SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eucarbon Tablets
Senokot Comfort Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
105 mg of Senna leaf (*Cassia senna* L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl),
25 mg of extract (as dry extract) from Rhubarb root (*Rheum palmatum* L. or *Rheum officinale* Baillon, or hybrids of these two species or a mixture) (3□ 5: 1)Extraction solvent : Ethanol 70% v/v
Corresponding to 2,65-3,95 mg of hydroxyanthracene glycosides (calculated as Rhein),
180 mg of Vegetable Charcoal.
50 mg of purified Sulfur

Excipient(s) with known effect:
Each tablet contains 43.4 mg of sucrose and 0.25 – 11.25 mg of lactose monohydrate.

For the full list of excipients, see section 6.

3 PHARMACEUTICAL FORM

Tablets for oral administration.
Grey-black, cylindric, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is a traditional remedy for short-term use in cases of occasional constipation.

4.2 Posology and method of administration

Posology

Adolescents over 12 years of age, adults, elderly

1-2 tablets with or after meals with liquid up to 3 times daily to obtain a laxative and purgative effect. If a stronger laxative effect is desired, the evening dose can be increased to 3 – 4 tablets of the product.
Herbal substance/preparation corresponding to 2.65 to 3.95 mg of hydroxyanthracene glycosides (calculated as Rhein) in one tablet.
The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to 8 tablets. The correct individual dose is the smallest required to produce a comfortable soft-formed motion.

Paediatric population

The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications).

Method of administration

For oral use.

Duration of use

Use for more than 1 - 2 weeks requires medical supervision.

If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted.

See also section 4.4 Special warnings and precautions for use.

4.3 Contraindications

Known hypersensitivity to the active substance.

Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn’s disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion.

Children under 12 years of age.

4.4 Special warnings and precautions for use

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking this product concomitantly.
Like all laxatives, this product should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting, unless advised by a doctor, because these symptoms can be signs of potential or existing intestinal blockage (ileus).
If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided.
If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.
This product should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.
When this product is administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces.
Patients with kidney disorders should be aware of possible electrolyte imbalance.

- Prolonged use may precipitate the onset of an atonic, non-functioning colon.
- Prolonged and excessive use may lead to fluid and electrolyte imbalance and hypokalaemia.
- Intestinal loss of fluids may promote dehydration. Symptoms may include thirst and oliguria.
- Laxatives do not help in long-term weight loss.

4.5 Interaction with other medicinal products and other forms of interaction

Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, with medicinal products, which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation.
Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage.
However, as a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. aloe-emodin, emodin, frangulin, chrysophanol and physcion, use is not recommended during pregnancy.

Lactation

Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk.
Small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported.

Fertility

Studies on fertility have not been carried out.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur.
This product may produce abdominal pain and spasm and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdose. In such cases dose reduction is necessary.
Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.
Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.
Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.
If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

The major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes, which should be replaced. Diarrhoea may especially cause potassium depletion, which may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, adrenocorticosteroids or liquorice root are being taken at the same time.
Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly.
Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: contact laxatives ATC-code: A06AB
The 1,8-dihydroxyanthracene derivatives of rhubarb and senna possess a laxative effect. The β-O-linked glycosides (e.g. sennosides) are not absorbed in the upper gut; they are converted by bacteria of the large intestine into the active metabolite (rhein anthrone). There are two different mechanisms of action:
1. stimulation of the motility of the large intestine resulting in accelerated colonic transit.
2. influence on secretion processes by two concomitant mechanisms viz. inhibition of absorption of water and electrolytes (Na+, Cl-) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon.
Defaecation takes place after a delay of 8 - 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.
Sulphur acts in the small intestine and the hydroxyanthracene derivatives of rhubarb and senna act in the large intestine. Apart from the purging effect the product has an adsorbing attribute due to the vegetable charcoal

5.2 Pharmacokinetic properties

The β-O-linked glycosides (sennosides) are neither absorbed in the upper gut nor split by human digestive enzymes. They are converted by the bacteria of the large intestine into the active metabolite (rhein anthrone). The absorbed

anthraquinone aglycones are transformed into their corresponding glucoronides and sulphate derivatives.
Aglyca are absorbed in the upper gut. Animal experiments with radio-labelled rhein anthrone administered directly into the caecum demonstrated absorption < 10%. In contact with oxygen, rhein anthrone is oxidised into rhein and sennidins, which can be found in the blood, mainly in the form of glucuronides and sulphates. After oral administration of sennosides, 3 - 6% of the metabolites are excreted in urine; some are excreted in bile.
Most of the sennosides (ca. 90%) are excreted in faeces as polymers (polyquinones) together with 2 - 6% of unchanged sennosides, sennidins, rhein anthrone and rhein. In human pharmacokinetic studies with senna pods powder (20 mg sennosides), administered orally for 7 days, a maximum concentration of 100 ng rhein/ml was found in the blood. An accumulation of rhein was not observed. Active metabolites, e.g. rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental passage of rhein is low.

5.3 Preclinical safety data

The active ingredients of the product have been used extensively over many years and are well established. No relevant pre-clinical data are therefore available.
Senna leaves:
There are no new, systematic preclinical tests for senna leaves or preparations thereof. Data derive from investigations with senna pods. Since the spectrum of constituents of senna leaf and fruit is comparable these data can be transferred to senna leaves. Most data refer to extracts of senna pods containing 1.4 to 3.5% of
anthranoids, corresponding to 0.9 to 2.3% of potential rhein, 0.05 to 0.15% of potential aloe-emodin and
0.001 to 0.006% of potential emodin or isolated active constituents, e.g. rhein or sennosides A and B. The acute toxicity of senna pods, specified extracts thereof, as well as of sennosides in rats and mice was low after oral treatment. As a result of investigations with parenteral application in mice, extracts are supposed to possess a higher toxicity than purified glycosides, possibly due to the content of aglyca.
In a 90-day rat study, senna pods were administered at dose levels from 100 mg/kg up to 1,500 mg/kg. The tested drug contained 1.83 % sennosides A-D, 1.6 % potential rhein, 0.11 % potential aloe-emodin and 0.014
% potential emodin. In all groups epithelial hyperplasia of the large intestine of minor degree was found and
was reversible within the 8-week recovery period. The hyperplastic lesions of the forestomach epithelium were reversible as well. Dose-dependent tubular basophilia and epithelial hypertrophy of the kidneys were seen at a dose of, or greater than 300 mg/kg per day without functional affection. These changes were also reversible. Storage of a brown tubular pigment led to a dark discoloration of the renal surface and still remained to a lesser degree after the

recovery period. No alterations were seen in the colonic nervous plexus. A no-observable-effect-level (NOEL) could not be obtained in this study.
A 104-week study on rats of both genders did not reveal any carcinogenic effects with the same senna pods preparation at oral dosages of up to 300 mg/kg.
In addition a specified senna extract given orally for 2 years was not carcinogenic in male or female rats. The extract investigated contained approximately 40.8% of anthranoids from which 35% were sennosides, corresponding to about 25.2% of potential rhein, 2.3% of potential aloe-emodin and 0.007% of potential emodin and 142 ppm free aloe-emodin and 9 ppm free emodin.
Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.
Sennosides displayed no specific toxicity when tested at doses up to 500 mg/kg in dogs for 4 weeks and up to 100 mg/kg in rats for 6 months.
There was no evidence of any embryolethal, teratogenic or foetotoxic actions in rats or rabbits after oral treatment with sennosides. Furthermore, there was no effect on the postnatal development of young rats, on rearing behaviour of dams or on male and female fertility in rats. Data for herbal preparations are not available.
An extract and aloe-emodin were mutagenic in in vitro tests, sennoside A, B and rhein gave negative results. Comprehensive in vivo examinations of a defined extract of senna pods were negative.
Laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.
Rhubarb:
Total rhubarb (rhizomes of *Rheum palmatum* L.) anthraquinones (TRAs) were orally administered for
13 weeks to Sprague Dawley rats at a dose of 0, 140, 794, 4,500 mg/kg bw. In the highest dose group, nephrotoxicity was discernible at 13 weeks.
In the *Salmonella*/microsome assay an ethanolic root extract of *Rheum officinale* Baillon was weakly mutagenic in strain TA 1537 with and without metabolic activation. No further toxicological data are available for rhubarb itself or preparations thereof.
Experimental data, mainly *in vitro* tests showed a genotoxic risk of several anthranoids in the Salmonella/microsome assay, aloe-emodin, emodin, chrysophanol and physcion were weakly mutagenic. No mutagenic effects were observed in the V79-HGPRT mutation assay and in the unscheduled DNA synthesis (UDS) assay for chrysophanol and physcion. Emodin was highly mutagenic in the V79-HGPRT mutation assay. In the UDS assay emodin was a string inducer of UDS in primary hepatocytes. Aloe-emodin showed a significant increase in net grains/nucleus. Emodin was also tested with respect to its transforming activity in C3H/M2 mouse fibroblasts in vitro. In the in vitro Salmonella/microsome mutagen test and the deoxyribonucleic acid (DNA) repair test of primary rat hepatocytes emodin and frangulin

showed a dose- dependent increase in the mutation rate or the induction of DNA repair.
However, in vivo studies of other anthranoid-containing herbal substance (senna) in rat hepatocytes (chromosome aberration test, mouse spot test, in vivo/in vitro UDS (unscheduled DNA synthesis) showed no evidence of any genetic effects.
In in vivo studies (micronucleus assay in bone marrow cells of NMRI mice; chromosome aberration assay in bone marrow cells of Wistar rats; mouse spot test [DBA/2J x NMRI]) no indication of a mutagenic activity of aloe emodin was found.
Sennoside B and rhein did not induce significant numbers of chromosomal aberrations or aberrant cells in bone marrow cells of Swiss mice.
Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.
A long-term study over 2 years on male and female rats with a senna pods preparation (anthranoid- containing herbal substance as well) gave no evidence of carcinogenic activity.
Chronic laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.
The short-term use of rheum as recommended can be regarded as safe.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize starch
Talc
Bolus alba (Heavy Kaolin)
Gum Arabic
Peppermint oil
Fennel oil

6.2 Incompatibilities

6.3 Shelf life

None known

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

250µ PVC/PVdC-blister packs with 25µ aluminium foil/circular shallow tins. Blister strips of 20, 30 tablets, tins of 100 tablets

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Trenka Chem-Pharm Fabrik GmbH.
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Goldeggasse 5
Vienna
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