscopically confirmed sinusitis were treated with Gelomyrtol® forte for a period of 10 days.[1]

According to the clinical symptoms such as purulent rhinitis or headache, the clinical course already showed an improvement in symptoms in almost half of the patients as early as the third day of treatment. In addition, there was at this time already a rapidly increasing proportion of patients who subjectively rated themselves as symptom-free, and this percentage was as high as 70 %–80 % by the end of the first week. By day 10 of treatment, none of the patients any longer complained of purulent rhinitis, and mild headache was reported by only one patient.

The subjective improvement correlates extensively with the radiographic progress of these patients: Four patients (31 %) no longer showed any shadow over the maxillary sinus on day 10, and 8 patients (69 %) showed a significant improvement in radiographic findings in comparison with the baseline condition.

---

3 Indication fields

3.1 Acute sinusitis

3.1.3 Open, clinical, single-centre study

3.1.3.3 Global assessment of efficacy

As part of the global assessment of efficacy, the patients in this study were asked whether their clinical condition had in their subjective opinion improved or even whether they felt completely free from symptoms. This revealed that between days 3 and 7 of treatment, an improvement was already felt by between 70\% and 90\% of the patients; a very high percentage. As paralleled by the clinical findings, practically every patient showed at least an improvement after 10 days of treatment, and 6 of these 13 patients (46.2\%) in fact showed complete freedom from symptoms.

These subjective assessments by the patients are matched by their individual global assessment of the tolerability: The tolerability of Gelomyrtol® forte was rated as ”very good” by eight patients, and as ”good“ by the other five patients.

---

This multicentre post marketing surveillance study evaluated the progress of the symptoms and the tolerability of Myrtol standardized in children with acute and chronic sinusitis and bronchitis as well as with sinobronchial syndrome\textsuperscript{[1]}.

A total of 511 children (54 % females) between 3 and 17 years of age were monitored at the sites of 91 paediatricians and primary care physicians in Germany over a two-week period of treatment, and the findings were recorded. The decision to prescribe Gelomyrtol\textsuperscript{®} (120 mg of Myrtol standardized) or Gelomyrtol\textsuperscript{®} forte (300 mg of Myrtol standardized) was made by the treating physician. The actually administered doses were very largely those recommended by the manufacturer, but sometimes also higher.

Antibiotics (23.3 %) and antitussives (18.4 %) were the most commonly reported concomitant medications.

Clinical interest centred on the course of the symptoms in the children with acute sinusitis (n = 128), and this is presented in the following section.

\textsuperscript{1} Sengespeik HC, Zimmermann T, Peiske C, de Mey C, Myrtol standardisiert in der Therapie von akuten und chronischen Atemwegserkrankungen bei Kindern, Arzneim.-Forsch./Drug Res. (1998) 48 (I), 10: 990 – 994
This prospective, multicentre, post marketing surveillance study evaluated the course of symptoms and the tolerability of Myrtol standardized in children with inflammatory airways diseases\(^1\).

Clinical interest centred on the progress of symptoms in children with acute sinusitis (n = 128). The percentage of children free from symptoms after a two-week period of treatment with Gelomyrtol\(^\circ\) (n = 56) or Gelomyrtol\(^\circ\) forte (n = 72) is shown above. All the symptoms or clinical signs included in the assessment showed a significant improvement. The percentage of children free from the individual leading symptoms/signs of acute sinusitis such as trigeminus tenderness, headache and sinus percussion pain was in fact always over 95 %.

These findings correlated with the global evaluation of the efficacy by all those involved: The therapy with Myrtol standardized was rated as "very good" or "good" in 91.0 % of cases by the treating physicians, in 77.2 % of cases by the treated children, and by 85.5 % of cases by the parents.

---

3 Indication fields

3.1 Acute sinusitis

3.1.4 Post marketing surveillance study in children

3.1.4.3 Ease of taking capsules by children

The question of the ease of taking capsules is a very important topic particularly in the treatment of children, although, interestingly enough, it is very rarely investigated. Without question, it depends on the individual child and, of course, on the size of the capsule.

A total of 79 % of all patients who received Gelomyrtol® (small capsule containing 120 mg of Myrtol standardized) were between 3 and 6 years of age, and 96.1 % of those taking Gelomyrtol® forte (larger capsule containing 300 mg of Myrtol standardized) were between 7 and 12 years of age. The data presented here show that all the age groups of children treated in this study (n = 511) on the whole showed no problems in swallowing the capsules. The percentage of school children who had no difficulty in taking the capsules was consistently over 80 %. The swallowing of the capsules was thus easily possible with the vast majority of children and did not have any adverse effect on compliance.

A retrospective post marketing surveillance study in 1994 evaluated the data of 246 children (51.4 % females; median age 11 years, 25th percentile 8 years, 75th percentile 13 years) with acute sinusitis\(^1\).

The information was recorded by general practitioners (47 %), ENT specialists (47 %) and paediatricians in Germany.

The administration of Gelomyrtol® or Gelomyrtol® forte was broken down as follows:

<table>
<thead>
<tr>
<th>Bodyweight (age)</th>
<th>Gelomyrtol®</th>
<th>Gelomyrtol® forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 30 kg (approx. 1 – 9 y.)</td>
<td>45.6 %</td>
<td>23.3 %</td>
</tr>
<tr>
<td>31 – 40 kg (approx. 9 – 11 y.)</td>
<td>29.1 %</td>
<td>27.6 %</td>
</tr>
<tr>
<td>41 – 50 kg (approx. 11 – 13.5 y.)</td>
<td>19.4 %</td>
<td>26.7 %</td>
</tr>
<tr>
<td>51 – 80 kg (approx. 13.5 – 18 y.)</td>
<td>5.8 %</td>
<td>22.4 %</td>
</tr>
</tbody>
</table>

The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 11.0 days (median in each case). Antibiotics (35.4 %) and rhinological preparations (44.6 %) were the most commonly reported concomitant medications.

---

1 Hanisch F & Bock P, Sekretolytika bei akuter Sinusitis bei Kindern, Myrtol standardisiert Dokumentation 1994
Indication fields

3 Indication fields

3.1 Acute sinusitis

3.1.5 Retrospective post marketing surveillance study in children

3.1.5.2 Freedom from symptoms in children

This retrospective post marketing surveillance study in 1994 evaluated the data of 246 children with acute sinusitis recorded by general practitioners, ENT specialists and paediatricians in Germany. The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 11.0 days (median in each case)[1].

The pain symptoms, which were recorded as headache, facial pain or trigeminus tenderness, decreased very considerably during the treatment period, and by the end of the treatment period more than 90 % of the patients were free from pain. The achieved freedom from pain must also have contributed considerably to the fact that the children also showed a substantial improvement in the general feeling of being unwell. Even the impaired nasal respiration and the rhinitis symptoms which predominantly affected only a single side were absent in about 90 % of children.

This almost complete disappearance of clinical symptoms with Gelomyrtol® or Gelomyrtol® forte is also reflected in the extremely positive assessment of the global efficacy and tolerability by the treating doctors:

The global efficacy was rated as "very good or good" in 91.6 % of cases for Gelomyrtol® and in 96.1 % of cases for Gelomyrtol® forte. The global tolerability was rated as "very good or good" in 95.7 % of cases for Gelomyrtol® and in 96.8 % of cases for Gelomyrtol® forte.

---

1 Hanisch F & Bock P, Sekretolytika bei akuter Sinusitis bei Kindern, Myrtol standardisiert Dokumentation 1994
3 Indication fields

3.2 Chronic sinusitis

3.2.1 Open, clinical, single-centre study

3.2.1.1 Study design

This open, clinical, single-centre study was performed between December 1986 and August 1987 in the ENT Outpatient Department of the Hannover Medical School under the direction of Senior Physician Dr. Laszig\[1\]. The study was conducted on 44 outpatients (40.9 % women) between 12 and 76 years of age with chronic radiographically and endoscopically confirmed sinusitis who received either Myrtol standardized (n = 11), cineole (n = 11), ambroxol (n = 11) or placebo (n = 11) for a duration of treatment of 10 days.

An x-ray of the paranasal sinuses (maxillary sinus 75 %, frontal sinus 13.6 %) of every patient was taken at the start of treatment to confirm the diagnosis, and this was repeated after 10 days of treatment. In addition, all patients underwent endoscopic examination of the paranasal sinuses at the start of treatment, and this confirmed maxillary sinusitis in 38 of 44 patients (86.4 %) and frontal sinusitis in 6 patients (13.6 %). Endoscopy revealed mucosal swelling in 39 of 44 patients (86.6 %) and hyperplastic mucosa in 29 patients (65.9 %). A greenish yellow and/or purulent secretion was observed in 23 patients, and a viscous consistency of the secretion was observed in 32 patients. A total of 42 of 44 patients showed no history of seasonal allergies. Exclusion criteria were an antibiotic indication at the start of treatment and previous treatments with antibiotics or mucosecretolytics in the preceding four weeks.

1 Laszig R, Gelomyrtol® forte bei Patienten mit chronischer Sinusitis, Myrtol standardisiert Dokumentation 1987
This open, clinical, single-centre study in the ENT Outpatient Department of the Hannover Medical School was conducted on 44 outpatients with chronic, radiographically and endoscopically confirmed sinusitis who received either Myrtol standardized (n = 11), cineole (n = 11), ambroxol (n = 11) or placebo (n = 11) for a duration of treatment of 10 days\textsuperscript{[1]}. A global evaluation of efficacy was performed on days 3, 7 and 10 of treatment.

As early as the 3rd day of treatment, the patients who received Myrtol standardized showed a remarkably high trend towards improvement (90 %), and this was more evident than under cineole or ambroxol and was clearly much better than in the placebo group. As far as the parameter "freedom from symptoms" is concerned, the subjective assessment of the efficacy revealed statistical-
3 Indication fields

3.2 Chronic sinusitis

3.2.1 Open, clinical, single-centre study

3.2.1.2 Global assessment of efficacy

ly significant differences between the treatment arms on the 7th (p = 0.01) and 10th (p = 0.01) days of treatment in favour of Myrtol standardized. On the 7th day of treatment, half of the patients under Myrtol standardized already felt themselves to be symptom-free, whilst under cineole and ambroxol this figure was only 40 % or less. The placebo group had clearly fallen behind; with only < 10 % of patients free from symptoms.

1 Laszig R, Gelomyrtol® forte bei Patienten mit chronischer Sinusitis, Myrtol standardisiert Dokumentation 1987
An x-ray of the paranasal sinuses (maxillary sinus 75 %, frontal sinus 13.6 %) of every patient was taken at the start of treatment to confirm the diagnosis: Homogenous shadows were observed in 36.4 % of cases under Myrtol standardized, 18.2 % under cineole, 45.5 % under ambroxol, and 36.4 % under placebo[1].

On the 10th day of treatment, a further x-ray of the paranasal sinuses was taken, and the results examined. A statistically significant change in the radiographic findings of the paranasal sinuses in favour of Myrtol standardized was observed after 10 days of treatment (p < 0.05), and this correlated with the global assessment of the efficacy. Radiographically clear sinuses were observed in nearly half of the patients under Myrtol standardized (45.5 %) but in only about 20 % of patients under ambroxol, and in none of the patients under cineole or placebo.

1 Laszig R, Gelomyrtol® forte bei Patienten mit chronischer Sinusitis, Myrtol standardisiert Dokumentation 1987
3 Indication fields
3.2 Chronic sinusitis
3.2.2 Retrospective post marketing surveillance study in adults
3.2.2.1 Study design

Retrospective post marketing surveillance study

101 patients with chronic sinusitis

ENT specialists (2/3), specialists for internal and
general medicine in Germany

Gelomyrtol® forte (n = 94)
Gelomyrtol® (n = 7)

Duration of treatment: 53.5 days (median)

A retrospective post marketing surveillance study in 1994 evaluated the data of 101 patients
(57.5 % women; median age 40 years) with chronic sinusitis[^1].

The information was recorded by ENT specialists (two thirds), specialists for internal and general medicine in Germany.

The average dosage was 900 mg of Myrtol standardized per day and the average duration of treatment was 53.5 days (median).

Antibiotics (34.4 %) and rhinological preparations (18.8 %) were the most commonly reported concomitant medications.

[^1]: Hanisch F & Bock P, Sekreolytika bei chronischer Sinusitis bei Erwachsenen, Myrtol standardisiert Dokumentation 1994
This retrospective post marketing surveillance study in 1994 evaluated the data of 101 patients with chronic sinusitis who were treated with an average daily dosage of 900 mg Myrtol standardized for an average duration of treatment of 53.5 days (median)\(^1\).

The pain symptoms, which were recorded as headache, facial pain and trigeminus tenderness, decreased very considerably during the treatment period, and by the end of the treatment period about 70 % of the patients were actually free from pain. The achieved freedom from pain must also have contributed considerably to the fact that the general feeling of being ill also shows a substantial improvement in the analysed patients. Even the impaired nasal respiration and the rhinitis symptoms which predominantly affected only a single side show an almost 60 % to 80 % rate of freedom from symptoms.

---

1 Hanisch F & Bock P, Sekretoyltyka bei chronischer Sinusitis bei Erwachsenen, Myrtol standardisiert Dokumentation 1994
3. Indication fields

3.2 Chronic sinusitis

3.2.3 Retrospective post marketing surveillance study in children

3.2.3.1 Study design

- A retrospective post marketing surveillance study in 1994 evaluated the data of 64 children (61.6% females; median age 10 years, minimum 4 years, maximum 14 years) with chronic sinusitis\(^1\).

- The information was recorded by ENT specialists (84%), specialists for internal and general medicine in Germany.

- The administration of Gelomyrtol® or Gelomyrtol® forte was broken down as follows:
  - Gelomyrtol® forte \((n = 40)\)
  - Gelomyrtol® \((n = 24)\)

- Duration of treatment: 26 days (median)

A retrospective post marketing surveillance study in 1994 evaluated the data of 64 children (61.6% females; median age 10 years, minimum 4 years, maximum 14 years) with chronic sinusitis\(^1\).

The information was recorded by ENT specialists (84%), specialists for internal and general medicine in Germany.

The administration of Gelomyrtol® or Gelomyrtol® forte was broken down as follows:

<table>
<thead>
<tr>
<th>Bodyweight (age)</th>
<th>Gelomyrtol®</th>
<th>Gelomyrtol® forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 30 kg (ca. 1 – 9 years)</td>
<td>52.4 %</td>
<td>22.5 %</td>
</tr>
<tr>
<td>31 – 40 kg (ca. 9 – 11 years)</td>
<td>23.8 %</td>
<td>52.5 %</td>
</tr>
<tr>
<td>41 – 50 kg (ca. 11 – 13.5 years)</td>
<td>19.0 %</td>
<td>17.5 %</td>
</tr>
<tr>
<td>51 – 80 kg (ca. 13.5 – 18 years)</td>
<td>4.8 %</td>
<td>7.5 %</td>
</tr>
</tbody>
</table>

The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 26 days (median in each case). Antibiotics (11.2%) and rhinological preparations (33.2%) were the most commonly reported concomitant medications.

---

\(^1\) Hanisch F & Bock P, Sekretylytica bei chronischer Sinusitis bei Kindern, Myrtol standardisiert Dokumentation 1994
This retrospective post marketing surveillance study in 1994 evaluated the data of 64 children with chronic sinusitis recorded by ENT specialists (84 %), specialists for internal and general medicine in Germany[1]. The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 26 days (median in each case)[1].

The pain symptoms, which were recorded as headache, facial pain and trigeminus tenderness, decreased very considerably during the treatment period, and by the end of the treatment period 80 to 90 % of the children were actually free from pain. The achieved freedom from pain must also have contributed considerably to the fact that the children also showed a substantial improvement in the general feeling of being unwell. Even the impaired nasal respiration and the rhinitis symptoms which predominantly affected only a single side showed an improvement in at least 70 to 80 % of cases.

This almost complete disappearance of the clinical symptoms with Gelomyrtol® or Gelomyrtol® forte is also reflected in the extremely positive assessment of the global efficacy and tolerability by the treating physicians:

The global efficacy was rated as "very good or good" in 85.0 % of cases for Gelomyrtol® and in 78.2 % of cases for Gelomyrtol® forte.

The global tolerability was rated as "very good or good" in 91.3 % of cases for Gelomyrtol® and in 97.5 % of cases for Gelomyrtol® forte.

---

1 Hanisch F & Bock P, Sekretolytika bei chronischer Sinusitis bei Kindern, Myrtol standardisiert Dokumentation 1994
3 Indication fields

3.3 Acute bronchitis

3.3.1 GCP-conforming, randomized, controlled, multicentre study

3.3.1.1 Study design

Randomized, double-blind, active-controlled and placebo-controlled, multicentre study

676 patients with acute bronchitis

40 medical centres in Poland

Gelomyrtol® forte: 4 x 300 mg/day for 14 days
Cefuroxime: 2 x 250 mg/day for days 1 – 6
Ambroxol: 3 x 30 mg/day for days 1 – 3
Placebo 2 x 30 mg/day for days 4 – 14

This randomized, double-blind, controlled, multicentre study according to international GCP standard investigated Myrtol standardized (Gelomyrtol® forte) against cefuroxime, ambroxol and placebo in patients with acute bronchitis over a treatment period of two weeks[1]. The study was performed at 40 centres in Poland.

A total of 676 outpatients (ITT population) with acute bronchitis of recent onset (5 days) and with at least 4 night-time awakenings due to cough and a FEV1 > 75 % were enrolled into the study. Patients with clinical evidence of chronic airways disease or additional serious diseases were excluded from the study.

The responder and non-responder rates, symptoms (such as nocturnal coughing fits, coughing fits during the day), clinical investigation findings, FEV1, global efficacy assessment, and the tolerability were evaluated. The primary endpoint of the study was the responder rate as assessed by the comparisons of Myrtol standardized versus placebo and Myrtol standardized versus cefuroxime, each over a treatment period of one week.

---

3 Indication fields

3.3 Acute bronchitis

3.3.1 GCP-conforming, randomized, controlled, multicentre study

3.3.1.2 Patient status at the start of the study

Status of the patients at the start of the study

- 58.1 % women
- 57.5 % non-smokers
- recent onset (< 5 days)
- 91 – 94 % with cough
- 72 – 78 % felt subjectively poor or very poor
- 36 % had a body temperature > 37.5°C
- 72 – 76 % had pathological auscultation findings

A total of 393 female and 283 male patients with a mean age of almost 40 years (eldest patient: 79 years) of whom 57.5 % were non-smokers were enrolled into the study\textsuperscript{[1]}. At admission to the study, the patients complained of a remarkably high burden of suffering (72 – 78 % of patients felt subjectively poor or very poor, and 72 – 76 % showed pathological findings on auscultation), so that from a clinical viewpoint viral/bacterial mixed infections could probably be presumed to be the cause of the acute bronchitis in every case\textsuperscript{[2]}. Patients with clinical evidence of a chronic airways disease and/or acute exacerbations of chronic bronchitis, recurrent acute bronchitis, asthma, pneumonia or concurrent bacterial infections or with a fever of over 39.5 °C rectal were excluded from the study.


\textsuperscript{2} Arzneimittelkommission der Deutschen Ärzteschaft, Empfehlungen zur Therapie akuter Infekte der oberen Atemwege und Bronchitiden, AVP-Sonderheft Therapieempfehlungen, 1. edition 1999, 1 – 17
The evaluation of the data of this GCP-conforming study contrasted all the individual parameters for both the intention-to-treat population (ITT) and the efficacy-analysable population (EAP)\cite{Matthys_H_2000}.

After one week of treatment, the non-responder rates of Myrtol standardized (5.3 % in ITT, 5.4 % in EAP) were the lowest of all four treatment groups. The three active treatment arms showed a noticeable separation from the placebo group, although the non-responder rates with cefuroxime and ambroxol were also slightly but clearly higher than with Myrtol standardized.

At the end of the second week of treatment, the separations were even greater. The patients who received Myrtol standardized showed a fairly negligible non-responder rate of 1.2 % (1.3 % in EAP), whilst the non-responder rates were higher by a factor of 4 to 5 in the other two active treatment groups and higher by a factor of 10 in the placebo group.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & Myrtol stand. & Placebo & Cefuroxime & Ambroxol \\
\hline
After 1 week & & & & \\
ITT & 5.3 % & 20.9 % & 7.6 % & 9.8 % \\
EAP & 5.4 % & 21.3 % & 7.6 % & 9.9 % \\
\hline
After 2 weeks & & & & \\
ITT & 1.2 % & 11.0 % & 5.3 % & 4.9 % \\
EAP & 1.3 % & 14.8 % & 5.9 % & 5.6 % \\
\hline
\end{tabular}
\caption{Non-responder rates}
\end{table}

3 Indication fields

3.3 Acute bronchitis

3.3.1 GCP-conforming, randomized, controlled, multicentre study

3.3.1.4 Non-responder rates after 1 and 2 weeks

The non-responder rates after 1 and 2 weeks of treatment analysed and presented here are those of the efficacy-analysable population (EAP)\(^1\). Myrtol standardized showed the lowest non-responder rate (5.4\%) of all four treatment groups after just one week. The three active treatment arms showed a clearly evident separation from the placebo group, but the non-responder rates with cefuroxime and ambroxol were slightly but clearly higher than with Myrtol standardized.

At the end of the second week of treatment, the separations were even greater. The patients who received Myrtol standardized showed a fairly negligible non-responder rate of 1.3\%, whilst the non-responder rates were higher by a factor of 4 to 5 in the other two active treatment groups and higher by a factor of 10 in the placebo group.

The non-responder rates after the second week of treatment considered only the non-responders that became apparent for the first time during the second week. In other words, the non-responders after the first week of treatment are not included here. Non-responder in this study means that no improvement in the acute bronchitis occurred under treatment. Myrtol standardized showed a non-responder rate of only 5.3\% after one week of treatment (5.4\% in EAP) and the risk that a deterioration may occur in the second week of treatment was in fact a negligible 1.2\% (1.3\% in EAP), and this is a significantly lower than in all the other treatment arms.

The primary endpoint of this GCP-conforming study was the responder rate of Myrtol standardized versus placebo and versus cefuroxime after one week of treatment. The striking difference between the responder rate in the group of patients treated with Myrtol standardized and the placebo group after one week of treatment was statistically highly significant ($p < 0.001$). Interestingly, no statistically significant difference ($p = 0.85$) could be seen in the responder rates of Myrtol standardized versus cefuroxime.

In the second week of treatment, the difference between Myrtol standardized and placebo was even more evident, and the difference in the responder rates between Myrtol standardized and cefuroxime remained the same.

One of the secondary parameters evaluated in this study were nocturnal coughing fits\textsuperscript{[1]}. When checking for effects of treatment, the symptom "nocturnal coughing fits" is superior to "coughing fits during the day" in general, as coughing fits during the day are often also overlaid by central nervous system effects\textsuperscript{[2,3]}.

At the start of the study, all the patients complained of awakening at least four times as a result of nocturnal coughing fits. After one week of treatment, half of the patients in the active treatment groups no longer reported nocturnal coughing attacks, and in the second week this even exceeded the 70 % mark (ITT) or the 80 – 90 % mark (EAP). Impairments due to disturbed sleep, which always play a very important role in the healing and recovery of every patient, improved significantly for the patients in the active treatment group.

---

\textsuperscript{1} Matthys H, de Mey C, Carls C, Ryš A, Geib A, Wittig T, Efficacy and Tolerability of Myrtol Standardized in Acute Bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol, Arzneim.-Forsch./Drug Res. (2000) 50(II), 8, 700 – 711

\textsuperscript{2} Matthys H, Expektorantien, in: Kummer F & Konietzko N (Hrsg.), Pharmakotherapie bronchialer Erkrankungen, Springer Verlag Wien, 1. edition 2000, 133 – 137

\textsuperscript{3} Matthys H et al., Schweiz. med. Wschr. (1985) 115: 307
Another of the secondary parameters evaluated in this study were coughing fits during the day[1]. Although the symptom ”nocturnal coughing fits” is superior to ”coughing fits during the day“ as a variable to assess the effects of treatment, coughing fits during the day is subjectively rated by the patients as no less of a nuisance. At the start of the study, 91 – 94 % of the patients complained of coughing fits during the day. In both the ITT and the EAP populations, a continuous rise in freedom from attacks of coughing during the day could be seen in all three active treatment groups. After two weeks of treatment, almost half of the ITT patients and more than half of the EAP patients no longer complained coughing fits during the day.

---

Pathological auscultation findings (mainly sibilant ronchi and buzzing over all the lung sections) were also evaluated as secondary parameters in this study. These were noted in 72 – 76% of all the patients at the start of the study[1].

Both in the ITT and in the EAP populations, all three active treatment groups show a continuous reduction in pathological auscultation findings. The patients who received Myrtol standardized showed pathological auscultation findings in 73% of cases at the start of the study. This could be reduced to 28% after just one week of treatment, and to a negligible 3% after two weeks. The progress in the Myrtol standardized group approximately matched that of the cefuroxime group, whilst the reduction under ambroxol took place rather more slowly. By contrast, the reduction in auscultation findings was markedly poorer under placebo.

References

3 Indication fields

3.3 Acute bronchitis

3.3.1 GCP-conforming, randomized, controlled, multicentre study

3.3.1.9 Global assessment of efficacy

The investigators assessed the global efficacy of Myrtol standardized after one week of treatment in this GCP-conforming study as good or very good in 79 % of cases, and also as such for cefuroxime in 74 % of cases and for ambroxol in 67 % of cases (ITT population in each case), whilst they gave placebo the same rating in only 42 % of cases\(^1\). The patient's assessment matched the investigator's assessment almost exactly, with the global efficacy being rated as good or very good in 78 % of cases under Myrtol standardized, 74 % under cefuroxime, 66 % under ambroxol, and 41 % under placebo.

As can be seen in the above right bar chart for the EAP population, Myrtol standardized was rated as good or very good in 90 % of cases after 2 weeks of treatment, and even in 92 % of the cases remaining in the study at the end-of-study visit after four weeks.

The secondary parameters evaluated in this study included not just the recording of all adverse events and adverse drug reactions according to the criteria stipulated by GCP but also the global assessment of tolerability by the individual investigators[1]. After global evaluation of the study, 56 cases of adverse drug reactions had at least possibly related to the study medication assessed by the investigator. These cases can be broken down according to treatment arms as follows: Myrtol standardized 18, placebo 4, cefuroxime 15, and ambroxol 19. Discontinuation of the study due to adverse drug reactions was occurred in 27.7% of cases (Myrtol standardized), 50% (placebo), 53.3% cefuroxime, and 10.5% (ambroxol). The investigators and patients uniformly assessed the global tolerability of all four treatment arms as good or very good in virtually 90% of cases after one week and after two weeks of treatment. Here, for once, there was no difference between Myrtol standardized and placebo.

In this randomized, double-blind, placebo-controlled, multicentre study according to international GCP standards, a total of 676 outpatients (ITT population) with acute bronchitis who received either Myrtol standardized (n = 170), cefuroxime (n = 171), ambroxol (n = 163) or placebo (n = 172) were investigated over a treatment period of two weeks\[1\].

Myrtol standardized was comparable to placebo with regard to tolerability, but clearly superior to placebo with regard to efficacy in the treatment of acute bronchitis. The improvement in the clinical condition was more rapid and more pronounced under Myrtol standardized. Although tolerated equally well as the other treatment forms, Myrtol standardized showed slight superiority to cefuroxime and to ambroxol with regard to several of the investigated parameters.

Antibiotics are still often prescribed in acute bronchitis, despite the sound recommendations of professionals. Although it cannot be doubted that they are effective, the effect is not in proportion to the risk associated with the resulting increase in resistance to antibiotics\[2,3\]. The study confirms that Myrtol standardized can be accepted as a well proven alternative to antibiotics for acute bronchitis, as they are evidently efficacious but carry no inherent risk to cause bacterial resistance.

---

3 Indication fields

3.3 Acute bronchitis

3.3.2 Retrospective post marketing surveillance study in children

3.3.2.1 Study design

Retrospective post marketing surveillance study

184 children with acute bronchitis

- General practitioners (83 %), ENT specialists and paediatricians in Germany
- Gelomyrtol® forte (n = 59)
- Gelomyrtol® (n = 125)

Duration of treatment: 10 days (median)

A retrospective post marketing surveillance study in 1994 evaluated the data of 184 children (55.4 % females; median age 10 years, minimum 1 year, maximum 14 years) with acute bronchitis[1]. The information was recorded by general practitioners (83 %), ENT specialists and paediatricians in Germany.

The administration of Gelomyrtol® or Gelomyrtol® forte was broken down as follows:

<table>
<thead>
<tr>
<th>Bodyweight (age)</th>
<th>Gelomyrtol®</th>
<th>Gelomyrtol® forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 30 kg (ca. 1 – 9 years)</td>
<td>49.1 %</td>
<td>23.4 %</td>
</tr>
<tr>
<td>31 – 40 kg (ca. 9 – 11 years)</td>
<td>32.7 %</td>
<td>29.8 %</td>
</tr>
<tr>
<td>41 – 50 kg (ca. 11 – 13.5 years)</td>
<td>16.4 %</td>
<td>27.7 %</td>
</tr>
<tr>
<td>51 – 80 kg (ca. 13.5 – 18 years)</td>
<td>1.8 %</td>
<td>19.1 %</td>
</tr>
</tbody>
</table>

The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 10.0 days (median in each case). Antibiotics (48.3 %) and analgesics (16.4 %) were the most commonly reported concomitant medications.

---

3 Indication fields

3.3 Acute bronchitis

3.3.2 Retrospective post marketing surveillance study in children

3.3.2.2 Cough in children

This retrospective post marketing surveillance study in 1994 evaluated the data of 184 children with acute bronchitis recorded by general practitioners (83%), ENT specialists and paediatricians in Germany\(^1\). The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 10 days (median in each case).

At the time of inclusion into the study, nearly 80% of the children complained of a severe cough. Under treatment both with Gelomyrtol® and with Gelomyrtol® forte, over 90% of the children showed an improvement in cough symptoms after a duration of treatment of 10 days (median). Over half of the children (54%) were cough-free under Gelomyrtol®, and this was even 84% of children under Gelomyrtol® forte.

---

\(^1\) Hanisch F & Bock P, Sekretoyltika bei akuter Bronchitis bei Kindern, Myrtol standardisiert Dokumentation 1994
Over 90% of the children in this retrospective post marketing surveillance study showed an improvement in cough symptoms; over half were cough-free under Gelomyrtol® and even 84% under Gelomyrtol® forte\[1\].

This remarkable improvement in cough symptoms with Gelomyrtol® or Gelomyrtol® forte is reflected in the extremely favourable global assessments of the efficacy and tolerability by the treating physicians:

- The global efficacy of Gelomyrtol® or Gelomyrtol® forte was rated as "very good or good" in 97.5% of cases.
- The global tolerability of Gelomyrtol® or Gelomyrtol® forte was also rated as "very good or good" in 97.5% of cases.

---

1 Hanisch F & Bock P, Sekretolytika bei akuter Bronchitis bei Kindern, Myrtol standardisiert Dokumentation 1994
3 Indication fields

3.4 Chronic bronchitis

3.4.1 GCP-conforming, randomized, controlled, multicentre study

3.4.1.1 Study design

Randomized, double-blind, placebo-controlled, multicentre study

246 patients with chronic bronchitis

19 specialists for respiratory, internal and general medicine in Germany

Gelomyrtol® forte: 3 x 300 mg/day

Placebo

Duration of treatment: 6 months

This randomized, double-blind, multicentre study according to GCP standard investigated Myrtol standardized (Gelomyrtol® forte) against placebo in patients with chronic bronchitis under long-term treatment (6 months) during the winter time. A total of 19 centres (6 specialists for respiratory medicine, 7 specialists for internal medicine and 6 specialists for general medicine) in Germany participated in this study[1].

A total of 272 patients with chronic bronchitis (according to WHO definition) and a FEV1 ≥ 50 % of the predicted value who had shown at least one acute exacerbation during the preceding winter were enrolled into the study. Any concomitant medication possibly necessary conformed with the current guidelines of the Deutsche Atemwegsliga and European Guidelines and was continued unchanged during the clinical phase. A total of 246 patients (Myrtol standardized: n = 122; placebo: n = 124) received test medication for at least one month (ITT population). The data of 215 patients (Myrtol standardized: n = 110; placebo: n = 105) were included in the efficacy evaluation as the per-protocol population (PP)[1].

This clinical study was considered in a systematic review of the Cochrane Collaboration[2] (only 23 of 400 studies were included in the review) and was one of the few to be given a Quality Score of 4 out of a possible 5 points[3].

2 Poole PJ & Black PN, Mucolytics in chronic bronchitis, Cochrane Database Syst. Rev. (2004) Issue 4
This multicentre study was performed on 272 outpatients (ITT population: n = 246) with chronic bronchitis (according to WHO definition), at least one acute exacerbation during the preceding 12 months, and a FEV1 ≥ 50 % of predicted value\(^1\). Any concomitant medication possibly necessary conformed with the current guidelines of the Deutsche Atemwegsliga and European Guidelines and was continued unchanged during the clinical phase.

Criteria for exclusion from the study encompassed an infection which in the view of the investigator required antibiotic therapy and any antibiotic treatment within the two months preceding inclusion into the study.

The ITT population comprised 246 outpatients (55.7 % women) with chronic bronchitis. The mean age of the ITT population was about 60 years, the youngest patient was 18 and the oldest was 95 years of age.

The mean FEV1 value was 75 %. The proportion of non-smokers or ex-smokers was 64 % in the Myrtol standardized group and 71 % in the placebo group.

---

3 Indication fields

3.4 Chronic bronchitis

3.4.1 GCP-conforming, randomized, controlled, multicentre study

3.4.1.3 Acute exacerbation: definition

Acute Exacerbation

Newly occurring or considerably increased mucopurulent or purulent sputum or cough plus at least one of the following symptoms

- Increased sputum thickness
- Difficulties in expectoration
- Breathlessness
- Impairment of general well-being
- Symptoms of a common coldlike symptoms
- Body temperature > 38° C

The primary endpoint of this GCP-conforming study was the proof of efficacy using the reduction of the exacerbation rate.

In order to assume the presence of an acute exacerbation, the criteria set out above must be fulfilled\cite{1-4}. The diagnosis of an exacerbation is thus based mainly on clinical criteria that are reported by the individual patients after they have been trained about the symptoms to be looked for.

Exacerbations that are separated by two or more symptom-free weeks were evaluated as separate events.

---

Patients with chronic bronchitis often suffer, particularly during the winter months, from acute exacerbations that can drastically worsen the clinical condition. For this reason, the question as to whether Myrtol standardized can exert a beneficial influence on the incidence and severity of acute exacerbation is of central medico-scientific interest. The primary endpoint of this multi-centre study was proof of efficacy on the basis of the reduction in the exacerbation rate\[1\].

In the "per-protocol population", 79/110 (71.8 %) of the patients under Myrtol standardized and 56/105 (53.3 %) of the patients under placebo showed no acute exacerbations during the six-month treatment period (p < 0.01).

The results for the ITT population were similar: 89/122 (72.9 %) of the patients under Myrtol standardized and 72/124 (58.0 %) of the patients under placebo showed no acute exacerbations (p < 0.05).

---

Because of the already described problem that patients with chronic bronchitis often become ill from acute exacerbations during the winter months, the key scientific point of interest in this randomized multicentre study was whether Myrtol standardized can exert a beneficial influence on the incidence and severity of acute exacerbations[1].

The above graphs show the course of the monthly and cumulative exacerbation rates of the patients enrolled in this study. The number of patients under Myrtol standardized with acute exacerbations varied between 7 and 8 per month, except in the last month of treatment when it was 3. In the placebo group, 5 patients showed an acute exacerbation during the first month of treatment, 18 during the third month, and 7 during the sixth month.

The treatment with Myrtol standardized had the result that the exacerbation peak typical for the time of year and observed in the placebo group between months two and four of treatment (corresponding to the months of December to February for most of the patients) was simply not evident in the Myrtol standardized group; Myrtol standardized actually seemed to abolish this seasonal, naturally occurring peak.

This multicentre clinical study investigated Myrtol standardized (Gelomyrtol® forte) against placebo in 246 patients with chronic bronchitis (ITT population) under long-term treatment during the winter time[1]. A total of 19 centres (6 specialists for respiratory medicine, 7 specialists for internal medicine and 6 specialists for general medicine) in Germany participated in this study.

It was striking and pleasing to see that the relative frequency of exacerbation-free patients in the Myrtol standardized group was equally high under all three groups of physicians. It is also evident that more patients were exacerbation-free under placebo when they were treated by a specialist for respiratory medicine.

What is the explanation of this centre effect? The patients treated by a specialist for respiratory medicine received concomitant drug therapy considerably more often than those treated by the other physicians. 35% of the patients treated by a specialist for respiratory medicine received oral and/or inhaled corticosteroids in addition to the test medication, whereas not a single one of the patients treated by the specialist for internal or general medicine required corticosteroids. This is also reflected in the different values for the lung function parameters. The mean FEV1 value fluctuated between 74 and 101% in the patients treated by a specialist for respiratory medicine, and was thus higher than in the patients treated by the other groups of physicians (66 – 78%).
This shows that Myrtol standardized possesses a pronounced prophylactic action in chronic bronchitis, but that the add-on effect in (therapy-intensive) corticosteroid-dependent bronchitis is small. However, although it is true the base therapy with sympathicomimetic agents and corticosteroids does protect effectively against exacerbations, it is justified to assume that a comparable protective effect can also be achieved with Myrtol standardized instead of these potentially more aggressive alternative medications.

The need for systemic antibiotic therapy is an important indicator for the severity of acute exacerbations. The question as to whether Myrtol standardized can also reduce the antibiotic requirement is also of particular scientific interest. In the Myrtol standardized group, 15 of 31 (48.4%) patients with an acute exacerbation required no antibiotics, as opposed to 19 of 49 (38.8%) patients in the placebo group. The duration of antibiotic therapy was also longer under placebo: 10 of 16 (62.5%) patients who received Myrtol standardized required antibiotics for up to 7 days, as opposed to 23 of 30 (76.7%) patients in the placebo group who required antibiotics for longer than seven days. This shows that the treatment with Myrtol standardized in this study reduces the requirement for antibiotics and also shortens the duration of their use.

This randomized, double-blind, multicentre study according to international GCP standards examined a total of 246 patients (ITT population) with chronic bronchitis who received either Myrtol standardized (Gelomyrtol® forte) or placebo as long-term treatment (6 months) during the winter time[1]. The Gelomyrtol® forte group contained statistically significantly more patients with no exacerbations than did the placebo group. The study documents that long-term treatment with Gelomyrtol® forte markedly reduces the frequency and severity of the acute exacerbations during a 6-month period of treatment in the winter time. The treatment with Gelomyrtol® forte also had the result that the exacerbation peak typical for the time of year and observed in the placebo group between months two and four of treatment (months of December to February for most patients) was not observed in the Gelomyrtol® forte group.

Myrtol standardized is tolerated just as well as placebo in the long-term treatment of patients with chronic bronchitis, but is clearly more effective in preventing acute exacerbations in winter. The severity and the frequency of the exacerbations, the antibiotic requirements, and the impairment of the quality of life due to cough and expectoration were statistically significantly and clinically relevantly lowered by Myrtol standardized. The favourable assessment of this clinical study in a systematic review of the internationally renowned Cochrane Collaboration[2] with Myrtol standardized as the only mucosecretolytic herbal medicine impressively rounds off this clinical study[1].

Between January and March 1989, a single-centre, double-blind phase-IV trial under the direction of Prof. Dr. Ulmer on patients with chronic obstructive bronchitis was performed at the Medical University and Outpatients Department of the “Berufsgenossenschaftliche Krankenanstalten Bergmannsheil Bochum”[1].

A total of 20 patients (16 men, 4 women) between 38 and 80 years of age (mean: 61.7 years) who required inpatient care owing to an exacerbation of their chronic-obstructive bronchitis were included.

The average duration of illness was 8.8 years (median). At the start of the study the patients received 4 x 1 capsules of Gelomyrtol® forte or placebo for a period of 14 days. Inhaled sympathicomimetics were permitted as concomitant medication, and all the patients were corticosteroid dependent.

The patients complained on admission of cough attacks several times daily (90 %) and of a usually severe feeling of difficulty in breathing (55 %). The mean resistance on admission was 8.39 cm H₂O/l/sec.

There were no significant differences between the active treatment and placebo group with regard to demographic details such as sex, age, bodyweight, height and duration or history or with regard to type and amount of concomitant medication.

---

A total of 20 patients with chronic obstructive bronchitis with moderate bronchial obstruction were admitted into the randomized, placebo-controlled, double-blind study. These patients then received either Myrtol standardized at a dosage of 4 x 300 mg/day or placebo and were treated as inpatients[1].

A clear majority of patients (90 %) complained on admission of several attacks of coughing daily. In the course of the 14 days of treatment, a continual increase in the percentage of cough-free patients could be seen in the Myrtol standardized group, and this exceeded the 60 % mark after two weeks.

An initial improvement was also apparent in the placebo group, but the proportion of cough-free patients did not remain stable. On the contrary, a falling trend in the number of symptom-free patients could be seen, and in the second week of treatment there was once again a significant proportion of patients (10 – 15 %) who complained of an increase in attacks of coughing and therefore a deterioration in their clinical condition.

The patients of this double-blind study complained on admission of usually severe feelings of difficulties in breathing (55 %)[1]. The mean resistance on admission was 8.39 cm H₂O/l/sec, which corresponds to moderate bronchial obstruction (normal: < 3.5 cm H₂O/l/sec[2]).

Here also, the course of the symptom observed over the two weeks of treatment closely correlated with the course of the symptom ”cough”. In the Myrtol standardized group there was a continual increase in the number of patients who had no feeling of difficulties breathing, and this was over 60 % after two weeks. None of the patients in the Myrtol standardized group showed a deterioration in lung function.

In the placebo group, there was also initially a moderate improvement. However, here also the number patients free from difficulties breathing did not remain stable. The proportion of symptom-free patients clearly decreased in the second week of treatment, and the number of patients who complained of an increase in difficulties in breathing rose in the second week of treatment to a value as high as 20 %.

2 Nolte D, Asthma, Urban & Schwarzenberg, 4. edition 1989, 80
3 Indication fields
3.4 Chronic bronchitis
3.4.3 Retrospective post marketing surveillance study in children
3.4.3.1 Study design

Retrospective post marketing surveillance study

25 children with chronic bronchitis

General practitioners (60 %), specialists of respiratory medicine and paediatricians in Germany

Gelomyrtol® forte (n = 12)
Gelomyrtol® (n = 13)

Duration of treatment: 37 days (median)

A retrospective post marketing surveillance study in 1994 evaluated the data of 25 children (52 % females; median age 10 years, minimum 6 years, maximum 14 years) with chronic bronchitis\(^1\). The information was recorded by general practitioners (60 %), specialists of respiratory medicine and paediatricians in Germany. The administration of Gelomyrtol® or Gelomyrtol® forte was broken down as follows:

<table>
<thead>
<tr>
<th>Bodyweight (age)</th>
<th>Gelomyrtol®</th>
<th>Gelomyrtol® forte</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 30 kg (ca. 1 – 9 years)</td>
<td>44.4 %</td>
<td>27.3 %</td>
</tr>
<tr>
<td>31 – 40 kg (ca. 9 – 11 years)</td>
<td>44.4 %</td>
<td>36.4 %</td>
</tr>
<tr>
<td>41 – 50 kg (ca. 11 – 13.5 years)</td>
<td>11.1 %</td>
<td>36.4 %</td>
</tr>
<tr>
<td>51 – 80 kg (ca. 13.5 – 18 years)</td>
<td>0.0 %</td>
<td>0.0 %</td>
</tr>
</tbody>
</table>

The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 37 days (median in each case). Secretolytics (40 %) and antitussives (30 %) were the most commonly reported concomitant medications.

\(^1\) Hanisch F & Bock P, Sekretolytika bei chronischer Bronchitis bei Kindern, Myrtol standardisiert Dokumentation 1994
This retrospective post marketing surveillance study in 1994 evaluated the data of 25 children with chronic bronchitis recorded by independent general practitioners (60 %), ENT specialists and paediatricians in Germany[1]. The average dosage was 360 mg (900 mg) of Myrtol standardized for Gelomyrtol® (Gelomyrtol® forte) per day and the average duration of treatment was 10 days (median in each case).

At the time of inclusion into the study, nearly all the children complained of a severe cough. Under treatment both with Gelomyrtol® and with Gelomyrtol® forte, almost 70 % of the children showed an improvement in cough symptoms after a duration of treatment of 37 days (median). Almost 30 % of the children were cough-free under Gelomyrtol®, and even 80 % under Gelomyrtol® forte.

1 Hanisch F & Bock P, Sekretolytika bei chronischer Bronchitis bei Kindern, Myrtol standardisiert Dokumentation 1994
This retrospective post marketing surveillance study in 1994 evaluated the data of 25 children with chronic bronchitis\textsuperscript{[1]}. Almost 70 % of the children showed an improvement in cough symptoms, with almost 30 % of the children cough-free under Gelomyrtol\textsuperscript{®} and even 80 % under Gelomyrtol\textsuperscript{®} forte.

This striking improvement in cough symptoms with Gelomyrtol\textsuperscript{®} and Gelomyrtol\textsuperscript{®} forte is reflected in the extremely favourable assessments of the global efficacy and tolerability by the treating physicians:

The global efficacy of Gelomyrtol\textsuperscript{®} or Gelomyrtol\textsuperscript{®} forte was rated as "very good or good" in 80.2 % of cases.

The global tolerability of Gelomyrtol\textsuperscript{®} or Gelomyrtol\textsuperscript{®} forte was furthermore rated as "very good or good" in every case (100 %).

\textsuperscript{[1]} Hanisch F & Bock P, Sekretolytika bei chronischer Bronchitis bei Kindern, Myrtol standardisiert Dokumentation 1994
Airways infections are the most common diseases to affect humans. The pathophysiological correlate of these airways diseases is disturbed mucociliary clearance sequelary to inflamed mucosal changes or a disturbed efferent secretion transport. The aims of therapy are to reduce symptoms, to prevent complications, and to reduce the illness-related time off work. Mucopharmaceuticals are for this reason the focus of new international attention. In addition to mucosecretolytic properties, antiinflammatory components of action have now also become the subject of scientific discussion.

This comprehensive book on the clinic documentation of Myrtol standardized impressively shows that Myrtol standardized possesses not only the classical mucosecretolytic properties that are associated with improvement in the mucociliary and cough clearance but also other additional properties that can be summarized as antioxidative or antiinflammatory. This is of major
clinical relevance for the pathophysiological core defect, namely, the mucosal inflammation, in both acute and chronic forms of the disease.

The efficacy of any medicinal product can only be regarded as proven once evidence to this effect is available from validated clinical trials. The therapeutic benefits of Myrtol standardized have been proven by several randomized, placebo-controlled, multicentre studies which were planned, performed and reported in accordance with the guidelines of Good Clinical Practice. The quality and size of these studies makes Myrtol standardized unique among mucosecretolytic herbal medicines. In acute diseases of the airways such as acute bronchitis and acute sinusitis, Myrtol standardized was able to demonstrate that the patients showed a more rapid and more pronounced improvement in symptoms than under placebo, and this was further effectively supported by a lower antibiotic requirement and a lower degree of incapacitation. In patients with chronic bronchitis, the severity and frequency of exacerbations and also the antibiotic requirement and impairment of quality of life due to cough and expectoration were statistically significantly and clinically relevantly lowered by Myrtol standardized.
I should like to thank Mrs. Marianne Boskamp, General Manager G. Pohl-Boskamp GmbH & Co. KG Hohenlockstedt, for her generous support and her invariably pleasant cooperation.
I should like to thank Mrs. Algeth Zierke, Logistics Manager, Mrs. Kerstin Femerling, née Siebken, Director Marketing, and Dr. rer. nat. Wolfgang Saupe-Thies, Key Account Manager, all of the firm G. Pohl-Boskamp GmbH & Co. KG Hohenlockstedt, for their constant availability for discussion and their valuable input.

My thanks also go to Mr. Michael Herold of Typografikdesign, Heiligenstedten, whose expert knowledge and skill made it possible for the book to take form.

Prof. Dr. med. Hans Behrbohm, Head of ENT-Department and Facial Plastic Surgery of the Park-Klinik Weissensee in Berlin, I wish to thank for the permission to use one of his pictures in this book.

Prof. Dr. med. Konrad Morgenroth of the Institute for Pathology of the Ruhr University of Bochum, I wish to thank for the permission to use his scanning electron microscope picture in this book.

And finally, I wish also to thank my wife Annette for her support and for her understanding of the many hours of working late.