Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eucarbon herbal Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
105mg of *Cassia senna* L. (*Cassia acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf), and 13.75 - 24.75 mg of extract (as dry extract) from *Rheum palmatum* L. or *Rheum officinale* Baillon, or hybrids of these two species or a mixture, radix (Rhubarb root) (3- 5: 1), (Extraction solvent : Ethanol 70% v/v), corresponding to a total amount of anthraquinone derivatives of 3.3 mg, and 180 mg of *Carbo ligni* (Vegetable Charcoal).

Excipient(s) with known effect:
Each tablet also contains 0.25 - 11.25 mg of lactose and 65 mg of sucrose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets
Grey-black, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

A traditional herbal medicinal product for the short-term relief of occasional constipation and for resulting mild digestive complaints such as bloating and flatulence exclusively based on long- standing use.

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 mild laxative and anti-bloating effect. If a stronger laxative effect is desired, the evening dose can be increased to 3 – 4 Eucarbon herbal Tablets.
Herbal substance/preparation equivalent to 2.65 to 3.95 mg of hydroxyanthracene derivatives, 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).

Duration of use
If symptoms worsen or persist during the use of Eucarbon herbal Tablets a doctor should be consulted. If there is no bowel movement after three days consult a doctor.
Prolonged continuous use is not recommended. See also section 4.4 Special warnings and precautions for use.

New users should start with the lowest dose and increase it, if necessary, by one half of the initial dose each day. Once regularity has been regained the dosage should be gradually reduced and stopped

Method of administration For oral short term use only.

4.3 Contraindications

- Do not use in cases of known hypersensitivity to any of the active ingredients of senna leaves, rhubarb extract or charcoal or to any of the excipients listed in section 6.1.
- Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis);
- abdominal pain of unknown origin;
- suspected gastric or intestinal ulcer
- Sudden change in bowel habit that persists for more than 2 weeks, undiagnosed rectal bleeding and failure to defaecate following the use of a laxative
- severe dehydration state with water and electrolyte depletion
- Children under 12 years of age
- Do not use during pregnancy or lactation

4.4 Special warnings and precautions for use

- If there is no bowel movement after three days consult a doctor.
- Prolonged continuous use is not recommended.
- Chronic abuse may cause hypokalaemia leading to risk of potentiation of the action of cardiac glycosides (e.g.digoxin) and interactions with antiarrhythmic medicinal products and medicinal products which may induce QT-prolongation (e.g. haloperidol).
- Concomitant use with other medicinal products inducing hypokalaemia e.g. diuretics, adrenocorticosteroids or liquorice root may further result in electrolyte imbalance.
- 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, Eucarbon herbal Tablets 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 and irregular bowel habits 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. Eucarbon herbal Tablets should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.
- When administering this product 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.
- If abdominal pain occurs or in cases of any irregularity of faeces, the use of this product should be discontinued and medical advice sought.
- If the condition worsens during use or symptoms persist for more than 1 week, a doctor should be consulted.
- Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.
- This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

In order to decrease the risk of gastrointestinal obstruction (ileus), this product should only be used together with medicinal products known to inhibit peristaltic movement (e.g. opioids, loperamide) under medical supervision

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, corticosteroids and liquorice root) may enhance electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Eucarbon herbal Tablets during pregnancy has not been established. Due to experimental data concerning a genotoxic risk of several anthranoids, e.g. aloe-emodin, emodin, frangulin, chrysophanol and physcion, Eucarbon herbal Tablets should not be used during pregnancy.

Lactation
Use during breastfeeding should be avoided as there are insufficient data on the excretion of metabolites in breast milk. After administration of other anthranoids, active metabolites, such as rhein, are excreted in breast milk in small amounts. 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

Based on its pharmacodynamic properties Eucarbon herbal Tablets are likely to have no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur. Meteorism occurring with the use of this product is common

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 overdosage. 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 qualified healthcare professional e.g. a doctor or 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 balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

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 cause potassium depletion, this may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, corticosteroids 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
Abdominal discomfort, flatulence and possibly intestinal obstruction may occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Senna glycosides, combinations, ATC code: A06AB

The mode of action and effectiveness of the natural constituents of Eucarbon herbal Tablets are well known. Eucarbon herbal Tablets contain only vegetable ingredients which provide a mild laxative, carminative, and adsorbent action.
The effect of this multi-compound is spread throughout the gastro-intestinal tract, therefore a broad basis for activity is provided.

1,8-dihydroxyanthracene derivatives possess a laxative effect. The ß-0-linked glycosides (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.

5.2 Pharmacokinetic properties

The ß-0-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).
Aglyca are absorbed in the upper gut. Animal experiments with radio-labeled 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 Eucarbon Herbal Tablets 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 effect. These changes were also reversible. Storage of a brown pigment in tubules 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 Extract:
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 another 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 showed 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.

Carbo Ligni:
Available toxicity studies on carbon were mainly done with activated charcoal. The toxicology of activated charcoal, can be transcribed to Carbo ligni (non-activated charcoal). However, due to the difference in adsorption power which is about ten times higher for activated charcoal compared to Carbo ligni some observed effects associated with the adsorption power maybe milder in Carbo ligni. Activated charcoal has no toxicity after single dose administration. The only pharmacological effect observed after administration of very high doses was a slow-down of the intestinal transit in the rat. After repeated or chronic administration of activated charcoal to rats and sheep no clinical relevant toxic effects were detected. Since activated charcoal is not absorbed in the intestinal tract neither studies to determine the genotoxic potential in vitro nor fertility and teratogenic studies were done. Preclinical data on activated charcoal reveal no special hazard for humans

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients in the herbal preparation:
Lactose monohydrate

Tablet excipients:
Sucrose
Maize starch
Talc
Kaolin, Heavy
Acacia
Peppermint oil
Bitter Fennel Fruit Oil

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original container in order to protect from light.

6.5 Nature and contents of container

250 micrometre PVC/PVdC-blister packs with 25 micrometre aluminium foil. Blister strips of 10, 20, 30, 50 or 100 tablets are contained in a cardboard carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 REGISTRATION HOLDER

F. Trenka chem.-pharm. Fabrik GmbH
Prinz-Eugen-Straße 70
1040 Vienna
Austria

8 REGISTRATION NUMBER(S)

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