

EUCARBON[®]
Tablets

Scientific Brochure

EUCARBON[®]

A natural intestinal regulator with a unique twofold action:

- as a mild laxative and
- as an agent against mild forms of diarrhoea



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1. Introduction to Eucarbon® Tablets

1.1 Characteristics

Eucarbon® was developed in 1909 by the pharmacist Mag. F. Trenka and by Prof. Dr. W. Pauli.

Eucarbon® tablets contain only vegetable and mineral active ingredients and are produced with up-to-date production methods in accordance with GMP-Standards. Eucarbon® stimulates the entire digestive system, increases colonic motility, has a mild laxative and spasmolytic effect, relieves gas pains and can also be regarded as a detoxifying agent (mild adsorbent).

Eucarbon® is a combination of anthranoid drugs (senna and rhubarb), sulfur, and the mild adsorbent vegetable charcoal (carbo ligni) - ingredients which as single drugs/substances or in different combinations have been used as remedies for centuries in patients with intestinal complaints, mainly with constipation. In the unique combination of this preparation the proven and generally accepted effects of the single ingredients have additional beneficial effects – presented in a standardized dosage form.

It is a medicinal product with mainly laxative effects. It also regulates digestion in a totally natural way and provides for regular functioning of the digestive system.

The action of the preparation is due to the content of vegetable charcoal and the stimulatory action of anthraquinones and sulfur.

Furthermore Eucarbon® has a double effect against pain:

- the essential mint and fennel oils have well-known spasmolytic and carminative effects,
- the amount of gas and tension in the abdominal cavity is reduced through adsorption, thus bringing about pain relief (mechanical effect).

1.2 Composition

Active ingredients:

Fol. sennae	– Senna Leaf	105,00 mg
Extractum Rhei	– Rhubarb Extract	25,00 mg
Carbo Ligni	– Wood Charcoal	180,00mg
(Vegetable charcoal)		

Sulfur depuratum – Sublimed Sulfur 50,00 mg
(Aetherol, Menthae 0,5 mg, Aetherol, Foeniculi 0,5 mg)

1.3 Uses

- Mild laxative, indicated for the relief of all forms of constipation
- sluggishness of the bowels
- haemorrhoidal obstipation
- fermenting and putrefying processes in the intestines
- meteorism
- flatulence (elevated diaphragm)
- intestinal auto-intoxication

(The indications are partly different in various countries.)

1.4 Dosage

Instructions for use:

- Adults and adolescents from 12 years on: 1 – 2 tablets 3 times a day (at or after meals) with some liquid. If a stronger effect is desired, the evening dose should be raised to 3 or 4 tablets.
- Children from 2 years on: ½ – 1 tablet up to 3 times a day at meals with some liquid

At low doses (1-3 tablets daily), Eucarbon® has an adsorbent effect, at higher doses (4-6 tablets daily), Eucarbon® has both, an adsorbent and laxative effect.

For X-ray purposes (adults): 6 to 8 tablets as a single dose in order to cleanse the digestive tracts and remove all gas.

In order to achieve intestinal regularity in the treatment of Irritable Bowel Syndrome (IBS) it will be necessary to observe two conditions:

- an average period of treatment of 4 to 6 weeks until regular transit is achieved and
- a progressive reduction of dosage in conformity with the progress of improvement of the intestinal functions

1.5 Safety

The efficacy and safety of Eucarbon® tablets have been established and highly acknowledged for nearly 100 years. There are no preparation-specific contra-indications known for Eucarbon®.

The overall tolerability and safety of Eucarbon® is known worldwide and traditionally documented. Using Eucarbon® as a drug of choice in constipation has never been associated with life-threatening adverse reactions. In the usual dosage regime, i.e. at the recommended doses, Eucarbon® does not even show preparation-related side effects, neither in the daily practice nor in clinical studies.

There are no findings on drug interactions for Eucarbon® so far nor any restrictions on the ability to drive or to operate machinery.

1.6 Drug interactions

Overdose of laxatives in general may upset the water and electrolyte balance so that for instance the tolerance of digitalis compounds may be lessened.

1.7 Contra-indications

- Hypersensitivity to one of the components

In case of

- Ileus or intestinal obstruction
- Enteritis, appendicitis or abdominal pain without known cause
- Serious disorder of water and electrolyte balance
- When gastric or intestinal ulcer is suspected any kind of laxative should be avoided; patient is to consult a doctor immediately.

1.8 Pack Details

Presentation: Original: 10, 30, 50 and 100 tablets
Hospital: 1000 tablets

2. Active Ingredients

Sennae folium:

Senna leaf consists of the dried leaflets of *Cassia senna* L. (*C. acutifolia* De Lile), known as Alexandrian or Khartoum senna, or *Cassia angustifolia* Vahl, known as Tinnevely senna, or a mixture of the two species. It contains not less than 2,5 percent of hydroxyanthracene glycosides, calculated as sennoside B (C₄₂H₃₈O₂₀; M, 863) with reference to the dried drug. The main active ingredients are anthraquinone glycosides.

The material complies with the German Monograph “Sennae folium” of the Commission E (15).

It is used as a laxative due to the main effects: reduced absorption of liquids and salts, increased peristaltic activity of small and large intestine, and stool softening.

Extractum Rhei:

Rhubarb consists of dried rhizome and roots of *Rheum officinale* Baillon or of *Rheum palmatum* Linné (Fam. Polygonaceae), or of other species (excepting *Rheum Rhaponticum* Linné), or of hybrids of *Rheum*, grown in China, deprived of the periderm tissues. The rheum species also contain anthraquinone glycosides (3 – 7,5% anthracene derivatives) and in addition tannins and antioxidative agents. The material complies with the German Monograph (14), DAB 10, ÖAB 90, Helv. VII and Ph. Eur.

It is used as a laxative as well and has the main effects as for senna. As a result the stool remains soft and the action of the bowels is made easier.

Anthraquinone-content of Eucarbon®:

Referring to the Chemical-, Pharmaceutical- and Biological Documentation of Eucarbon®, the total content of anthraquinone is 3,30 ± 0,65 mg/tablet (2,65 – 3,95 mg/tablet).

Herbal Charcoal:

Synonym: Carbo Ligni, vegetable charcoal

Charcoal is a fine odourless, tasteless, black powder, free from grittiness. It is made from common charcoal by repeated nealing in closed containers and has a particularly detoxicating effect.

Classical experiments showed that vegetable charcoal has

the potential to adsorb inorganic poisons as well as viruses, bacteria and their metabolites (bacterial toxins). It can adsorb many drugs including digoxin, yellow oleander, barbiturates, and tricyclic antidepressants. Charcoal neutralises gases and toxins through adsorption and helps in cases of diarrhoea and acute oral poisoning (21).

Sulfur:

Sulfur is an element of molecular weight 32. It is yellow, tasteless and odourless and usually used in the form of precipitated sulfur, which is an amorphous or microcrystalline powder.

It melts at around 118 - 120°C to form a yellow liquid, which becomes dark and viscous at around 160°C. It is soluble only to a slight extent in water and alcohol, but quite freely soluble in carbon disulfide, light petroleum and turpentine (22). The element is present in all living tissues.

When taken by mouth, sulfur is converted in the gut into alkali sulfides with mild disinfectant properties, stimulation of peristalsis and promotion of a mild laxative effect.

The **essential mint and fennel oils** have well-known spasmolytic and carminative effects.

All active and inactive substances are subject to Pharmacopoeial specification with the exception of vegetable charcoal, which deviates from European Pharmacopoeia specification.

Eucarbon® components





				
Name	Herbal charcoal	Purified sulphur	Senna Leaves	Rhubarb root
Quantity	180 mg	50 mg	105 mg	25 mg

Figure 1: Eucarbon® components and composition.

3. Indications

3.1 Constipation

Chronic constipation is one of the most common complaints in clinical medicine. It is a rising problem in modern society affecting approximately one-fifth of all adults in industrialized countries.

Chronic constipation (Figure 2) is defined as the delayed evacuation of dry, hard stools (16) or the passage of small hard faeces infrequently and with difficulty (6).

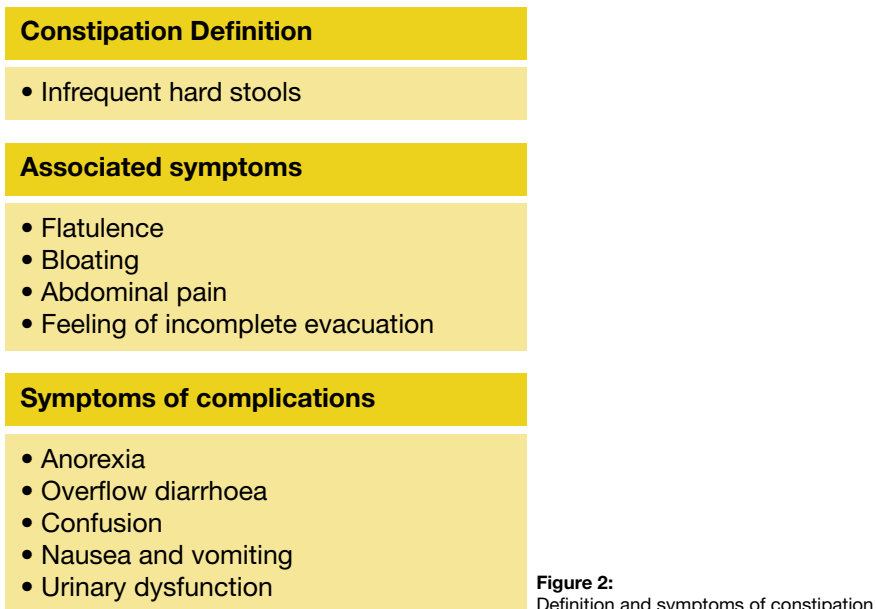


Figure 2: Definition and symptoms of constipation

Constipation has several possible causes (Figure 3). The most common ones are associated with nutritional factors such as the consumption of food with poor dietary fibre content, which results in insufficient filling of the intestine. Furthermore, intake of readily absorbed food with a reduced water-binding capacity or the lack of exercise may lead to constipation. Other causes include factors related to organ dysfunction or organ damage including gastro-intestinal disorders, changes in the intestinal

wall (due to a tumour or chronic inflammation e.g.), metabolic and endocrine disorders (diabetes mellitus e.g.), functional and organic disturbances of the nervous system, such as Parkinson's disease, or may be caused by the side-effects of drugs such as analgesics, antidepressants, antispasmodics or sedatives (26).

Constipation per se is diagnosed if no bowel movements occur for three days or more and if this irregularity persists for longer than six days.

Causes of constipation	
<p>Caused by diseases</p> <ul style="list-style-type: none"> • Abdominal tumours • Hypercalcaemia • Intra-abdominal or pelvic disease • Spinal cord compression • Cauda equina syndrome • Depression 	<p>Caused by treatment</p> <ul style="list-style-type: none"> • Antidepressants • Analgesics • Opioids • Antiemetics • Anticholinergics • Aluminium salts • Non-steroidal anti-inflammatory drugs
<p>Associated with debility</p> <ul style="list-style-type: none"> • Weakness • Inactivity or bed rest • Poor nutrition • Poor fluid intake • Confusion • Inability to reach the toilet 	<p>Concurrent disorders</p> <ul style="list-style-type: none"> • Haemorrhoids • Anal fissure • Endocrine dysfunction

Figure 3:
Causes of constipation

Many of the associated symptoms may mimic features of the underlying disease. About half of the patients admitted to specialist palliative care units report constipation, but about 80% of patients require laxatives (24).

3.2 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a benign relapsing chronic disorder, characterised by recurrent abdominal pain and altered bowel function. It is estimated that 9 to 22% of the general population has clinical symptoms of IBS (25) but only about 5% seek medical care. IBS is the most common diagnosis

made by gastroenterologists and accounts for approximately 50% of all referrals. It contributes significantly to disability, days off work or school and health care costs; 69 to 85% of the patients report that they experienced difficulties in carrying out their daily activities (3).

Patients complain of general symptoms of abdominal pain (most frequently located in the lower left quadrant), abdominal cramping, changes in bowel habits / stools (e.g., stools may be soft-formed with pencil-size diameter), flatulence and / or abdominal distension with the onset of symptoms usually weeks or months prior to seeking medical attention.

The cause of IBS is still unknown and abnormalities in gut motility fail to explain the diverse features of IBS. Symptoms of IBS may be related to stress, to depression, anxiety or other psychological manifestations, and food intolerance (most commonly lactose and gluten) or enteric infections. IBS is considered as a complex disease whereby clinical and therapeutical management is particularly difficult.

3.3 Radiological Examinations

Intestinal gas in excess impairs the quality of abdominal ultrasonic and X-ray investigations. Thus it is important to cleanse the bowel of its contents thoroughly before sonographic or radiological procedures such as barium enema or urography (4, 5).

Standard regimens for emptying of the bowel prior to radiographic or sonographic examinations are laxatives and diet for 24 hours, occasionally supplemented by oral ingestion of an electrolyte polyethylene glycol solution or by an enema. Especially for the elderly, the bowel preparation providing optimum cleansing of the bowel with the least associated discomfort and inconvenience for the patient must be found.



Figure 4:
Contrast radiograph of the colon
(patient with megacolon).
Minimum of bloating or flatulence after
Eucarbon® intake.

3.4 Further Indications

In some countries Eucarbon® is used as well in pregnant women suffering from constipation, gas, haemorrhoids and anal fissures, in post surgery situations for bedridden patients, in cases of constipation under the prescription of neuroleptics as well as in cases of bad breath caused by constipation.

4. Pharmacology

Eucarbon® tablets contain only vegetable and mineral ingredients. Eucarbon® stimulates the entire digestive system, increases colonic motility, has a mild laxative and spasmolytic effect, relieves gas pains and can also be regarded as a detoxifying agent.

4.1 Pharmacodynamics of Eucarbon®

As a combination of senna, rhubarb and carbo ligni as well as sulfur, Eucarbon®, by its pharmacological and pharmacodynamical properties, belongs to the stimulant laxatives. For the laxative effect these agents stimulate accumulation of water and electrolytes in the colonic lumen, and enhance intestinal motility, too. Due to the mild adsorptive activity of carbo ligni Eucarbon® also is a mild adsorbent and therefore a medicine against general digestive disorders (19).

The effects of Eucarbon® as a stimulant laxative on intestinal fluxes of electrolytes and water are readily demonstrated in vitro or in situ under conditions in which effects on motility are excluded (7). Concentrations of these agents that reduce net absorption of electrolytes and water also increase the permeability of the mucosa, possibly by making tight junctions leaky. The stimulant laxatives may inhibit intestinal Na⁺, K⁺-ATPases. This action could account for at least a portion of their laxative effect. Many of the stimulant laxatives also increase the synthesis of prostaglandins and cyclic AMP, and this action may contribute to increased secretion of water and electrolytes. Inhibition of prostaglandin synthesis with indomethacin does reduce the effects of many of these agents on net water flux (1). The mode of action of Eucarbon® is shown in Figure 5.

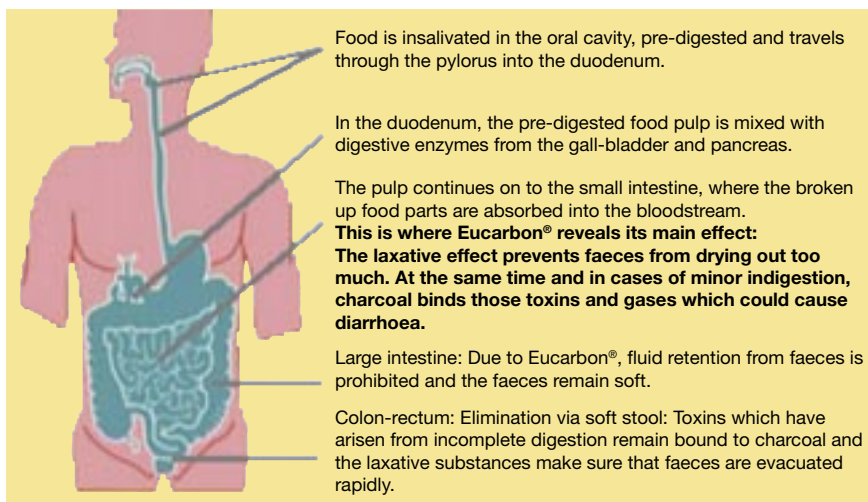


Figure 5:
Mode of action of Eucarbon®

4.2 Pharmacokinetics, Bioavailability of Eucarbon®

Since Eucarbon® is a combination product of senna, rhubarb, carbo ligni and sulfur, and since none of the active substances are absorbed but act in situ, no pharmacokinetic studies for Eucarbon® were conducted.

Adequate bioavailability can be supposed because efficacy has been shown for decades in daily practice and in several studies with the constituents as well as with the combination preparation Eucarbon®.

4.3 Toxicity Data of Eucarbon®

Information on the toxicity of the different components of Eucarbon® such as senna, rhubarb, carbo ligni (vegetable charcoal) as well as that of Eucarbon® tablets was collected, examined and evaluated in detail (7).

The results of the review and an acute toxicity study show that Eucarbon® was well tolerated without specific toxic effects. Eucarbon® caused no death among rats (19).

In spite of the fact that Eucarbon® was a well-tolerated drug, a purgative or laxative effect of Eucarbon® was noticed, which was dose dependent but did not give cause for concern as regards safety.

5. Clinical Efficacy of Eucarbon®

Eucarbon® has been on the market for nearly 100 years. The safety and efficacy of the ingredients per se is accepted by German Commission E monographs, European Pharmacopoeias and their inclusion in the “General Sales List” in the UK.

5.1 Clinical Studies with Eucarbon®

A number of clinical studies have been performed and clinical data have been systematically collected for Eucarbon®. Main outcome variables from clinical studies were Likert scales for severity of complaints, symptomatology, well-being as well as global assessment for efficacy and safety/tolerance, modified Clinical Global Impressions Score (CGI) (17) and modified Francis IBS-Score (8), which summarises the actual complaints, incorporating pain, distension, bowel dysfunction, classified as mild, moderate or severe.

Table 1: Tabular Overview of the Clinical Trials with Eucarbon®

Study Number	Author (Ref.-No)	Year	Title	Number of Patients treated with Eucarbon®
1	Breier (2)	1980	Clinical Results after the Application of Eucarbon® in Patients with Constipation	102
2	Pezzoli (20)	1981	Clinical Report on the Tolerance and Efficacy of Eucarbon®	31
3	Schmidbauer (23)	1985	Intestinal Cleaning before Uroradiology and Urosonography	28
4	N'dri Yoman (18)	1993	The Use of Eucarbon® in Preparing Radiology (Abdominal X-ray, Echography)	15
5	El Mirini (5)	1994	Evaluation of the Clinical Efficacy of Eucarbon® in the Preparation of Urography and Urologic Surgery	44
6	Machavariani (12)	2003	Use of Eucarbon® for the Treatment of Patients Suffering from Irritable Bowel Syndrome and from Constipation	35
7	Dumitrascu (4)	2003	A Combination of Charcoal and Senna Improves the Accuracy of Abdominal Ultrasonographic Investigation	14
8	Hübner / Alken (10)	2004	Treatment of Patients Suffering from Constipation with Eucarbon®	61

The following clinical study has been performed with modified Eucarbon tablets (containing as active ingredients 180mg carbo ligni, 105mg fol. sennae, 25mg extr. rhei) without sulfur (“Eucarbon herbal”). The remaining composition is unchanged and thus may give strong evidence for efficacy and safety in conformance with the original Eucarbon® tablets.

9	Hübner / Moser (9)	2002	Charcoal Tablets in the Treatment of Patients with Irritable Bowel Syndrome	145
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In all indications investigated Eucarbon® could prove its efficacy, namely in the relief of complaints in constipated patients or in patients suffering from irritable bowel syndrome as well as for the preparation of radiological or sonographic examinations (11).

In a recent drug-monitoring study (10), efficacy and safety of Eucarbon® tablets were investigated in patients suffering from constipation, especially those with spasmodic complaints. After the 12-week treatment period, 61 patients were available for analyses, whereby the following questionnaires were used: global assessment for efficacy and safety/tolerance, modified Clinical Global Impressions Score (CGI) (17) and modified Francis Score (IBS-Score) (8). The majority of patients took 3x2 tablets daily. All major symptoms and complaints like abdominal pain, altered frequency of stool, flatulence, hyperperistalsis, tenderness on pressure, tympanitic resonance, decreased during treatment. The global assessment of efficacy after 12 weeks treatment with Eucarbon® by physician and patient was consistent (Figure 6): the physicians rated the efficacy of the treatment at 93.5 % as “very good” and “good”, the patients at 93.4%. The medication was very well tolerated and efficacy and safety of the natural drug Eucarbon® in the indication constipation could be confirmed.

Global Assessment of Efficacy after 12 Weeks Treatment with Eucarbon®

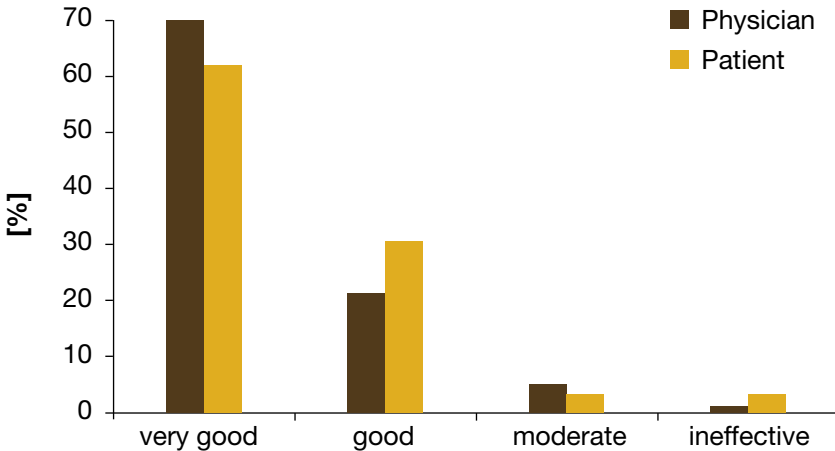


Figure 6: Global assessment of efficacy after 12 weeks treatment with Eucarbon® by physician and patients (10).

In some countries modified Eucarbon tablets without sulfur (“Eucarbon herbal”) are available (registered in some Eastern European, Asian and African countries). Although the tablets are modified by taking out sulfur, the remaining composition is unchanged and thus may give strong evidence for the same efficacy and safety profile as the original Eucarbon® tablets.

This could be shown in a double blind, controlled, randomised, multi-centre, prospective clinical trial in comparison to carbo ligni (C.l.) containing tablets (9). 284 patients between 19-70 years suffering from IBS started treatment (“Eucarbon herbal” group 145, C.l. group 139). After the 12-weeks treatment period 262 patients were available for ITT analysis, whereby changes of the disease and improvement in overall well-being were evaluated with a visual analogue scale (VAS) as the primary endpoint.

Symptoms decreased in the ITT population under “Eucarbon herbal” treatment by about 60%, but surprisingly the relative gain in terms of efficacy over the control group was only about 9% (Fig. 7). On the other hand a number of clinical

observations and subgroup analyses showed that “Eucarbon” has been much more effective, e.g. in the subgroup of patients suffering from constipation. Both treatments were well tolerated, adverse events occurred with similar frequency in both groups (22% of patients treated with “Eucarbon herbal” vs. 17% treated with C.I.). In most cases it was not possible to distinguish the event from symptoms of IBS. The results of this trial are regarded as supportive data, as the test preparation “Eucarbon herbal” had a modified composition compared to the original commercially available Eucarbon® containing no sulfur. Nevertheless regarding drug safety the data from this trial support the traditionally well-known good tolerance of Eucarbon® tablets.

Primary endpoint

Means of overall feeling VAS over visits (ITT population, n=262)

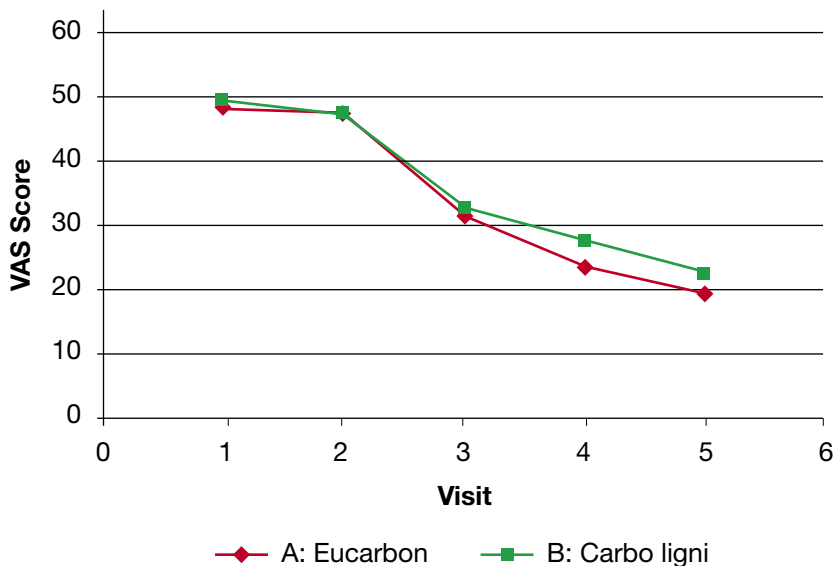


Figure 7: Improvement in overall well-being evaluated with a visual analogue scale (VAS) as the primary endpoint. Symptoms decreased in the ITT population under “Eucarbon herbal” treatment by about 60% (9).

6. Safety

The overall tolerability and safety of Eucarbon® is known worldwide and traditionally documented. Using Eucarbon® as a drug of choice in constipation has never been associated with life-threatening adverse reactions. In the usual dosage regime, i.e. at the recommended doses, Eucarbon® does not even show preparation-related side effects, neither in the daily practice nor in the studies mentioned (11).

There are neither findings on drug interactions so far nor any restrictions on the ability to drive or to operate machinery. No side effects are to be expected, if the doses are properly adhered to.

The MCA report “Safety of Herbal Medicinal Products” published in July 2002 (13) mentioned for rhubarb and senna as potential adverse events only “purgative, irritant to GI tract” – thus known effects - but recommended to avoid non-standardised preparations during pregnancy. Thus the excellent safety of the drugs could be confirmed.

Long-time experience and clinical studies have demonstrated that patients taking Eucarbon® for one or two weeks get relief of abdominal swelling and of dyspeptical troubles.

In case of suspected stomach or intestinal ulcers, appendicitis or intestinal obstruction, any kind of laxative should be avoided; patient is to consult a doctor immediately.

In general some undesirable effects have been reported under the intake of anthrachinone-laxatives:

Rarely occur abdominal pain and diarrhoea, uncommon are slight red chromaturia on its alcalic reaction. Rare are nausea and vomiting with anthrachinone-laxatives on central condition. Long-time administration in high doses of laxative may induce electrolyte losses, especially potassium losses, which can aggravate constipation (intestinal atony and constipation).

7. Summary

Eucarbon® is a combination of anthranoid drugs (senna and rhubarb), sulfur, and the mild adsorbent vegetable charcoal (carbo ligni) - ingredients which as single drugs/substances or in different combinations have been used as remedies for centuries in patients with intestinal complaints, mainly with constipation. In the unique combination of this preparation the proven and generally accepted effects of the single ingredients have additional beneficial effects – presented in a standardized dosage form.

It is a medicinal product with mainly laxative effects. The action of the preparation is due to the content of vegetable charcoal and the stimulatory action of anthraquinones and sulfur. The use of vegetable charcoal, rather than activated charcoal, avoids the significant drug binding of anthranoids and potential interactions. The adsorption properties of carbo ligni are regarded for the effect to cure complaints due to intestinal gases and support the antiputrefactive action of sulfur. This adsorbent activity of carbo ligni, although definitely lower compared to activated charcoal, has been extensively studied in the last 20 years. It could be demonstrated that carbo ligni adsorbs many chemical entities, but does not inhibit the release and efficacy of the anthrachinone glycosides from Eucarbon®. The detoxifying effect also has been studied and shown in in-vivo studies from various study groups (24). At low dosage of 1 to 3 tablets per day Eucarbon® exhibits its adsorption power, at higher dosages of 4 to 6 tablets per day Eucarbon® acts as a laxative.

The efficacy and safety of Eucarbon® have been established and highly acknowledged for nearly 100 years. There are no preparation-specific contra-indications known for Eucarbon®. Long-time experience and clinical studies have demonstrated that patients taking Eucarbon® for one or two weeks get relief of abdominal swelling and of dyspeptical troubles. The action of Eucarbon® is gradual, mild and prolonged. This determines its value. Eucarbon® is a well-tolerated product. Nevertheless patients have to take care – as for every drug treatment - and must not abuse it.

In case of constipation the herbal laxative ingredients in Eucarbon® have the effect, within six to eight hours, of

softening the faeces, thereby facilitating defecation. In the event of slight diarrhoea, the mild adsorbent carbo vegetabilis is capable of binding toxic substances in the intestine. Mild laxatives are capable of eliminating toxins, which may cause diarrhoea.

Eucarbon® possesses unique properties and is a valuable tool in the therapy of general digestive disorders with special regard to the indications (chronic) constipation, irritable bowel syndrome and in the preparation for improvement of X-ray and/or ultrasonic abdominal investigations. Because of its good tolerance and lack of drug-drug interactions it seems to be especially appropriate for the elderly and for long-term treatment.

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