European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

ASSESSMENT REPORT ON *HYPERICUM PERFORATUM* L., HERBA

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I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments [2]
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Italy	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

II. ASSESSMENT REPORT

Hypericum perforatum L., herba

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

(WELL-ESTABLISHED USE)

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut, dried flowering tops of *Hypericum perforatum* L., harvested during flowering time.
Herbal preparation(s)	See monographs
Pharmaceutical forms	Herbal substance or comminuted herbal substance for liquid dosage forms for cutaneous use or liquid and solid dosage forms for oral use.
Rapporteur	Reinhard Länger

II.1 INTRODUCTION

II.1.1 Description of the herbal substance(s), herbal preparation(s) or combinations thereof

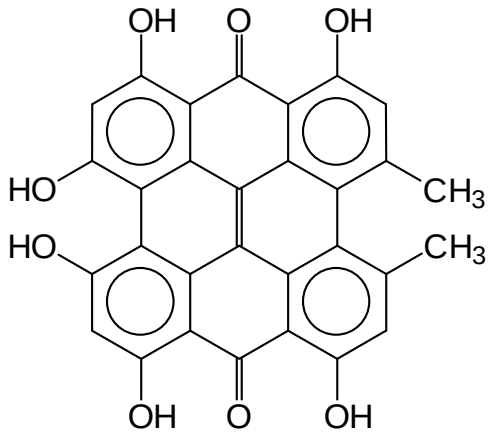
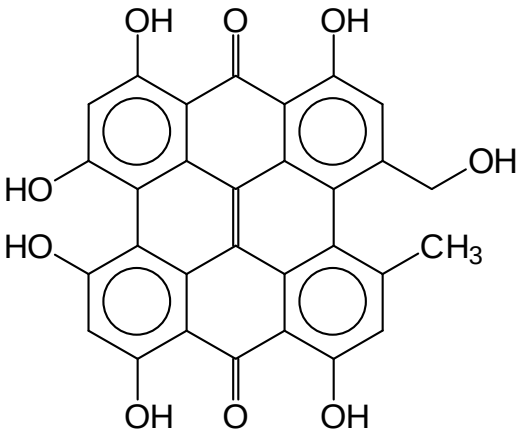
II.1.1.1 Herbal substance:

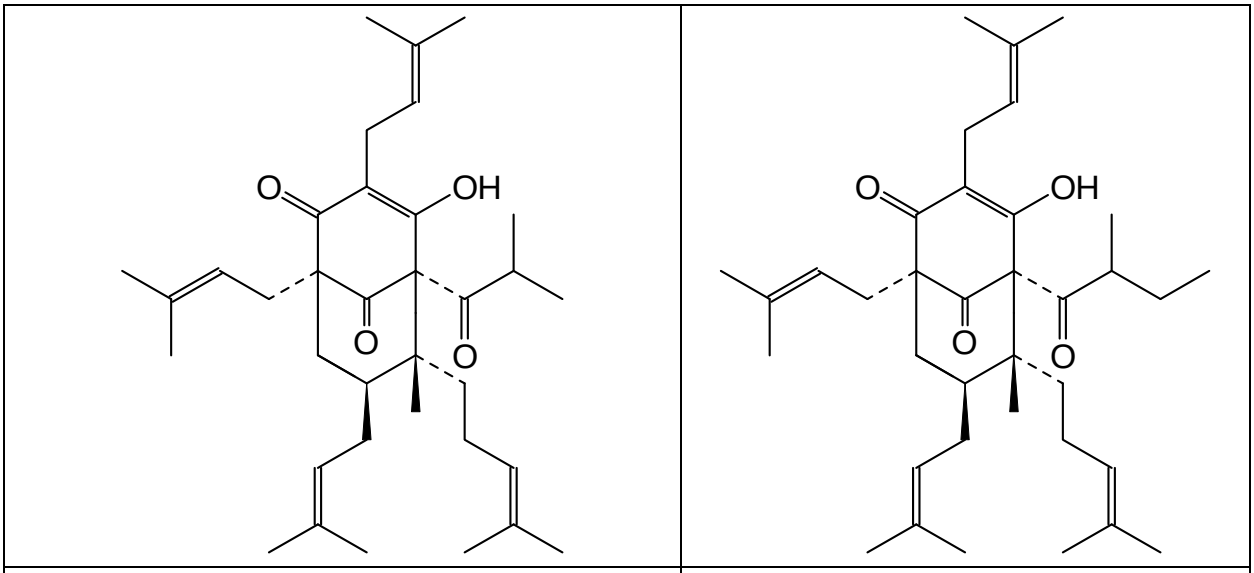
Hyperici herba (European Pharmacopoeia)

Hyperici herba consists of the whole or cut, dried flowering tops of *Hypericum perforatum* L., harvested during flowering time. It contains not less than 0.08% of total hypericins expressed as hyericin calculated with reference to the dried drug.

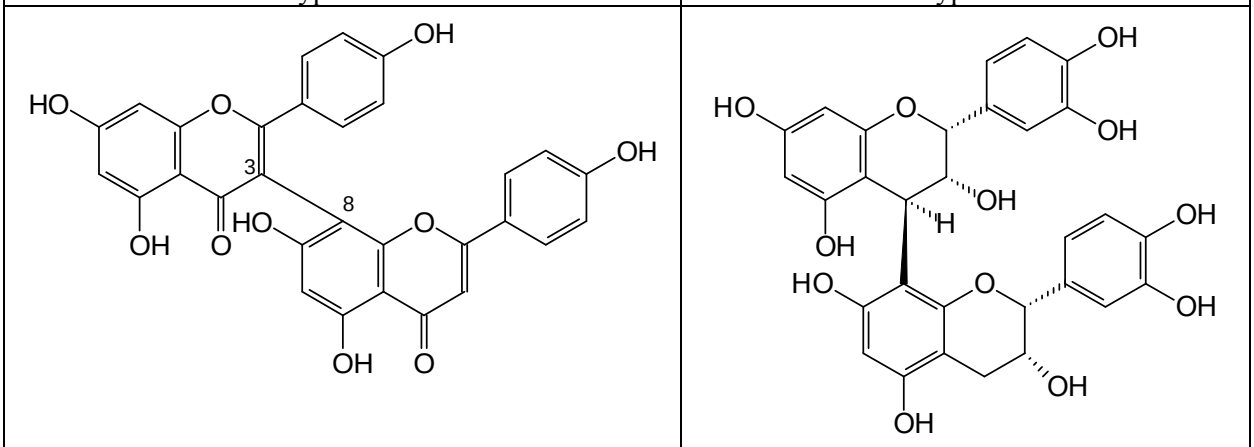
Consituents (Wichtl 2002; Bradley 2006, Hänsel & Sticher 2007, figure 1)

- Phloroglucinol derivates: 0.2-4%, depending on the age of the herbal drug, mainly hyperforin and its homologue adhyperforin, furanohyperforin
- Naphtodianthrones: 0.06-0.4%, mainly pseudohypericin and hypericin, protohypericin, protopseudohypericin, cyclopseudohypericin, skyrinderivatives. The amount of pseudohypericin is about 2-4 times higher than that of hypericin.
- Flavonoids: 2-4%, mainly glycosides of the flavonol quercetin: hyperoside, rutin, isoquercitrin, quercitrin; also biflavones (I3,II8-Biapigenin, Amentoflavone)
- Procyanidines: e.g. procyanidine B_2, tannins with catechin skeletal (6-15%)
- Xanthones: in trace amounts
- Essential oil: 0.1-0.25%; the essential oil of dried flowering tops contains as main compounds 2-methyloctane (16%) and α-pinene (10.6%). In the essential oil of leaves of Indian origin 58 components were identified, α-pinene (67%) being dominant; the other components included caryophyllene, geranyl acetate and nonane (each about 5%)
- Other constituents: include small amounts of chloregenic acid and other caffeoylquinic and p-coumaroylquinic acids, and also free amino acids.

	
Hypericin	Pseudohypericin



Hyperforin | Adhyperforin



Biapigenin | Procyanidin B_2

Figure 1: Structures of the main constituents of Hyperici herba.

II.1.1.2 Herbal preparation(s):

St. John's wort dry extract, quantified extract (Pharm. Eur. ref. 07/2008:1874)
Extraction solvents ethanol (50-80% v/v) or methanol (50-80% v/v). Content of total hypericins (expressed as hypericin) 0.10-0.30%, content of flavonoids (expressed as rutin) minimum 6.0%, content of hyperforin maximum 6.0% and not more than the content stated on the label.
Wurglics *et al.* (2001a, 2002, 2003) report that in commercial batches the content of hypericin is between 0.16 and 0.32%, the content of hyperforin is <0.2% (Ze 117) or in the range between 1.5 and 4.4% (partly with considerable differences between batches [Wurglics *et al.* 2001b, Wurglics *et al.* 2003]). The content of total flavonoids is between 6 and 8%. Dissolution test revealed considerable differences in the dissolution of flavonoids between authorized products in Germany.

Herbal preparations with evidence of tradition according Dir. 2004/24:

A) Dry extract, DER 4.6-6.5:1, extraction solvent ethanol 38% v/v. This type of extract is in medicinal use since more than 30 years. The content of hypericin is approximately 0.3 – 0.7%, the content of hyperforin is between 0.3 and 1.6%.
B) Liquid extract (DER 1:4-20), extraction solvent vegetable oil (e.g. olive oil, sunflower oil, linseed oil, wheat germ oil).
   Preparation:
   According to the German "Ergänzungsbuch" to the German Pharmacopoeia 6 (Erg.-B6. 1941): The crushed fresh flowers of *H. perforatum* (25 parts) are doused with olive oil (100 parts) in a white glass. The mixture is allowed to ferment at a warm place. After completion of

the fermentation the glass has to be sealed. It is then stored at a sunny place for about 6 weeks until the oil is bright red. The herbal substance has to be pressed out, the oil is dried with sodium sulphate (6 parts).

According to Swiss Pharmacopoeia (Pharm. Helv. 8 2001): The comminuted fresh flowering tops of *H. perforatum* are overflowed with 40.0 g refined sun flower oil. The mixture is reshuffled frequently; extraction and fermentation take place at a temperature of 15-30 °C. After 50-80 days the herbal substance is pressed out, the water layer is removed. It is allowed to dilute the oil to a maximum of 80 g of sunflower oil, the content of hypericin is at least 0.001% (spectrophotometric determination).

According to the company 'Caelo', Germany: the dried herbal substance (according to Pharm. Eur.) is macerated with olive oil in a DER of 1:20. The mixture is agitated under light exposure for at least 40 hours. The content of hypericin is at least 0.005% (spectrophotometric determination).

Consituents of Hyperici oleum

Hyperici oleum does not contain hypericin. By using the sunlight maceration method described in the supplement to DAB 6 (EB 6), lipophilic breakdown products of this compound are obtained which lend the oil its red colour. The stability of hyperforin is limited; sufficient shelf-life could only be achieved by hot maceration of dried flowers with eutanol G and storage in the absence of air. The action of light during preparation of the oil led to a rise in the content of flavonoids (Maisenbacher & Kovar. 1992).

As a consequence the spectrophotometric determination used for the specification of the St. John's wort oils mentioned above detects primarily artefacts of hypericin.

Schempp *et al.* (2000) used for the test of the influence of *Hypericum* extracts on skin sensitivity *Hypericum* oil containing 110 µg/ml hypericin. It is not transparent, whether the authors determined hypericin or the oil derivatives.

C) Liquid extract (DER 1:13), extraction solvent maize oil: on the market in DE at least since 1976. Hypericin: approximately 0.0013%; hyperforin: approximately 0.01% (Müller *et al.* 2004)

D) Tincture (DER 1:10), extraction solvent ethanol 45-50% v/v: The external use of a tincture (no further details on DER and extraction solvent) is mentioned in Irion (1955) as an equivalent to *Hypericum* oil. Also Madaus (1938) mentions the use of a tincture, details about the DER are lacking. A tincture with a DER of 1:10 (extraction solvent ethanol 45-50% v/v) is mentioned as traditional herbal preparation in Barnes *et al.* (2002) and Gruenwald *et al.* (2004).

E) Tincture (DER 1:5), extraction solvent ethanol 50% v/v: mentioned in Bradley (2006). The evidence of tradition of this tincture has to be proved.

F) Liquid extract DER 1:2, extraction solvent ethanol 50%
The product 'Hyperforat-drops', contains a liquid extract with DER of 1:2, extraction solvent ethanol 50% (no details v/v or m/m). This is in contrast to details given in the review of Linde (2007) with respect to the DER: Hyperforat is cited in the study with a DER of 5-7:1, which would indicate a dry extract. This difference is due to obvious incorrect data in the German "Rote Liste". The first clinical study with this liquid extract is published 1979, therefore the extract is in medicinal use at least 30 years at the time of publication of the monograph.

G) Liquid extract 1:5-7, ethanol 50%. Trade name Psychotonin®, since 1963 in medicinal use.

H) Expressed juice from the fresh herb (DER 1.25-2.5:1): on the market in DE at least since 1976. Hypericin: approximately 0.003%; hyperforin: approximately 0.018% (Müller *et al.* 2004).

I) Comminuted herbal substance: cut herbal substance used for tea preparation; powdered herbal substance in solid dosage forms for oral use on the market in DE at least since 1976. Hypericin: approximately 0.1-0.5%; hyperforin: approximately 0.5% (Müller *et al.* 2004).

Further dry extracts:
Dry extract (DER 3.5-6:1), extraction solvent ethanol 60% (m/m): on the market in DE at least since 1976.
Dry extract (DER 5-7:1), extraction solvent ethanol 70% (m/m): on the market in DE at least since 1976.
Both extracts are covered by dry extracts mentioned under well-established use.

Further liquid extracts:
Since the edition 1993 of Hager's Handbuch (Hänsel *et al.* 1993) a liquid extract with a DER 1:6, extraction solvent ethanol 70% is mentioned. This type of extract is not mentioned in previous literature. The period of 30 years of medicinal use is therefore not fulfilled.

The request for marketed products in the EU revealed that numerous further extracts are on the market. However, they neither do fulfil the criteria for traditional use nor are they supported by clinical evidence.

Influence of the extraction solvent on the composition of the extract:
When using extraction solvents containing more than 50% of ethanol or methanol in water the content of hypericin in the extract seems to be very similar independent of the actual concentration of the extraction solvent. In contrast the extraction of hyperforin and adhyperforin depends strongly on the concentration of the extraction solvent. Best yield (60% of the hyperforin in the herbal substance, 45% of adhyperforin in the herbal substance) is achieved with 70% (e.g. ethanol), while with 50% ethanol only 20% of hyperforin and no adhyperforin are extracted (Meier 1999).

II.1.1.3 Combinations of herbal substance(s) and/or herbal preparation(s)

Not applicable.

II.1.1.4 Vitamin(s)

Not applicable.

II.1.1.5 Mineral(s)

Not applicable.

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

II.1.2.1 Type of tradition, where relevant

European tradition.

II.1.2.2 Bibliographic/expert evidence on the medicinal use

II.1.2.2.1 Evidence regarding the indication/traditional use

Traditional indications for oral use of herbal teas, liquid extracts (extraction solvent ethanol) and dry extracts

Nervous system disorders, psychiatric disorders:

Indication	References
Psychovegetative disturbances	Hamacher *et al.* (2003), Wichtl (2004), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Commission E monographs (1998), Dingermann *et al.* (2004), DAC (1991-1999)
Mood depression	Hamacher *et al.* (2003), Bradley (2006), Irion (1955), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Auster *et al.* (1958), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Commission E monographs (1998), Dingermann *et al.* (2004), DAC (1991-1999), Flamm *et al.* (1940)
Mild depression	Escop 2003
Anxiety and/or nervous restlessness	Wichtl (2004), Bradley 2006 (including menopausal anxiety), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Madaus (1938), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Barnes *et al.* (2002), Commission E monographs (1998), Dingermann *et al.* (2004), DAC (1991-1999), Martindale (2002) (particularly if associated with the menopause)
Insomnia	Gerlach (2008), Irion (1955), List & Hörhammer (1976), Madaus (1938), Barnes *et al.* (2002), Martindale (2002)
Support of emotional balance	Gerlach (2008), ESCOP (2003)
'Weak nerves', vegetative dystonia	Gerlach (2008), Irion (1955)
Agitation, excitability, irritability	List & Hörhammer (1976), Barnes *et al.* (2002), Upton (1997)
After mental efforts	Madaus (1938)
Neuralgia, Neurasthenia	List & Hörhammer (1976), Madaus (1938), Barnes *et al.* (2002), Flamm *et al.* (1940), WHO monographs (2002)
Traumatic damages of nerves, paralysis	Madaus (1938)
Migraine, headache	Flamm *et al.* (1940), WHO monographs (2002)
Sciatica	Barnes *et al.* (2002), WHO monographs (2002)

Gastrointestinal disorders:

Indication	References
Gastritis	Wichtl (2002), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (2004), Böhme (2006)
Ulcers, dyspepsia	WHO monographs (2002)
Unspecific catarrhs of the gastro-intestinal tact	Gerlach (2008), Irion (1955), Flamm *et al.* (1940)
Nervous gastric diseases	Gerlach (2008), Blaschek *et al.* (2008), Hänsel *et al.* (1993)
Abdominal pain	Madaus (1938)
Diarrhoea	Wichtl (1984), List & Hörhammer (1976), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Madaus (1938), Gruenwald *et al.* (2004), Flamm *et al.* (1940), Karsten *et al.* (1962)
Haemorrhoids	Irion (1955), List & Hörhammer (1976), Flamm *et al.* (1940), WHO monographs (2002)
Digestion disorders	Polish Medicines Agency (2008)

Hepatobiliary disorders:

Indication	References
Gallbladder diseases	Wichtl (2004), Irion (1955), List & Hörhammer (1976),

	Blaschek *et al.* (2008), Hänsel *et al.* (1993), Madaus (1938), Gruenwald *et al.* (2004), Böhme (2006), WHO monographs (2002)
As a choleretic	Blaschek *et al.* (2008), Hänsel *et al.* (1993)

Renal and urinary disorders:

Indication	References
Nocturnal enuresis	Gerlach (2008), Wichtl (1984), Irion (1955), List & Hörhammer (1976), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Madaus (1938), Gruenwald *et al.* (2004), Flamm *et al.* (1940), Dingermann *et al.* (2004), Schneider (1990)
Kidney stones, bladder stones, inflammations of the urogenital tract	Irion (1955), Flamm *et al.* (1940), WHO monographs (2002)
Irritable bladder, incontinence	Hamacher & Wahl (2003), WHO monographs (2002)
As a diuretic	Wichtl (1984), List & Hörhammer (1976), WHO monographs (2002)

Respiratory, thoracic and mediastinal disorders:

Indication	References
Cough, bronchitis, asthma	Irion (1955), Blaschek *et al.* (2008) Hänsel *et al.* (1993), Madaus (1938), Gruenwald *et al.* (2004), Flamm *et al.* (1940), WHO monographs (2002)
Common cold	WHO monographs (2002)

Infections and infestations:

Indication	References
Worm infestations	Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (2004), Flamm *et al.* (1940), Zörnig (1911)
As an antimalaria agent	WHO monographs (2002)

Endocrine disorders:

Indication	References
Polymenorrhoea, oligomenorrhoea, dysmenorrhoea, endometritis	Madaus (1938), Irion (1955), Flamm *et al.* (1940), Heinrich *et al.* (2004)
As emmenagogue	WHO monographs (2002)
Diabetes	Irion (1955), Auster & Schäfer (1958), WHO monographs (2002)

Musculoskeletal and connective tissue disorders:

Indication	References
Rheumatism	Wichtl (1984), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Auster & Schäfer (1958), Gruenwald *et al.* (2004)

Metabolism and nutrition disorders:

Indication	References
Gout	Wichtl (1984), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (2004)
Metabolic disorders	List & Hörhammer (1976)

Traditional indications for oral use of liquid extracts (extraction solvent vegetable oil)

Indication	References
Dyspepsia	Hamacher & Wahl (2001), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Commission E monographs (1998), DAC (1991)
Nervous gastric diseases	Gerlach (2008), Blaschek *et al.* (2008), Hänsel *et al.* (1993)
As a choleretic	Blaschek *et al.* (2008), Hänsel *et al.* (1993)
Abdominal pain	Madaus (1938)

Discussion and assessment of traditional indications for oral use:

Since the *Hypericum* oil differs considerably in the nature of the constituents from aqueous and ethanolic liquid extracts these types of herbal preparations are discussed separately.

a) **Aqueous extracts (herbal teas), liquid extracts prepared with ethanol, dry extracts:**

Infusions prepared with water are widely used in the traditional medicine at least in Central Europe (Gerlach 2008). The indication 'depression' is unknown in traditional medicine; *Hypericum* is used in order to 'strengthen the nerves', to restore emotional balance. The wording which is found in literature reflects this fact, although put into different words. This traditional indication is plausible because of the pharmacological and clinical data which are available for isolated compounds and alcoholic extracts of *H. perforatum*.

The numerous further traditional indications mentioned in the literature for these kinds of extracts are not plausible.

Since for the indication of a traditional herbal medicinal product terms like 'depression' or 'depressed mood' are not suitable, special care is taken to the wording.

Proposals:

Somatoform disorders (ICD-10 F45.0):

The main feature is repeated presentation of physical symptoms together with persistent requests for medical investigations, in spite of repeated negative findings and reassurances by doctors that the symptoms have no physical basis. If any physical disorders are present, they do not explain the nature and extent of the symptoms or the distress and preoccupation of the patient.

Neurasthenia (ICD-10 F48.0)

Considerable cultural variations occur in the presentation of this disorder, and two main types occur, with substantial overlap. In one type, the main feature is a complaint of increased fatigue after mental effort, often associated with some decrease in occupational performance or coping efficiency in daily tasks. The mental fatigability is typically described as an unpleasant intrusion of distracting associations or recollections, difficulty in concentrating, and generally inefficient thinking. In the other type, the emphasis is on feelings of bodily or physical weakness and exhaustion after only minimal effort, accompanied by a feeling of muscular aches and pains and inability to relax. In both types a variety of other unpleasant physical feelings is common, such as dizziness, tension headaches, and feelings of general instability. Worry about decreasing mental and bodily well-being, irritability, anhedonia, and varying minor degrees of both depression and anxiety are all common. Sleep is often disturbed in its initial and middle phases but hypersomnia may also be prominent.

Adjustment disorders (ICD-10 F43.2)

States of subjective distress and emotional disturbance, usually interfering with social functioning and performance, arising in the period of adaptation to a significant life change or a stressful life event. The stressor may have affected the integrity of an individual's social network (bereavement, separation experiences) or the wider system of social supports and values (migration, refugee status), or represented a major developmental transition or crisis (going to school, becoming a parent, failure to attain a cherished personal goal, retirement). Individual predisposition or vulnerability plays an important role in the risk of occurrence and the shaping of the manifestations of adjustment disorders, but it is nevertheless assumed that the condition would not have arisen without the stressor. The manifestations vary and include depressed

mood, anxiety or worry (or mixture of these), a feeling of inability to cope, plan ahead, or continue in the present situation, as well as some degree of disability in the performance of daily routine. Conduct disorders may be an associated feature, particularly in adolescents. The predominant feature may be a brief or prolonged depressive reaction, or a disturbance of other emotions and conduct.

All these three types of disorders reflect partly the traditional oral use of *H. perforatum*. The definition of the somatoform disorders includes characteristics which are not suitable for THMPs. Particularly the persistent request for medical investigation is in contrast to the concept that the products are intended for use without medical supervision.
The traditional use seems to be covered in a most suitable way by the definition of 'neurasthenia'. However, the very broad definition also includes symptoms which should be treated under medical supervision. Therefore the indication should be restricted to 'temporary mental exhaustion'.
The plausibility of the efficacy in this traditional indication is supported by an observational study (Grube *et al.* 1996). *Hypericum* dry extract LI 160 was administered corresponding to 900 µg hypericin daily (= approximately 540 mg extract) to patients with mild temporary depressed mood.
Additionally the indication should be clearly different from the proposed health claims for food supplements (contributes to emotional balance and general wellbeing; contributes to optimal relaxation; helps to support relaxation and mental and physical wellbeing; helps to maintain a healthy sleep; helps maintain a positive mood).

Proposed traditional indication (oral use, aqueous extracts, liquid ethanolic extracts, dry extracts)
Indication 1)
Traditional herbal medicinal product for the relief of temporary mental exhaustion.
The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

In addition the herbal tea is a traditional medicinal product in Poland used for treatment of digestion disorders.
Indication 3)
Traditional herbal medicinal product for the symptomatic relief of mild gastrointestinal discomfort.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

b) **Liquid extracts prepared with vegetable oil (*Hypericum* oil):**
The indications mentioned in the references cannot be explained by the constituents of the *Hypericum* oil, data from pharmacological experiments are lacking. Therefore the mentioned indications are not plausible. There is no traditional indication for the oral use of *Hypericum* oil.

Traditional indications for cutaneous use of liquid extracts (extraction solvent vegetable oil)

Skin and subcutaneous tissue disorders:

Indication	References
First degree burns, sunburn	Gerlach (2008), Wichtl (1984), Wichtl (2004), Bradley (2006), Irion (1955), Flamm *et al.* (1940), Schneider (1990), Wagner & Bauer (1999), Böhme (2006), WHO monographs (2002), Hamacher & Wahl (2001), Hamacher & Wahl (2006), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Comission E monographs (1998), DAC (1991), DAC (1998)
Wound healing	Gerlach (2008), Wichtl (1984), Wichtl (2004), Bradley (2006), Irion (1955), Hager (1878), Fischer & Hartwich (1902), Frerichs *et al.* (1938), List &

	Hörhammer (1976), Auster & Schäfer (1958), Flamm *et al.* (1940), Wagner & Bauer (1999), Schneider (1990), WHO monographs (2002), Hamacher & Wahl (2001), Hamacher & Wahl (2006), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Commission E monographs (1998), DAC (1991), DAC (1998), Madaus (1938)
Gingivits, stomatitis	Gerlach (2008)
Fibrositis	Barnes *et al.* (2002)
Neurodermatitis	Wagner Bauer (1999)
Eczema	Irion (1955)
Prevention of decubitus	Hänsel & Sticher (2007)
Shingles, viral infections	Bradley (2006), WHO monographs (2002)

Musculoskeletal and connective tissue disorders:

Indication	References
Myalgia	Hamacher & Wahl (2001), Hamacher & Wahl (2006), Länger & Kubelka. (2001), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Gruenwald *et al.* (1998), Gruenwald *et al.* (2004), Comission E monographs (1998), DAC (1991), DAC (1998), Flamm *et al.* (1940), Wagner & Bauer (1999)
Rheumatism	Gerlach (2008), Irion (1955), Flamm *et al.* (1940), Hager (1878), Blaschek *et al.* (2008), Hänsel *et al.* (1993), Wagner & Bauer (1999), Auster & Schäfer (1958)
Lumbago	Blaschek *et al.* (2008), Hänsel *et al.* (1993), Flamm *et al.* (1940), Madaus (1938)
Ischialgia, neuralgia	Irion (1955), Flamm *et al.* (1940), Böhme (2006)
Articular pain	Gerlach (2008)
Sprains	Flamm *et al.* (1940), Madaus (1938)
Bruises	Bradley (2006), Irion (1955), Flamm *et al.* (1940)
Swellings	Bradley (2006), Flamm *et al.* (1940), Madaus (1938)

Metabolism and nutrition disorders:

Indication	References
Gout	Gerlach (2008), Irion (1955), Flamm *et al.* (1940), Madaus (1938)

Traditional indications for cutaneous use of liquid extracts (extraction solvent ethanol)

Skin and subcutaneous tissue disorders:

Wound healing	Gerlach (2008), Irion (1955)

Traditional indications for cutaneous use of liquid extracts (extraction solvent water)

Skin and subcutaneous tissue disorders:

Wound healing	WHO monographs (2002)

Discussion and assessment of traditional indications for cutaneous use:

The traditional use of liquid preparations of *Hypericum* for wound healing is supported by pharmacological data. Antiinflammatory activity, analgesic activity, astringent activity and antibacterial activity are documented, *in-vivo* data are poor, clinical data are lacking. In contrast the

traditional use for the treatment of symptoms caused by an injury or related to rheumatism is not yet plausible. Antiviral effects are documented for several types of viruses, but not for Varicella zoster. Therefore the traditional use in the treatment of shingles cannot be supported.

Proposed traditional indication (cutaneous use, liquid extracts, extraction solvents vegetable oil, ethanol or water)
Indication 2)
Traditional herbal medicinal product for the symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in healing of minor wounds.
The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

II.1.2.2.2 Evidence regarding the specified posology

Oral administration

Comminuted herbal substance for tea preparation:
The single dose for tea preparation is 1 teaspoon per cup, which is equivalent to 1.8 to 2 g of herbal substance. The recommendation of the daily dose is 1-2 cups equivalent to 1.8 to 4 g of herbal substance (Wichtl 2004, Hänsel *et al.* 1993, ESCOP 2003), only few references recommend higher daily dosages (Duke 2002: up to 8 g; Madaus 1938: up to 7 g; Irion 1955 and Barnes *et al.* 2002: up to 12 g).

Proposal for the posology of the comminuted herbal substance for tea preparation:
Adults, elderly: single dose 1.5-2 g; daily dose 3-6 g
Children and adolescents: Since no data on the safe traditional use in children are available the use in children and adolescents is not recommended.

The powdered herbal substance is in medicinal use in solid dosage forms longer than 30 years. The proposed posology (single dose 300-500 mg, daily dose 900-1000 mg) reflects the posology of the authorized products.

Herbal preparations:
Dry extracts: Traditionally dry extracts are administered in considerably lower doses than those used for the treatment of mild to moderate depression.
Tincture (DER 1:5): 3-4.5 ml daily dose (Bradley 2006).
Tincture (DER 1:5) (= ESCOP 2003, posology with reference to a product from Steigerwald): 3-4.5 ml daily = equivalent to 0.6 – 0.9 g herbal substance.
Tincture (DER 1:10), 45% ethanol: 2-4 ml 3 x daily (Barnes *et al.* 2006, Duke 2002) = equivalent to 0.6-1.2 g herbal substance.
Tincture (DER 1:2): Single dose 0.8-1.2 ml, daily dose 2.4-3.6 ml.
Tincture (DER not given): 10-15 drops (= approximately 0.5-0.75 ml), 2-3 x daily (= 1-2.25 ml) (Madaus 1938). Because of the lack of data of the DER this posology cannot be considered.
Powdered herbal substance: usual maximum daily dose of 1000 mg.
The posology of the further mentioned herbal preparations reflects the posology of the authorized products.

Children and adolescents: Since no data on the safe traditional use in children are available the use in children and adolescents below 18 years of age is not recommended.

Cutaneous administration
Strength of the preparations:

Hypericum oil is administered undiluted.
Hypericum tea prepared with a DER of 1:5 (WHO monographs 2002)

Children and adolescents: Since no data on the safe traditional use in children are available the use in children below 12 years of age is not recommended.

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

II.2.1.1.1 Effects associated with depression

The mechanisms of action as well as the responsible compounds of *Hypericum* extracts are still under discussion. Several actions contributing to clinical efficacy are reported: Blockade of the reuptake of serotonin (5-HT), noradrenalin and dopamine; upregulation of postsynaptic 5-HT_1 and 5-HT_2 receptors and of dopaminergic receptors; increased affinity for GABAergic receptors. Constituents which contribute to the activity are hypericin, pseudohypericin, flavonoids, and oligomeric procyanidins. The relevance of hyperforin is discussed controversially. As a consequence the entire extract has to be considered as the active substance.

Effects of constituents (primarily according to a review from Butterweck & Nahrstedt 2003a**)**

Flavonoids, Biflavonoids

In vitro the flavonols inhibit the monoaminooxidase (MAO), a fraction rich in flavonols also inhibits the catechol-O-methyltransferase (COMT). The concentrations which were necessary to achieve the results were considerably higher than concentrations which could be expected in therapeutic dosages.

Amentoflavon, which occurs only in traces in the flowers, inhibits in very low concentrations the binding of flumazenil on the benzodiazepine binding sites of the GABA receptor (Baureithel *et al.* 1997) as well as to the δ-subunit of the opioid receptor. I3,II8 bBiapigenin, which is present in much higher concentrations, is not investigated up to now, because it is commercially not available.

A flavonoid fraction, free of hypericins and hyperforin, induces a reduction of the β-adrenergic receptors in the frontal cortex of the rat brain in similar manner like imipramine.

It is not known whether the flavonoids or their metabolites are responsible for these effects.

Hyperosid directly stimulates the endocytosis of β1-receptors and reduces their lateral mobility (Häberlein *et al.* 2008).

Quercetin (10-40 mg/kg) altered dose-dependently the pattern in an electropharmacogram of rats, the changes resembled those of the MAO-A inhibitor moclobemide and the MAO-B inhibitor selegiline (Dimpfel 2008).

Naphthodianthrones

Pure naphthodianthrones are only poorly soluble in water. The solubility is increased by letter compounds of the extract. For example procyanidines are able to increase the solubility in water 10-fold. Rutin and hyperoside may also contribute to the better solubility of hypericin in extracts.

Hyperoside and the procyanidines increase the serum level of hypericin considerably.

Isolated hypericin has no influence on the MAO-A and -B. *In vitro* it inhibits the dopamine-β-hydroxylase, interacts with β-adrenergic receptors and possesses a high affinity to the σ-receptor as well as to the D_3-receptor.

Hypericin alters the concentration of several neurotransmitters after 8 weeks of treatment comparable to imipramine. Eight weeks treatment also increases the serotonin concentration in the hypothalamus, while the concentration of metabolites of dopamine is reduced. Hypericin induces a reduction of the β-receptors in he frontal cortex of the rat brain, after 8 weeks of treatment a significant change could be observed.

Hypericin reduces, similar to imipramine, the expression of mRNA of the corticotrophin releasing hormone in the hypothalamus as well as the ACTH and corticosterone levels in the plasma of rats. An overview presenting chemical and biological properties of hypericin has been published by Lavie *et al.* (1995).

Phloroglucinol derivatives

Müller *et al.* (1998) and Chatterjee *et al.* (1998) revealed that hyperforin plays an important role in the inhibition of neurotransmitter reuptake. *In vitro* the IC_{50} value for the inhibition of the synaptosomal

reuptake of serotonin, dopamine, noradrenaline, GABA and glutamate caused by hyperforin is in the range of 80 to 1234 nM. After a daily intake of 900 mg of *Hypericum* extract a blood level of 180 nM of hyperforin was detected. Therefore it could be concluded that sufficient amounts of hyperforin for the inhibition of the reuptake of some neurotransmitters could be achieved during therapy.
Several mechanisms for these effects are in discussion: Inhibition of calcium channels of the P-type, a reserpine-like action, increase of the intracellular sodium concentration.
Isolated hyperforin does not influence the density of β-receptors in rats, while an extract rich in hyperforin induces a down-regulation of the β-receptor density.
Hyperforin directly causes the endocytosis of β1-receptors and reduces their lateral mobility (Häberlein *et al.* 2008).

Xanthones
Due to the low content of xanthones in the herbal substance (about 0.0004%) it is not likely that the experimentally documented inhibition of MAO A and B is of clinical relevance.

Effects of extracts (examples of publications)
The results on MAO inhibition are controversial. At concentration of 10^{-4} to 10^{-3} mol/l of a methanolic extract (Bladt & Wagner 1994) and of an ethanolic extract (Thiede & Walper 1994) MAO could be inhibited up to 82%. In a later study a methanolic extract exhibited a rather weak potency as MAO inhibitor *in vitro* (Müller *et al.* 1997).

The inhibition of synaptosomal reuptake of several neurotransmitters could be demonstrated for different kinds of extracts (different extraction solvent, different amounts of hypericin, hyperforin).

Long-term treatment of rats with a methanolic extract (500 mg/kg p.o.) significantly increased the serotonin (5-HT) levels in the hypothalamus of rats; the 5-HT turnover was significantly lowered in hippocampus and hypothalamus (Butterweck *et al.* 2002).
Misane & Ogren. (2001) found that an ethanolic extract given in high doses affects the neuronal 5-HT uptake more like tricyclic antidepressants than SSRIs.
Calapai *et al.* (2001) investigated an extract standardised to 50% flavonoids, 0.3% hypericin and 4.5% hyperforin. After acute oral administration (250 – 500 mg/kg) dose-dependently the contents of 5-HT and 5-hydroxyindolacetic acid (5-HIAA) were significantly enhanced in all brain regions examined. Noradrenaline and dopamine levels were significantly increased in the diencephalon; in the brainstem only noradrenaline was significantly enhanced.
The down regulation of β-receptors could be demonstrated with an ethanolic extract (0.2% hypericin) dose dependently (Kientsch *et al.* 2001).
A methanolic extract (4.5% hyperforin) interacted with a GABA A receptor, an extract rich in hyperforin did not show an interaction. Data on the inhibition of specific bindings to the dopamine transporters indicate that the hyperforin content cannot explain effects of extracts on receptors (Gobbi *et al.* 2001).
A methanolic extract could also inhibit the binding of flumazenil to the benzodiazepine binding site of the GABA A receptor *in vitro*.
Simbrey *et al.* (2004) used quantitative radioligand receptor binding studies to examine the effects of short-term (2 weeks) and long-term (8 weeks) administration of different *Hypericum* extracts and constituents on β-adrenergic binding in rat frontal cortex. The effects were compared to those of the standard antidepressants imipramine and fluoxetine. A lipophilic CO_2 extract decreased beta-AR-binding (13%) after two weeks and slightly increased the number of β-receptors after 8 weeks (9%). Short-term treatment with the methanolic *Hypericum* extract decreased β-receptor-binding (14%), no effects for this extract were observed after 8 weeks. Treatment with hypericin led to a significant down-regulation (13%) of β-receptors in the frontal cortex after 8-weeks, but not after 2 weeks, while hyperforin (used as trimethoxybenzoate), and hyperoside were ineffective in both treatment paradigms. Compared to the *Hypericum* extracts and single compounds the effect of imipramine on β-receptor-binding was more pronounced in both treatment paradigms.
Teufel-Mayer & Gleitz (1997) could demonstrate that a methanolic extract significantly increased the numbers of 5-HT receptors, whereas the affinity of these receptors remained unchanged.

Hypericum extract inhibited the binding of naloxone to the μ- and κ-opioid receptor (IC_{50} values 25 and 90 μg/ml). Isolated flavonoids like quercetin, kaempferol as well as quercitrin did not inhibit naloxone binding. The authors suggest that this inhibition may contribute to the anti-depressant activity (Simmen *et al.* 1998).

II.2.1.1.2 Antidepressant activity in animal models

Forced swimming test (FST)

In the FST pure naphthodianthrones were active in high concentrations only, after addition of a fraction rich in procyanidines (which itself is inactive in the FST) hypericin was active in a concentration of 0.009 mg/kg (Butterweck *et al.* 1998).

Hyperoside, isoquercitrin and miquellianin showed activity in low concentrations (0.6 mg/kg) in the FST. Rutin, when administered as isolated compound, has no activity in the FST. However, extracts with a low content of rutin show only a weak activity in the FST, but when pure rutin is added to the extract, an activity could be demonstrated. Unfortunately the contents of the naphthodianthrones were not presented in the study (Butterweck *et al.* 2000).

Daily administration of 3 mg/kg isorhamnetin, a main metabolite from quercetin, for 9 days induced a statistically significant decrease in the immobility time in the FST (Paulke *et al.* 2008).

Noldner & Schotz (2002) found that an ethanolic extract (doses 30-300 mg/kg, 7 days oral treatment) shortened the time spent immobile in a dose dependent manner, while a methanolic extract was inactive. After addition of rutin to the methanolic extract a strong effect comparable to the ethanolic extract could be demonstrated.

Beijamini & Andreatini (2003) investigated the same methanolic extract. The rats received 150 to 500 mg/kg extract in 3 portions starting 24 hours before the experiment. All doses significantly reduced the immobility time.

Two different hydroethanolic extracts (4.5% and 0.5% hyperforin) and a stable salt of hyperforin were tested in the forced swimming test by Cervo *et al.* (2002). All test substances caused a significant reduction of immobility; the effect was more pronounced in the extract containing more hyperforin. The authors therefore conclude that hyperforin plays an important role in the antidepressant-like activity.

Calapai *et al.* (2001) found that an extract standardised to 50% flavonoids, 0.3% hypericin and 4.5% hyperforin was able to reduce the immobility time by about 30-40% compared to control. The effect was antagonised by the co-administration of sulpiride and methergoline. The effect was also significantly lower in animals pre-treated with 6-hydroxydopamine, which destroys noradrenergic neurons. The authors suggest that the action is probably mediated by serotonergic, noradrenergic and dopaminergic system activation.

Learned-helplessness paradigm

Chatterjee *et al.* (1998) compared an ethanolic extract (4.5% hyperforin) and a supercritical CO_2 extract (38.8% hyperforin). Oral doses of 300 mg/kg/day of the ethanolic extract and 30 mg/kg/day of the CO_2 extract were almost equieffective to 10 mg/kg/day of imipramine (52% reduction).

Model of escape deficit

Usai *et al.* (2003) compared 2 hydroethanolic extracts (4.5% hyperforin, 7.47% hyperforin). Both extracts exhibit a strong protective effect to prevent the development of escape deficit in rats. The extract with 4.5% hyperforin was effective in doses 8 times lower than of the other extract.

II.2.1.1.3 Anxiolytic effects

Kumar *et al.* (2000) reported anxiolytic effects of a *Hypericum* extract (ethanol 50%) of Indian origin in animal models, the dosage was relatively high (100 and 200 mg / kg p.o.).

Flausino *et al.* (2002) investigated the effects of acute and chronic oral treatment with *H. perforatum* L. (HP LI 160, 62.5-500 mg/kg) in rats submitted to different anxiety models: the elevated T-maze (for inhibitory avoidance and escape measurements), the light/dark transition, and the cat odour test. These models were selected for their presumed capacity of evidencing specific subtypes of anxiety disorders as recognized in clinical practice. The results showed that acute HP (125 mg/kg) impaired

elevated T-maze inhibitory avoidance, an anxiolytic effect, without altering escape performance. Chronic HP (250 mg/kg) enhanced avoidance latencies only in animals that were preexposed to the open arms of the maze. Preexposure shortens escape latency, improving it as an escape index. Differently from the reference drug imipramine (IMP, 15 mg/kg), chronic HP did not impair escape from the open arms of the maze. On the other hand, similarly to IMP, the extract increased the number of transitions between the two compartments in the light/dark transition model. Treatment regimens with HP and IMP did not alter behavioural responses of rats to a cloth impregnated with cat odour. These observations suggest that HP LI 160 exerts anxiolytic-like effects in a specific subset of defensive behaviours, particularly those related to generalized anxiety.

The aim of a study from Beijamini & Andreatini (2003) was to evaluate the putative antipanic/anxiolytic effect of standardised *H. perforatum* extract (LI 160) on rats tested in the elevated T-maze, an animal model of innate (panic) and learned (generalised) anxiety, at doses that exhibit antidepressant-like activity. *H. perforatum* (150, 300 and 500 mg/kg, administered orally 24, 18 and 1h before the test) decreased the immobility time in the forced swim test. Rats were treated orally with *H. perforatum* (150 or 300 mg/kg) or paroxetine (5mg/kg) 24, 18, and 1h before being tested in the elevated T-maze (subacute treatment). Immediately after this test, the animals were submitted to the open field to evaluate locomotor activity. Paroxetine was used as a positive control. Other groups of animals were submitted to the same drug treatment for 7 days (subchronic treatment). Paroxetine (5mg/kg) impaired inhibitory avoidance after subacute treatment, while subchronic administration increased one-way escape latency. Subacute treatment with *H. perforatum* (300 mg/kg) exerts a partial anxiolytic-like effect in the inhibitory avoidance task. Repeated administration of *H. perforatum* (300 mg/kg) induced an anxiolytic effect (decreased inhibitory avoidance) and an antipanic effect (increased one-way escape). No effect on locomotor activity was found with any treatment. Thus, the results suggest that *H. perforatum* extract could exert an anxiolytic and antipanic effect.

Grundmann *et al.* (2006) used exposure to an open field (OF) as inescapable stressor to mice. Exposure of male BL6/C57J mice to OF stress significantly increased body temperature (DeltaT = 1.8 +/- 0.13 degrees C, $p < 0.05$). Anxiolytic drugs (the benzodiazepine diazepam; 5 mg/kg, and the 5HT (1A) receptor agonist buspirone; 10 mg/kg) significantly reduced DeltaT, whereas antidepressants (imipramine and fluoxetine) had no effect on DeltaT. Oral administration of *Hypericum* extract significantly reduced DeltaT in doses of 250 and 500 mg/kg. Higher doses (750 and 1000 mg/kg) as well as a lower dose (125 mg/kg) did not affect DeltaT after stress, indicating a U-shaped dose-response curve. Hypericin (0.1 mg/kg, p. o.) administered 60 min prior to testing significantly decreased DeltaT ($p < 0.05$) whereas hyperforin (1-10 mg/kg, p. o.) had no effect in this test paradigm. The flavonoids hyperoside, isoquercitrin and quercitrin (all at 0.6 mg/kg, p. o.) and rutin (1 mg/kg, p. o.) only partially blocked OF-induced hyperthermia. If compared to all other flavonoids, the quercetin 3-O-glucuronide miquelianin (1.2 mg/kg, p. o.) was the most potent compound tested in this experimental design. From the biflavonoids in *Hypericum*, only amentoflavone decreased stress-induced hyperthermia in a dosage of 0.1 mg/kg. These findings could be interpreted as putative anxiolytic effects of *Hypericum* extract and single constituents.

II.2.1.1.4 Neuroprotection, memory impairment, nootropic effects

Kaltschmidt *et al.* (2002) analyzed the effect of hypericin on nuclear factor kappa B (NF-κB) activation. Hypericin alone was able to induce short-time activation of NF-κB, which declined to basal levels after 24 h. Cell death was induced by hypericin at a concentration of 10 µM. A profound synergistic action in inducing apoptosis was detected in co-treatment of hypericin together with $FeSO_4$. In contrast, hypericin in low concentrations was able to partly prevent cell death induced by amyloid-beta-peptide (Abeta). Hypericin (10 µM) synergistically enhanced Abeta neurotoxicity. The data describe NF-κB in the same primary neuronal culture as stimulus-dependent, anti-apoptotic, or pro-apoptotic factor.

Extracts of *H. perforatum* exhibited upgrading and significant protective effects on the trauma of PC12 cells induced by 200 µM H_2O_2 in a dose-dependent manner within 24-hour treatment (Lu *et al.* 2004). Cell viability was assessed by the MTT method, and in situ cellular hydrogen peroxide (H_2O_2)-induced oxidative stress was examined by measurement of reactive oxygen species (ROS) formation

using 6-carboxy-2′,7′-dichlorodihydrofluorescein diacetate (CDCFH) procedures. Intra- and extracellular ROS levels decreased significantly to 71.9% and 50.0% of the control at a moderate concentration of 20 µg/ml, respectively, suggesting that *Hypericum* extract could easily enter the cells and play important roles in reducing ROS levels. The results were proved by detection of DNA fragmentation and inspection of cell morphology of PC12 cells. *Hypericum* extract can obviously block DNA fragmentation and prevent the cells from shrinking and turning round of H_2O_2-induced apoptosis in PC12 cells at concentrations of 10 approximately 100 µg/ml. The authors conclude that *Hypericum* extracts may be a candidate for application in neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease.

Genovese *et al.* (2006) evaluated the effect of *H. perforatum* (given at 30 mg/kg) in an experimental animal model of spinal cord injury, which was induced by the application of vascular clips to the dura via a four-level T5 through T8 laminectomy. The degree of (a) spinal cord inflammation and tissue injury (histological score), (b) nitrotyrosine, (c) polyadenosine diphosphate-ribose, (d) neutrophils infiltration, and (e) the activation of signal transducer and activator transcription 3 was markedly reduced in spinal cord tissue obtained from *H. perforatum* extract-treated mice. It could be demonstrated that *H. perforatum* extract significantly ameliorated the recovery of limb function.

Froestl *et al.* (2003) studied the effect of hyperforin on the processing of the amyloid precursor protein (APP) in rat pheochromocytoma PC12 cells, stably transfected with human wildtype APP. The authors observed transiently increased release of secretory APP fragments upon hyperforin treatment. Unique features, like a strong reduction of intracellular APP and the time course of soluble APP release, distinguished the effects of hyperforin from those of alkalizing agents and phorbol esters, well known activators of secretory processing of APP. Carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP), a protonophore, induced an almost identical decrease in intracellular pH in PC12 cells as does hyperforin. Despite this, FCCP induced a less pronounced release of soluble APP fragments and only slightly reduced intracellular APP levels. These results suggest that hyperforin is an activator of secretory processing of APP.

Silva *et al.* (2004) assessed the neuroprotective role of a *H. perforatum* ethanolic extract and obtained fractions in amyloid-beta peptide (Abeta(25-35))-induced cell death in rat cultured hippocampal neurons. Lipid peroxidation was used as a marker of oxidative stress by following the formation of TBARS (thiobarbituric acid-reactive substances) in rat cortical synaptosomes, after incubation with ascorbate/Fe2+, alone or in the presence of EC97 effective concentrations of *H. perforatum* fractions. Induced lipid peroxidation was significantly inhibited by fractions containing flavonol glycosides, flavonol and biflavone aglycones, and by a fraction containing several phenols, mainly chlorogenic acid-type phenolics (21%, 77% and 98%, respectively). Lipid peroxidation evaluated after incubation with 25 µM Abeta(25-35), was significantly inhibited by *H. perforatum* extract. Cell viability was assessed by use of the Syto-13/PI assay. The total ethanolic extract (TE) and fractions containing flavonol glycosides, flavonol and biflavone aglycones, reduced Abeta(25-35)-induced cell death (65%, 58% and 59%, respectively). These results were further supported by morphological analysis of cells stained with cresyl violet. Peptide beta-amyloid(25-35) induced a decrease in cell volume, chromatin condensation and nuclear fragmentation, alterations not evident in the presence of the TE and fractions containing hypericins (hypericin concentration = 11.02 µM), or fractions containing flavonoids (quercetin concentration = 21.13 µM). Dendritic lesion, an evidence of neurodegeneration, was observed by neuronal staining with cobalt following insult with Abeta(25-35), but prevented after exposure to the peptide plus the fractions referred above. The results suggest that *H. perforatum* extracts may be endowed with neuroprotective compounds able to prevent Abeta(25-35)-induced toxicity.

The major protein constituent of amyloid deposits in Alzheimer's disease (AD) is the amyloid beta-peptide (Abeta). Dinamarca *et al.* (2006) have determined the effect of hyperforin on Abeta-induced spatial memory impairments and on Abeta neurotoxicity. Hyperforin decreases amyloid deposit formation in rats injected with amyloid fibrils in the hippocampus, decreases the neuropathological changes and behavioural impairments in a rat model of amyloidosis, and prevents Abeta-induced neurotoxicity in hippocampal neurons both from amyloid fibrils and Abeta oligomers, avoiding the increase in reactive oxidative species associated with amyloid toxicity. Both effects could be explained

by the capacity of hyperforin to disaggregate amyloid deposits in a dose and time-dependent manner and to decrease Abeta aggregation and amyloid formation.

Acute administration of *Hypericum* extract (4.0, 8.0, 12.0, and 25.0 mg/kg i.p.) in mice before retrieval testing increased the step-down latency during the test session. The same doses of *Hypericum* extract, on the other hand, failed to reverse scopolamine-induced amnesia of a two-trial passive avoidance task. Pre-treatment of the animals with 5-HT1A receptor antagonist (-)-pindolol (0.3, 1.0, and 3.0 mg/kg), 5-HT2A receptor blocker spiperone (0.01, 0.03, and 0.1 mg/kg), alpha adrenoceptor antagonist phentolamine (1, 5, and 10 mg/kg), beta receptor antagonist propranolol (5, 7.5, and 10 mg/kg), D1 receptor antagonist SCH 23390 (0.01, 0.05, and 0.1 mg/kg), and D2 receptor antagonist sulpiride (5, 7.5, and 10 mg/kg) revealed the involvement of adrenergic and 5-HT1A receptors in the facilitatory effect of *Hypericum* extract on retrieval memory. It is concluded that *Hypericum* extract may be a better alternative for treatment of depression commonly associated with dementia than other antidepressants known to have anticholinergic side effects causing delirium, sedation and even exacerbating already existing impaired cognition (Khalifa 2001).

The effects of a *Hypericum* extract and hyperforin sodium salt were evaluated in rat and mouse avoidance tests by Klusa *et al.* (2001). In a conditioned avoidance response (CAR) test on the rat, oral daily administration of hyperforin (1.25 mg/kg/day) or of the extract (50 mg/kg/day) before the training sessions considerably improved learning ability from the second day onwards until the day 7. In addition, the memory of the learned responses acquired during 7 consecutive days of administration and training was largely retained even after 9 days without further treatment or training. The observations made using different doses indicate that these learning-facilitating and/or memory-consolidating effects by the agents follow inverse U-shaped dose-response curves in dose ranges lower than (for hyperforin) or equal to (for *Hypericum* extract) their effective dose in the behavioural despair test for antidepressants. In a passive avoidance response test on the mouse, a single oral dose (1.25 mg/kg) of hyperforin not only improved memory acquisition and consolidation, but also almost completely reversed scopolamine-induced amnesia. The single *Hypericum* extract dose tested (25 mg/kg) did not reveal any significant effects in the passive avoidance response (PAR) test on the mouse. These observations suggest that the *Hypericum* extract could be a novel type of antidepressant with memory enhancing properties, and indicate that hyperforin is involved in its cognitive effects. Pure hyperforin seems to be a more potent antidementia agent than an antidepressant.

Kumar *et al.* (2000, 2002) found that orally administered extracts of *H. perforatum* of Indian origin (doses 100 mg and 200 mg/kg) to rats showed effects which could be interpreted as possible nootropic action.

Widy-Tyszkiewicz *et al.* (2002) investigated the effects of long-term *H. perforatum* treatment on spatial learning and memory in rats. A *Hypericum* powder (HP) standardized to 0.3% hypericin content was administered orally for 9 weeks in doses of 4.3 and 13 µg/kg corresponding to therapeutic dosages in humans of 0.3 and 0.9 mg of total hypericins daily. A Morris water maze paradigm was used. The mean escape latency over 4 days for the control group (21.9 s) and HP 4.3 group (21.7 s) was significantly greater than the latency of the HP 13 group (15.8 s). In the probe trial on day 5, the HP 13 group crossed the correct annulus in the SE quadrant more often (4.5) than the other groups: Con (2.4) and HP 4.3 (3.1). After completion of the behavioural experiment, the regional brain concentrations of monoamines and metabolites were estimated in selected brain regions, i.e. prefrontal cortex, hippocampus and hypothalamus. Significant differences in the content of monoamines and metabolites between the treatment groups compared to the control were detected. The increased 5-HT levels in the prefrontal cortex correlated positively with the retention of spatial memory. These findings show that the long-term administration of *H. perforatum* can improve learning and spatial memory with significant changes in the content of monoamines in several brain regions.

Administration of *H. perforatum* (350 mg / kg daily for 21 days) significantly enhanced recall of passive avoidance behaviour (PAB), but had no effect on the acquisition of conditioned avoidance responses (CARs). Rats stressed chronically (2 h daily for 21 days) displayed diminished recall of the PAB and this effect was abolished by St John's wort. Chronic administration of the "equivalent" to the stress dose of exogenous corticosterone (5 mg/kg daily for 21 days) also impaired recall of PAB, and

this effect was also reversed by *H. perforatum*. None of the treatments produced significant motor coordination impairments as tested in a 'chimney' test. It appears that *H. perforatum* prevents stress-induced deterioration of memory in rats (Trofimiuk *et al.* 2005, 2006).

Mohanasundari *et al.* (2006, 2007) tested the effect of an extract of *H. perforatum* in chemically induced Parkinson's disease in mice. Treatment with *H. perforatum* extract resulted in an inhibition of monoamine oxidase-B activity and reduced astrocyte activation in striatal area. The effects were more pronounced when *Hypericum* was combined with bromocriptine.

Sanchez Reus *et al.* (2007) designed a study to investigate the pro-oxidant activity of rotenone, the protective role of standardized extract of *H. perforatum* (SHP), as well as the mRNA levels of antioxidant enzymes, in brain homogenates of rats following exposure to rotenone and SHP extract. Quercetin in liposomes, one active constituent, was tested in the same experimental conditions to serve as a positive control. The animals received pretreatment with SHP (4 mg/kg) or quercetin liposomes (25 and 100 mg/kg) 60 min before of rotenone injection (2 mg/kg). All treatments were given intraperitoneally in a volume of 0.5 ml/kg body weight, for 45 days. SHP extract exerted an antioxidant action which was related to a decrease of manganese superoxide dismutase (MnSOD) activity and mRNA levels of some antioxidant enzymes evaluated. One possible mechanism of action of SHP extract may be related to quercetin in protecting neurons from oxidative damage.

El-Sherbiny *et al.* (2003) investigated the effect of acute administration of *H. perforatum* extract (4.0, 8.0, 12.0, and 25.0 mg/kg ip) on the brain oxidative status of naive rats treated with an amnestic dose of scopolamine. The results showed that the administration of 1.4 mg/kg of scopolamine impaired the retrieval memory of rats. Pretreatment of the animals with *Hypericum* extract (4, 8, and 12 mg/kg) resulted in an antioxidant effect through altering brain malondialdehyde, glutathione peroxidase, and/or glutathione level/activity.

II.2.1.1.5 Support in smoking cessation

Catania *et al.* (2003) investigated the effects of an extract of *H. perforatum* (Ph-50) on withdrawal signs produced by nicotine abstinence in mice. Nicotine (2 mg/kg, four injections daily) was administered for 14 days to mice. Different doses of Ph-50 (125-500 mg/kg) were administered orally immediately after the last nicotine injection. In another experiment, Ph-50 (500 mg/kg) was orally administered in combination with nicotine, i) starting from day 8 until the end of the nicotine treatment period, or ii) during nicotine treatment and after nicotine withdrawal, or iii) immediately after the last nicotine injection. The locomotor activity reduction induced by nicotine withdrawal was abolished by Ph-50, which also significantly and dose-dependently reduced the total nicotine abstinence score when injected after nicotine withdrawal.

Mannucci *et al.* (2007) investigated the possible involvement of 5-HT in the beneficial effects of *H. perforatum* on nicotine withdrawal signs. With the aim to induce nicotine dependence, nicotine (2 mg/kg, four intraperitoneal injections daily) was administered for 14 days to mice (NM). After nicotine withdrawal the measurement of 5-HT metabolism in the cortex showed a reduction of the 5-HT content while animals treated only with *Hypericum* extract showed a significant reduction of total abstinence score compared to controls. A selective 5-HT receptor antagonist inhibited the reduction of total abstinence score induced by *H. perforatum*. Moreover, 5-HT1A expression has been evaluated 30 days after nicotine withdrawal. The results show a significant increase of cortical 5-HT content in NM treated with *H. perforatum*, with a concomitant significant increase of 5-HT1A receptor.

II.2.1.1.6 Treatment of alcoholism

Several studies were performed in order to investigate the influence of *Hypericum* extracts on alcohol intake in animals (Rezvani *et al.* 1999, Perfumi *et al.* 1999, Perfumi *et al.* 2005, Perfumi *et al.* 2005a, Coskun *et al.* 2006). All studies report beneficial effects on ethanol withdrawal symptoms,

additionally a reduction of alcohol intake in alcohol preferring animals was observed. *Hypericum* extracts and opioid receptor antagonists act synergistically (Perfumi *et al.* 2003).
The changes in the alcohol drinking behaviour may be caused by hyperforin (Perfumi *et al.* 2001, Wright *et al.* 2003). In contrast, De Vry *et al.* (1999) reported a reduction in alcohol preference after administration of an extract with very low hyperforin content. Clinical data are missing (Uzbay 2008).

II.2.1.1.7 Antibacterial activity

Gibbons *et al.* (2002) screened extracts of 34 species and varieties of the genus *Hypericum* for activity against a clinical isolate of methicillin-resistant *Staphylococcus aureus*, which in addition possessed a multidrug efflux mechanism conferring a high level of resistance to therapeutically useful antibiotics. Thirty-three of the 34 chloroform extracts showed significant activity in a disk diffusion assay, and five extracts had minimum inhibitory concentrations of 64 μg/ml.

II.2.1.1.8 Antiinflammatory activity

Schempp (2000) investigated the alloantigen presenting function of human epidermal cells (EC) exposed to *Hypericum* ointment *in vivo* in a mixed epidermal cell lymphocyte reaction (MECLR). The effect of *Hypericum* ointment was compared with the immunosuppressive effect of solar-simulated radiation (SSR). Subsequently, the authors tested purified hyperforin *in vivo* and *in vitro* in a MECLR to evaluate its possible contribution to the effect of the *Hypericum* ointment. Furthermore, the effect of hyperforin on the proliferation of peripheral blood mononuclear cells (PBMC) *in vitro* was assessed. Compared with untreated skin, treatment with *Hypericum* ointment resulted in a significant suppression of the MECLR ($P \leq 0.001$) that was similar to the effect of SSR. The combination of *Hypericum* ointment plus SSR was not significantly different from either treatment alone. EC isolated from skin treated with the hyperforin containing ointment also showed a reduced capacity to stimulate the proliferation of allogenic T cells ($P \leq 0.001$). Similarly, *in vitro* incubation of EC with hyperforin suppressed the proliferation of alloreactive T cells (P </= 0.001). Furthermore, hyperforin inhibited the proliferation of PBMC in a dose-dependent manner, without displaying pronounced toxic effects as determined by Trypan blue staining. The results demonstrate an inhibitory effect of *Hypericum* extract and of its metabolite hyperforin on the MECLR and on the proliferation of T lymphocytes that may provide a rationale for the traditional treatment of inflammatory skin disorders with *Hypericum* extracts.

Three preparations of *H. perforatum* L. (a hydroalcoholic extract, a lipophilic extract and an ethylacetic fraction) and the pure compounds hypericin, adhyperforin, amentoflavone, hyperoside, isoquercitrin, hyperforin dicyclohexylammonium (DHCA) salt and dicyclohexylamine were evaluated for their topical anti-inflammatory activity (Sosa *et al.* 2007). *H. perforatum* preparations provoked a dose-dependent reduction of Croton-oil-induced ear oedema in mice, showing the following rank order of activity: Lipophilic extract > ethylacetic fraction > hydroalcoholic extract (ID50 220, 267 and >1000 mg cm^{-2}, respectively). Amentoflavone (ID50 0.16 micromol cm^{-2}), hypericin (ID50 0.25 micromol cm^{-2}), hyperforin DHCA salt (ID50 0.25 micromol cm^{-2}) and adhyperforin (ID50 0.30 micromol cm^{-2}) had anti-inflammatory activity that was more potent or comparable to that of indometacin (ID50 0.26 micromol cm^{-2}), whereas isoquercitrin and hyperoside were less active (ID50 about 1 micromol cm^{-2}). As dicyclohexylamine alone was inactive, the effect of hyperforin DHCA salt can be attributed completely to the phloroglucinol moiety. The pharmacological activity and phytochemical profile of the tested extracts and fraction suggest that different constituents are involved in the topical antiphlogistic property of *H. perforatum in vivo*.

Eckert & Müller (2001) tested the effects of hyperforin on the fluidity of crude brain membranes from young guinea pigs. Hyperforin modifies specific membrane structures in different ways. It decreases the flexibility of fatty acids in the membrane hydrocarbon core, but fluidizes the hydrophilic region of membrane phospholipids. Relatively low concentrations of hyperforin (0.3 μmol/l) significantly decreased the annular fluidity of lipids close to membrane proteins. These findings are remarkable, as inhibition of several neurotransmitter-uptake systems and modulation of several ionic conductance mechanisms by hyperforin occur in the same concentration range. However, bulk fluidity was unchanged by this low hyperforin concentration. The results emphasise a physicochemical interaction

of hyperforin with specific membrane structures that probably contribute to its pharmacological properties.

Quercetin and I3,II8-biapigenin were found to be responsible for the antiinflammatory and gastroprotective activity of oil extracts in rats (Zdunic *et al.* 2009). An oil prepared by maceration with 96% ethanol followed by extraction with sunflower oil on a water bath exhibited in a dose of 1.25 ml/kg p.o. the highest antiinflammatory and gastroprotective effect.

II.2.1.1.9 Wound healing

The wound-healing effect of *H. perforatum* extract was evaluated by comparing with dexpanthenol and titrated extract of Centella asiatica (TECA) on cultured chicken embryonic fibroblasts (Ozturk *et al.* 2006). Chicken embryonic fibroblasts from fertilized eggs were incubated with the plant extract, dexpanthenol and TECA. The wound-healing activity of *H. perforatum* extract seems to be mainly due to the increase in the stimulation of fibroblast collagen production and the activation of fibroblast cells in polygonal shape, which plays a role in wound repair by closing damaged area. The findings demonstrated the wound-healing activity of *H. perforatum*, which has previously been based on ethnomedical data.

II.2.1.1.10 Photodynamic therapy

Hypericin is considered as a potential agent in the photodynamic therapy of cancer (Agostinis *et al.* 2002). However, since only isolated hypericin and not extracts have been tested, this approach is out of the scope of this assessment.

II.2.1.1.11 Other effects

A dry extract prepared by successive extraction with petroleum ether, 1,2-dichloroethane and ethanol (50%) orally administered at 26.5 mg/kg induced a marked sedation in mice (Girzu *et al.* 1997). Also an increase in the sleep duration induced by pentobarbital was observed.

Capasso *et al.* (2005) evaluated the effect of *Hypericum* on rat and human vas deferens contractility. *Hypericum* extract (1 to 300 microM) decreased in a concentration dependent manner the amplitude of electrical field stimulation and agonist induced contractions with the same potency, suggesting direct inhibition of rat vas deferens smooth muscle. Of the chemical constituents of *Hypericum* extract tested hyperforin but not hypericin or the flavonoids quercitrin, rutin and kaempferol inhibited phenylephrine induced contractions. *Hypericum* extract and hyperforin also inhibited phenylephrine induced contractions in human vas deferens. These results might explain delayed ejaculation described in patients receiving *Hypericum* extract.

Effects of different extracts of *H. perforatum* on the kindling epileptic discharges were analyzed by Ivetic *et al.* (2002). The experiment was carried out on Chinchilla rabbits with chronically implanted electrodes in cortical structures and hippocampus. Water, n-butanol and ether fractions (mass concentrations 0.1 g/ml) of crude ethanol extract of *H. perforatum* were used. The particular extracts were given intramuscularly in a single dose of 1 ml/kg BW. The bioelectric activity was registered before and after applications of each extract. The obtained results show that the effect depends on the constituents present in particular fractions. Most polar constituents that remained in water fraction exerted highest antiepileptic activity in all (100%) animals tested. Substances present in butanol fraction repressed the epileptic manifestations in 40% of animals with kindling epilepsy, whereas lipid-soluble constituents in ether fraction potentiated the epileptic activity.

Hypericin, pseudohypericin and hyperforin at doses as low as 2.5 µmol/l are potent antioxidants in the low-density lipoprotein (LDL) oxidation systems used. These results indicate that these derivatives have possible antiatherogenic potential (Laggner *et al.* 2007). An extract rich in flavonoids lowered serum levels of total cholesterol, total triglycerides and LDL (Zou *et al.* 2005).

Free radical scavenging and antioxidant activities of a standardized extract of *H. perforatum* were examined for inhibition of lipid peroxidation, for hydroxyl radical scavenging activity and interaction with 1,1-diphenyl-2-picrylhydrazyl stable free radical (DPPH) by Benedi *et al.* (2004). The results suggest that *Hypericum* extracts show relevant antioxidant activity both *in vitro* and in a cell system, by means of inhibiting free radical generation and lipid peroxidation.

Antioxidative and radical scavenging effects are also reported for the flavonoid fraction of *H. perforatum* (Zou *et al.* 2004) and for several commercially available formulations (Hunt *et al.* 2001). The antioxidative properties protect human neuroblastoma cells against induced apoptosis (Jang *et al.* 2002).

Genovese *et al.* (2006) evaluated the effect of *H. perforatum* extract on acute pancreatitis induced by cerulein administration in male CD mice. The degree of pancreatic inflammation and tissue injury (histological score), expression of Inter-Cellular Adhesion Molecule 1 (ICAM-1), the staining for nitrotyrosine and poly-ADP-ribose (PAR), and myeloperoxidase activity was markedly reduced in pancreatic tissue sections obtained from cerulein-treated mice administered *H. perforatum* extract (30 mg/kg, suspended in 0.2 ml of saline solution, o.s.). Moreover, the treatment with *H. perforatum* extract significantly reduced the mortality rate at 5 days after cerulein administration.

Following the traditional use of *Hypericum* against viruses of the Herpes family in Greece Axarlis *et al.* (1998) found antiviral activity of a methanolic extract against Human Cytomegalovirus.

Panossian *et al.* (1996) concluded that the antiviral, antiinflammatory and antitumor effects of hypericin may result from the inhibition of the PKC-mediated signalling pathway demonstrated in human leukocytes, which influences the arachidonic acid metabolism and the interleukin-1-alpha production resulting in an immunosuppressive effect.

II.2.1.2 Assessor's overall conclusions on pharmacology

There are numerous pharmacological findings published which propose a similar pharmacology to established synthetic antidepressant drugs. However, the discussion on the responsible compounds in the extract is still ongoing. Since several hydroethanolic and hydromethanolic extracts with different contents of hypericin and hyperforin have been tested positively, it could be concluded that the naphthodianthrones and the phloroglucine derivatives are of minor relevance for the antidepressant activity.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Wurglics *et al.* (2006) published a review on pharmacokinetic data of compounds of *Hypericum* extracts. The hyperforin plasma concentration in humans was investigated in a small number of studies. The results of these studies indicate a relevant plasma concentration, comparable with that used in *in vitro* tests. Furthermore, hyperforin is the only ingredient of *H. perforatum* that could be determined in the brain of rodents after oral administration of alcoholic extracts. The plasma concentrations of the hypericins were only one-tenth compared with hyperforin and until now the hypericins could not be found in the brain after oral administration of alcoholic *H. perforatum* extracts or pure hypericin.

The intestinal absorption characteristics of protohypericin were studied and compared with those of hypericin by Kamuhabwa *et al.* (1999). The Caco-2 model was used as a model of the intestinal mucosa to assess transepithelial transport and cell uptake. Following application of the individual compounds (80-200 microM) to the apical side of the monolayers, the appearance in the basolateral compartment was found to be very low (<0.5%/5 h), but was comparable for both compounds. A lag-time of 2-3 h was observed, suggesting gradual saturation of binding sites on the membrane or inside the cells. Uptake experiments of protohypericin and hypericin by Caco-2 cells revealed a very

significant cellular accumulation (4-8%); uptake was characterised by saturation after 3 h. The findings of this study suggest that protohypericin has comparable absorption characteristics as hypericin.

Investigations by Sattler *et al.* (1997) indicate that a significant accumulation of hypericin in the cell membrane and the cell nucleus membrane of Caco-2-cells takes place. The authors conclude that hypericin is absorbed through the intestinal epithelium by passive transcellular diffusion and that increasing its solubility by cyclodextrin appears as a promising approach to increase its oral bioavailability for pharmaceutical formulations.

Plasma levels of hypericin in rats in the presence and absence of procyanidin B2 or hyperoside were determined by reversed phase HPLC using fluorimetric detection (Butterweck *et al.* 2003). Both compounds increased the oral bioavailability of hypericin by ca. 58% (B2) and 34% (hyperoside). Procyanidin B2 and hyperoside had a different influence on the plasma kinetics of hypericin; median maximal plasma levels of hypericin were detected after 360 min (Cmax : 8.6 ng/ml) for B2, and after 150 min (Cmax : 8.8 ng/ml) for hyperoside. It can be speculated that, when administered together with these compounds, a significant accumulation of hypericin in rat plasma in the presence of both polyphenols might be responsible for the observed increased *in vivo* activity.

Juergenliemk *et al.* (2003) examined the pathway of miquelianin (quercetin 3-O-beta-D-glucuronopyranoside), a flavonoid with antidepressant activity, from the small intestine to the central nervous system. The permeability coefficient of miquelianin (Pc = 0.4 +/- 0.19 x 10(-6) cm/sec) was in the range of orally available drugs assuming sufficient absorption from the small intestine. The permeability coefficients (blood-brain-barrier: Pc = 1.34 +/- 0.05 x 10(-6) cm/sec; blood-CSF-barrier: Pc = 2.0 +/- 0.33 x 10(-6) cm/sec) indicate the ability of miquelianin to cross both barriers to finally reach the CNS.

Paulke *et al.* (2008) suggested that not the genuine flavonoid glycosides reach the plasma. After oral uptake they are deglycosylated in the small intestine, after absorption the quercetin aglycone is glucuronidated (yielding e.g. miquelianin). Further methylation is possibly leading to isorhamnetin and tamarixetin. These metabolites have the ability to penetrate the blood-brain-barrier. Moreover, a significant accumulation of these metabolites in the CNS tissue is observed. After a single dose of a *Hypericum* extract (1600 mg/kg rat) the quercetin plasma level increased rapidly and reached the maximum of about 700 ng/ml after 4 hours. After 24 hours, 50% of the Cmax was still measurable. In contrast the concentration level of isorhamnetin/tamarixetin increase much slower, the maximum was reached after 24 hours with a Cmax of 903 ng/ml. Repeated doses of 1600 mg/kg rat yielded a continuous increase in the plasma levels of quercetin and isorhamnetin for 5 days, after that time the concentration remained constant.

Hyperforin is a high affinity ligand for pregnan x receptor (PXR) and activates the promoters of CYP3A4 and CYP2B6 through activation of PXR and PXR-specific cis-elements. The PXR-mediated activation of CYP2C9 by 0.2 nM hyperforin is consistent with the high affinity of this compound as a ligand for PXR (Chen *et al.* 2004). Hypericin did not mediate transactivation and coactivator recruitment by steroid x receptor (Wentworth *et al.* 2000).

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

The few data on pharmacokinetics do not allow a final conclusion about absorption, distribution, metabolism and excretion of the constituents of *Hypericum* extracts. Additionally it is not clear whether putative active constituents of *Hypericum* extracts reach the brain tissue in sufficient concentration.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

II.2.3.1.1 Single-dose toxicity

For a methanolic extract (DER 3-6:1) the following data are published in the SPC of products containing the extract LI 160:

Species	Application	LD_{50} (mg / kg BW)
Mouse	oral	≥ 5000
Rat	oral	≥ 5000
Mouse	intraperitoneal	1780
Rat	intraperitoneal	1000

Intravenous application of hypericin was well tolerated by rhesus monkeys at a dose of 2 mg/kg, at 5 mg/kg transient severe photosensitivity rash occurred (Fox *et al.* 2001). The amount of hypericin administered daily in usual therapeutic dosages is not more than 3 mg for adults (= 0.04 mg/kg).

II.2.3.1.2 Repeated-dose toxicity

Studies on long-term toxicity (900 mg/kg and 2700 mg/kg extract per day (LI 160, extraction solvent methanol 80%, DER 3-6:1), 26 weeks treatment) in rats and dogs revealed only minor non-specific symptoms (weight loss, minor pathological changes in liver and kidney). All changes reverted to normal when treatment was stopped (Leuschner 1996, Greeson *et al.* 2001). The dosages were approximately 70 and 200 times the mean therapeutic dosage.

II.2.3.1.3 Mutagenicity

The genotoxicity testing of ethanolic extracts showed weak positive results in the AMES-test (Salmonella typhimurium TA 98 and TA 100, with and without metabolic activation). After chromatographic separation the effect could be assigned to quercetin (Poginsky *et al.* 1988, Schimmer *et al.* 1994).
Okpanyi *et al.* (1990) tested an ethanolic extract (DER 1:5-7, 0.2-0.3% hypericin, 0.35 mg/g quercetin) in several *in vivo* (mammalian spot test in mice, chromosome aberration test in Chinese hamsters) and *in vitro* test systems (HGPRT hypoxanthine-guanine-phosphoribosyl-transferase test, UDS unscheduled DNA synthesis test, cell transformation test). The authors could not detect any signs of a mutagenic potential of the extract.

II.2.3.1.4 Carcinogenicity

Tests on the carcinogenic potential have not been published.

II.2.3.1.5 Phototoxicity

In order to estimate the potential risk of phototoxic skin damage during antidepressive therapy, Bernd *et al.* (1999) investigated the phototoxic activity of hypericin extract using cultures of human keratinocytes and compared it with the effect of the well-known phototoxic agent psoralen. The absorbance spectrum of the *Hypericum* extract revealed maxima in the whole UV range and in parts of the visible range. Human keratinocytes were cultivated in the presence of different *Hypericum* concentrations. The determination of the bromodeoxyuridine incorporation rate showed a concentration- and light-dependent decrease in DNA synthesis with high hypericin concentrations (≥ 50 µg/ml) combined with UVA or visible light radiation. In the case of UVB irradiation a clear phototoxic cell reaction was not detected. The authors found phototoxic effects even with 10 ng/ml psoralen using UVA with the same study design as in the case of the *Hypericum* extract. These results confirm the phototoxic activity of *Hypericum* extract on human keratinocytes. However, the blood levels that are to be expected during antidepressive therapy are presumably too low to induce phototoxic skin reactions.

Schempp *et al.* (2002) assessed the phototoxic and apoptosis-inducing capacity of pseudohypericin (PH) compared to hypericin (H) in a cell culture model with human leukemic lymphoma cells (Jurkat-cell line). Treatment with both photoactivated H and PH resulted in a dose-dependent inhibition of cell proliferation, whereas not photoactivated H and PH had no effect at the concentrations tested. The

half-maximal inhibitory concentration (IC50) of H was lower (100 ng/ml) as compared to PH (200 ng/ml) ($p < 0.05$). In an apoptosis assay the authors found a dose-dependent increase of DNA fragmentation after treatment with both photoactivated H and PH. The cytotoxic potential of PH should be taken into account during systemic therapy with *Hypericum* extracts, since PH is about two times more abundant than H in *H. perforatum*.

Wilhelm *et al.* (2001) investigated the phototoxic potential of three *H. perforatum* extracts from different sources as well as some of its main constituents. *H. perforatum* extracts demonstrated cytotoxicity and photocytotoxicity in a dose and UVA-dose dependent manner. Hypericin itself also evoked severe phototoxic effects and was thus identified as the main phototoxic constituent. Among the tested flavonoids quercitrin was found to be cytotoxic, while rutin unexpectedly demonstrated phototoxicity whereas quercitrin was effective to control the phototoxic activity of *H. perforatum* extracts.

Clinical evidence suggests that administration of *H. perforatum* extracts containing the photo-activated hypericin compounds may cause fewer skin photosensitization reactions than administration of pure hypericin. Schmitt *et al.* (2006) conducted a study to determine whether the phototoxicity of hypericin in HaCaT keratinocytes could be attenuated by *H. perforatum* extracts and constituents. Two extracts, when supplemented with 20 microM hypericin: (1) an ethanol re-extraction of residue following a chloroform extraction (denoted ethanol(-chloroform)) (3.35 microM hypericin and 124.0 microM total flavonoids); and (2) a chloroform extract (hypericin and flavonoids not detected), showed 25% and 50% ($p<0.0001$) less phototoxicity than 20 microM hypericin alone. Two *H. perforatum* constituents, when supplemented with 20 microM hypericin: (1) 10 microM chlorogenic acid; and (2) 0.25 microM pyropheophorbide, exhibited 24% ($p<0.05$) and 40% ($p<0.05$) less phototoxicity than 20 microM hypericin alone. The peroxidation of arachidonic acid was assessed as a measure of oxidative damage by photo-activated hypericin, but this parameter of lipid peroxidation was not influenced by the extracts or constituents. However alpha-tocopherol, a known antioxidant also did not influence the amount of lipid peroxidation induced in this system. These observations indicate that hypericin combined with *H. perforatum* extracts or constituents may exert less phototoxicity than pure hypericin, but possibly not through a reduction in arachidonic acid peroxidation.

Schmitt *et al.* (2006a) examined the cytotoxicity of *H. perforatum* extracts prepared in solvents ranging in polarity, fractions of one extract, and purified compounds in three cell lines. All extracts exhibited significant cytotoxicity; those prepared in ethanol (no hyperforin, 3.6 microM hypericin, and 134.6 microM flavonoids) showed between 7.7 and 77.4% cell survival ($p < 0.0001$ and 0.01), whereas the chloroform and hexane extracts (hyperforin, hypericin, and flavonoids not detected) showed approximately 9.0 ($p < 0.0001$) and 4.0% ($p < 0.0001$) survival. Light-sensitive toxicity was observed primarily with the ethanol extracts sequentially extracted following removal of material extracted in either chloroform or hexane. The absence of light-sensitive toxicity with the *H. perforatum* extracts suggests that the hypericins were not playing a prominent role in the toxicity of the extracts.

A study of Traynor *et al.* (2005) used HaCaT keratinocytes to investigate the photoclastogenic ability of hypericin on irradiation with UVA. The results show that although the combination of hypericin and UVA light increased the genotoxic burden, when all factors are taken into account, the risk of significant photogenotoxic damage incurred by the combination of H. extracts and UVA phototherapy may be low in the majority of individuals.

Ocular phototoxicity

To determine if hypercin could be phototoxic to the eye, He *et al.* (2004) exposed human lens epithelial cells to 0.1-10 microM hypericin and irradiated them with 4 J/cm2 UV-A or 0.9 J/cm2 visible light. Neither hypericin exposure alone nor light exposure alone reduced cell viability. In contrast, cells exposed to hypericin in combination with UV-A or visible light underwent necrosis and apoptosis. The ocular antioxidants lutein and N-acetyl cysteine did not prevent damage. Thus, ingested H. extract is potentially phototoxic to the eye and could contribute to early cataractogenesis.

Lens alpha-crystallin, isolated from calf lenses, was irradiated in the presence of hypericin (5 x 10(-5) M, 10 mM ammonium bicarbonate, pH 7.0) and in the presence and absence of light (> 300 nm, 24 mW/cm2). Hypericin-induced photosensitized photopolymerization was assessed by sodium dodecylsulfate-polyacrylamide gel electrophoresis. Further analysis of the oxidative changes occurring in alpha-crystallin using mass spectrometry showed specific oxidation of methionine, tryptophan and histidine residues, which increased with irradiation time. Hypericin did not damage the lens protein in the dark. Damage to alpha-crystallin could undermine the integrity of the lens directly by protein denaturation and indirectly by disturbing chaperone function. Therefore, in the presence of light, hypericin can induce changes in lens protein that could lead to the formation of cataracts. The authors conclude that appropriate precautions should be taken to protect the eye from intense sunlight while on this antidepressant medication (Schey *et al.* 2000).

Wahlman *et al.* (2003) found that the total accumulated protein leakage was positively correlated (r = 0.9) with variability in focal length. Lenses treated with hypericin and irradiated with UVB had an increase in focal length variability as compared with the lenses that were only UVB-irradiated. Lenses without UVB irradiation had much lower focal length variability than irradiated lenses. For non-hypericin-treated lenses, UVB-irradiated lenses had a larger variability (4.58 mm) than the unirradiated lenses (1.78 mm). The lenses incubated in elevated glucose concentrations had a focal length variability (3.23 mm) equivalent to that of the unirradiated hypericin-treated lenses (3.54 mm). The authors conclude that photooxidative damage by hypericin results in changes in the optical properties of the lens, protein leakage and finally cataract formation. In contrast to this, high concentrations of glucose induced protein leakage but not changes in optical properties or the opacity associated with a cataract. This work provides further evidence that people should protect their eyes from intense sunlight when taking St. John's Wort.

To determine if hypericin might be phototoxic to the human retina, Wielgus *et al.* (2006) exposed human retinal epithelial cells to 10(-7) to 10(-5) M hypericin. Fluorescence emission detected from the cells ($lambda_{exc}$ = 488 nm; $lambda_{em}$ = 505 nm) confirmed hypericin uptake by human RPE. Neither hypericin exposure alone nor visible light exposure alone reduced cell viability. However when irradiated with 0.7 J/cm^2 of visible light (lambda > 400 nm) there was loss of cell viability as measured by MTS and LDH assays. The presence of hypericin in irradiated hRPE cells significantly changed the redox equilibrium of glutathione and a decrease in the activity of glutathione reductase. Increased lipid peroxidation as measured by the TBARS assay correlated to hypericin concentration in hRPE cells and visible light radiation. Thus, ingested *Hypericum* extract is potentially phototoxic to the retina and could contribute to retinal or early macular degeneration.

II.2.3.1.6 Reproductive Toxicity

Ondrizek *et al.* (1999) incubated zona-free hamster oocytes for 1 hour in *H. perforatum*, or control medium before sperm-oocyte interaction. The DNA of herb-treated sperm was analyzed with denaturing gradient gel electrophoresis. Pre-treatment of oocytes with 0.6 mg/ml of St. John's wort resulted in zero penetration. A lower concentration (0.06 mg/ml) had no effect. Exposure of sperm to St. John's wort resulted in DNA denaturation. Sperm exposed to 0.6 mg/ml of St. John's wort showed mutation of the BRCA1 exon 11 gene. The data suggested in the view of the authors that St. John's wort at high concentrations damage reproductive cells. St. John's wort was mutagenic to sperm cells. Since the concentrations used were several orders of magnitude higher than considered as therapeutically relevant these effects should be considered with caution (Greeson *et al.* 2001).

Gonzalez *et al.* (1999) studied the impact of antenatal *Hypericum* exposure on cognition in mice. *Hypericum* (182 mg/kg/day) was consumed for 2 weeks before mating and throughout gestation. This dose has antidepressant efficacy in mice. Prenatal exposure to a therapeutic dose of *Hypericum* did not have a major impact on selected cognitive tasks in mice offspring.

Assessor's comment: No details were published about the nature of the Hypericum preparation.

Cada *et al.* (2001) investigated the influence of *Hypericum* extract on gestation and offspring of rats.
35 rats were exposed to diets containing 0, 180, 900, 1800 or 4500 ppm *Hypericum* extract (0.3% hypericin) (= 1-25 times the recommended human dose). Duration: gestational day 3 – offspring weaning at postnatal day 21.
Post-weaning behavioural assessment. There were no effects on maternal weight gain and on the duration of gestation. Offspring body weights were similar to controls from post natal day 2 until day 56 after which, some treated groups weighed significantly less than the controls. There were no signs of *Hypericum*-related behavioural alterations. Whole and regional brain weights of offspring at adulthood did not indicated any significant effects of *Hypericum*.

Chan *et al.* (2001) studied the influence of hypericin on rat embryos. Embryos from Sprague-Dawley rats were explanted at gestational day 9.5 and were cultured *in vitro* for 48 hours. To the medium 0 – 142 ng/ml hypericin was added to the medium. At gestational day 11.5 the embryos were examined. High concentrations of hypericin (71 and 142 ng/ml) exhibited significant morphological changes in the embryos.
After ingestion of 1800 mg *Hypericum* extract the mean peak plasma hypericin concentration was 29.5 ng/ml with a range of 0-77.9 ng/ml (Schempp 1999). Therefore the concentrations used in the study are clinically achievable in human subjects. Hypericin is potentially teratogenic in rats in concentrations which are achievable during clinical use.

Assessor's comment: In the setting of the study hypericin comes into direct contact with the embryos, while in situ embryos are protected by the placental barrier.

Rayburn *et al.* (2000) studied the effect of antenatal exposure to *Hypericum* on neurobehaviour of developing mice. The extract was standardised to 0.3% hypericin. 0.75 mg extract was mixed with each gram of feed (= 180 mg/kg/day). In a randomized and placebo-controlled behavioural testing 45 mice received *Hypericum* extract equivalent to the dosage for humans over 2 weeks before conception and throughout gestation (placebo group: 42 mice). The antenatal exposure showed no long-term deficits on selected behavioural tasks by developing mice offspring.
In a following study with similar design (Rayburn *et al.* 2001) no effect on long term growth and physical maturation of exposed mouse offspring was detectable. With the same herbal preparation Rayburn *et al.* (2001a) found that prenatal exposure to a therapeutic dose for *Hypericum* did not have a major impact on certain cognitive tasks in mice offspring.

The purpose of a study of Gregoretti *et al.* (2004) was to investigate the effects of a treatment with *Hypericum* administered prenatally and during breastfeeding (from 2 weeks before mating to 21 days after delivery) in Wistar rats. Two doses of the extract were chosen, 100 mg/kg per day, which, based on surface area, is comparable to the dose administered to humans, and 1000 mg/kg per day. A microscopic analysis of livers, kidneys, hearts, lungs, brains, and small bowels was performed. A severe damage was observed in the livers and kidneys of animals euthanized postnatally on days 0 and 21. The lesions were more severe with the higher dose and in animals that were breastfed for 21 days; however, an important renal and hepatic damage was evident also with the dose of 100 mg/kg per day. In addition, similar serious hepatic and renal lesions were evident also in animals that were exposed to *Hypericum* only during breastfeeding. In particular, a focal hepatic damage, with vacuolization, lobular fibrosis, and disorganization of hepatic arrays was evident; in the kidney, a reduction in glomerular size, disappearance of Bowman's space, and hyaline tubular degeneration were found. All important in-life data regarding dams and offspring did not show significant differences between the treatment groups. The results obtained in this study indicate that further, appropriate histological studies should be performed in other animal species to better evaluate the safety of *Hypericum* extracts taken during pregnancy and breastfeeding.

Borges *et al.* (2005) treated inseminated rats orally with a methanolic extract of *H. perforatum*. A dosage of 36 mg/kg was given on days 9-15 of pregnancy (= period of organogensis). No clinical

signs of maternal toxicity were found. In the administered dose *Hypericum* extract did not interfere with the progress of gestation during organogenesis in rats.

II.2.3.2 Assessor's overall conclusions on toxicology

The few data available on acute and subchronic toxicity do not reveal signs of a risk to the patient. The weak positive outcome of tests on mutagenicity of ethanolic extracts can be explained with the presence of quercetin in the extracts. Numerous publications deal with the potential phototoxicity of hypericin and *Hypericum* extracts. Extracts exert less phototoxicity than pure hypericin. Considering the outcome of clinical tests on phototoxicity herbal preparations of *H. perforatum* can be considered as safe when administered in the proposed dosage. The data on reproductive toxicity are contradictory. Tests on reproductive toxicity demonstrated no differences between *Hypericum* extract (108 mg/kg) and placebo in mice. However, isolated hypericin seems to have teratogenic properties. For safety reasons the oral use of *Hypericum* during pregnancy and lactation should not be recommended.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

An EEG study with the extract Ze 117 (Böttcher *et al.* 2000) showed marked increase in the amplitude of delta and theta waves indicating typical antidepressant profile.

In a placebo controlled design the neurophysiological effects of *Hypericum* extract LI 160 were compared with respect to the subjective state as well as to the performance (Johnson *et al.* 1992). The authors suggest that *Hypericum* shows central effects (cognitive activation) similar to known antidepressants.

II.3.1.1.2 Assessor's overall conclusions on Pharmacodynamics

There is limited data published which would confirm the findings of *in vivo* pharmacological testing in humans.

II.3.1.2 Pharmacokinetics

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

Biber *et al.* (1998) investigated the pharmacokinetics of hyperforin after oral administration of 300, 600 and 1200 mg of two different ethanolic extracts (5% and 0.5% hyperforin). Maximum plasma levels of hyperforin were reached after 2.8 to 3.6 hours. The 5% extract yielded a total $AUC_{0-\infty}$ of 1336, 2215 and 3378 h x ng/ml. The hyperforin pharmacokinetics were linear up to 600 mg of the extract, higher dosages resulted in a lower concentration than would be expected after linear extrapolation. The plasma concentrations of hyperforin were considerably lower after the administration of the other extract. In a repeated dose study no accumulation of hyperforin could be detected, the steady state plasma concentration after 3 x 300 mg/day of the extract was approximately 100 ng/ml.

Schempp *et al.* (1999) describe the HPLC detection of hypericin and semiquantitative detection of pseudohypericin in human serum and skin blister fluid after an oral single dose (1 x 6 tablets) or after steady-state (3 x 1 tablet/day for 7 days) administration of the *Hypericum* extract LI 160 in healthy volunteers (n = 12). Serum levels of hypericin and pseudohypericin were always significantly higher than skin levels ($p </= 0.01$). After oral single-dose administration of *Hypericum* extract the mean

serum level of total hypericin (hypericin + pseudohypericin) was 43 ng/ml and the mean skin blister fluid level was 5.3 ng/ml. After steady-state administration the mean serum level of total hypericin was 12.5 ng/ml and the mean skin blister fluid level was 2.8 ng/ml. These skin levels are far below hypericin skin levels that are estimated to be phototoxic (>100 ng/ml).

Schulz *et al.* (2005b) investigated pharmacokinetic parameters of the *Hypericum* extract STW3 (612 mg extract per dose) in 18 volunteers. Data were collected after single dose or multiple doses over 14 days.
Single dose administration:
Hypericin: Cmax 3.14 ng/ml, elimination half-life 23.76 h, MRT 34.74 h
Pseudohypericin: Cmax 8.5 ng/ml, elimination half-life 25.39 h, MRT 28.17 h
Hyperforin: Cmax 83.5 ng/ml, elimination half-life 19.64 h, MRT 21.77 h
Quercetin: Cmax1 47.7 ng/ml, Cmax2 43.8 ng/ml, elimination half-life 4.16 h, MRT 7.44 h
Isorhamnetin: Cmax1 7.6 ng/ml, Cmax2 9.0 ng/ml, elimination half-life 4.45 h, MRT 8.86 h
Steady state: Similar results.

The same study design was applied for the *Hypericum* extract STW 3-VI (900 mg extract per dose, Schulz *et al.* 2005a).
Single dose administration:
Hypericin: Cmax 3.8 ng/ml, elimination half-life 18.71 h, MRT 28.67 h
Pseudohypericin: Cmax 10.2 ng/ml, elimination half-life 17.19 h, MRT 20.21 h
Hyperforin: Cmax 122.0 ng/ml, elimination half-life 17.47 h, MRT 20.88 h
Quercetin: Cmax1 89.5 ng/ml, Cmax2 79.1 ng/ml, elimination half-life 2.60 h, MRT 4.68 h
Isorhamnetin: Cmax1 12.5 ng/ml, Cmax2 14.6 ng/ml, elimination half-life 5.61 h, MRT 10.29 h
Steady state: Similar results.

A study from Johne *et al.* (2004) evaluated the influence of cimetidine and carbamazepine on the pharmacokinetics of hypericin and pseudohypericin. In a placebo-controlled, double blind study, 33 healthy volunteers were randomized into three treatment groups that received *Hypericum* extract extract (LI 160) with different comedications (placebo, cimetidine, and carbamazepine) for 7 days after a run-in period of 11 days with *Hypericum* extract alone. Hypericin and pseudohypericin pharmacokinetics were measured on days 10 and 17. Between-group comparisons showed no statistically significant differences in AUC(0-24), C(max), and t(max) values for hypericin and pseudohypericin. Within-group comparisons, however, revealed a statistically significant increase in hypericin AUC(0-24) from a median of 119 (range 82-163 mg h/l) to 149 mg h/l (61-202 mg h/l) with cimetidine comedication and a decrease in pseudohypericin AUC(0-24) from a median of 51.0 (16.4-102.9 mg h/l) to 36.4 mg h/l (14.0-102.0 mg h/l) with carbamazepine comedication compared to the baseline pharmacokinetics in each group. Hypericin and pseudohypericin pharmacokinetics were only marginally influenced by comedication with the enzyme inhibitors and inducers cimetidine and carbamazepine.

With the extract Ze 117 maximum hypericin plasma concentration of 0.21 to 1.33 µg/L were achieved 6-12 hours after a single dose. The terminal half life was 15.1 to 63.1 hours after a single dose. Steady state hypericin plasma concentrations following multiple bid doses of 250 mg extract were 2 to 3 µg/L. Steady state was reached before 14 days (Böttcher *et al.* 2000).

Wang *et al.* (2001) studied the influence of *Hypericum* extract (3 x 300 mg per day, 900 µg hypericin per capsule) on different types of cytochrome P450 enzymes. 12 healthy volunteers received tolbutamide (CYP2C9), caffeine (CYP1A2), dextrometorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A4), and intravenous midazolam (hepatic CYP3A4) before, with short-term *Hypericum* dosing and after 2 weeks of intake. No change in CYP2C9, CYP1A2, CYP2D6 were detected. In contrast a significant and selective induction of CYP3A4 activity in the intestinal wall was observed.

Whitten *et al.* (2006) concluded that in three studies in which the daily exposure to hyperforin was less than 4 mg, no significant effect on CYP3A4 could be detected. Brattström (2005, unpublished data, cited in Whitten *et al.* 2006) tested the extract ZE 117 in 16 females in a dose of 500 mg daily for

14 days. The women started 3 months prior to the study taking 20 µg ethinyl estradiol and 150 µg desogestrel daily. Pharmacokinetic testing on days 7 and 22 after the treatment with ZE 117 revealed no significant differences in ethinyl estradiol or 3-ketodesgestrel (active metabolite). It is not known whether a longer treatment with ZE 117 would induce CYP3A4.

Arold *et al.* (2005) report from a pharmacokinetic interaction study with 240 mg *Hypericum* extract daily containing 3.5 mg hyperforin. After treatment for 11 days no significant changes in the primary kinetic parameters of alprazolam, caffeine, paraxanthine, tolbutamide, 4-hydroxytolbutamide and digoxin were observed.

CYP1A2 appears to be induced by *Hypericum* extract only in females, the activities of CYP2D6, N-acetyltransferase 2, and xanthinoxidase were not affected by *Hypericum* extract (Wenk *et al.* 2004).

Dresser *et al.* (2003) studied the effects of *Hypericum* extract on CYP3A and multidrug resistance protein (MDR1 = p-glycoprotein). 21 young healthy subjects got 12 days pretreatment with *Hypericum* (LI160); midazolam was administered orally and intravenously in order to assess CYP3A activity, fexofenadine after oral dose for a measure of MDR1 (= P-glycoprotein) function; the oral plasma concentration profile of cyclosporine was considered to reflect both CYP3A and MDR1 activities..
The disposition of all drugs was altered. Although a common molecular mechanism may be involved, the quantitative aspects of induction are complex and depend on the particular drug and the relative contributions of CYP3A and MDR1 in its disposition.

The elevated activity of CYP3A returns to basal level approximately 1 week after termination of *Hypericum* administration (Imai *et al.* 2008).

L'homme *et al.* (2006) conducted a phase I pharmacokinetic study. A single 200 mg dose of nevirapine was administered; in phase 2 of the study one group (4 participants) received *Hypericum* tea bid for 14 days.
Hypericum tea had no influence on the half life of nevirapine, which is explained by the low content of hyperforin (reference to Mueller SC *et al.* 2004 and Zhou *et al.* 2004).

The role of hyperforin for interactions with cyclosporine was studied by Mai *et al.* (2004). In a crossover study 10 renal transplant patients received cyclosporine and *Hypericum* extract (900 mg/day) either with a high amount of hyperforin (LI 160) or with a low amount (LI 160 after removal of hyperforin by extraction with supercritical carbon dioxide) for 2 weeks.
LI 160: One capsule contained 7.0 mg hyperforin (2.3%), 0.45 mg total hypericin, 16.16 mg total flavonoids (5.4%)
Low-hyperforin extract: One capsule contained 0.1 mg hyperforin (0.03%), 0.45 mg total hypericin, 15.6 mg total flavonoids (5.2%)
The low hyperforin extract did not alter significantly the pharmacokinetics of cyclosporine, while the high hyperforin extract reduced the plasma levels of cyclosporine significantly.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Pharmacokinetic data on the most compounds which are considered to contribute to the activity are available. The long elimination half-life has to be considered after overdose. The possible role of metabolites is not addressed yet.

II.3.2 Clinical Efficacy[3]

II.3.2.1 Dose response studies

II.3.2.2 Clinical studies (case studies and clinical trials)

II.3.2.2.1 Studies on the treatment of depression

[3] In case of traditional use the long-standing use and experience should be assessed.

Extract LI 160

Extract	LI 160
Extraction solvent	80% methanol
DER	3-6:1, initially 4-7:1
Total hypericins	0,12-0,28%
Hyperforin	Approximately 4.5% (Mueller *et al.* 2006)
Flavonoids	Approximately 8.3% (Mueller *et al.* 2006)

From several notes in publications it can be assumed that the content of hyperforin is in the range from 3 to 6%.

Study	**Bjerkenstedt *et al.* 2005**	
Indication	Mild to moderate major depression (DSM-IV: 296.31, 296.32); minimum of a total score of 21 on the 21-item Hamilton Depression scale	
Duration of use	4 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	20 mg fluoxetine
	multicentre	n=15
	number of patients	163
Outcome	HAMD reduction: LI 160: from 24.9±4.5 to 15.0±8.4 (-9.9±8.1) Fluoxetine: from 23.8±3.7 to 14.9±8.4 (-8.9±8.0) Placebo: from 25.2±4.6 to 15.5±6.7 (-9.7±7.0) Conclusion: LI 160 and fluoxetine are not more effective in short-term treatment in mild to moderate depression than placebo. *Hypericum* is better tolerated than fluoxetine	
Comment	Short time of treatment; high number of drop-outs in all groups (*Hypericum* start n=59, end n=38; fluoxetine start n=57, end n=37; placebo start n=58, end n=40)	

Study	**Fava *et al.* 2005**	
Indication	Major depressive disorder (HAMD-17 ≥ 16)	
Duration of use	12 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	20 mg/d fluoxetine
	multicentre	n=2
	number of patients	135
Outcome	HAMD reduction (ITT-analysis): LI 160: -38%, from 19.6± 3.5 to 10.2 ± 6.6 Fluoxetine: -30%, from 19.6 ± 3.1 to 13.3 ± 7.3 Placebo: -21%, from 19.9 ± 2.9 to 12.6 ± 6.4	

	Conclusion: LI 160 is significantly more effective than fluoxetine and superior to placebo. It is well tolerated and safe.
Comment	Sample smaller than originally planned; the lack of efficacy of fluoxetine is explained by the fixed-dose approach.

Study	**Brenner *et al.* 2000**	
Indication	Mild to moderate depression (HAMD: ≥ 17, according to DSM IV)	
Duration of use	7 weeks	
Daily dosage	600 mg (1st week) 900 mg (6 weeks)	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no?
	reference-controlled	50 mg sertraline (1st week) 75 mg sertraline (6 weeks)
	multicentre	no
	number of patients	30
Outcome	HAMD reduction: LI 160: -40% ± 30 %; from 21.3 ± 3.2 to 12.7 ± 6.7) Sertraline: -42% ± 24 %, from 21.7 ± 2.7 to 12.5 ± 5.6) Conclusion: LI 160 is as effective as sertraline in the treatment of mild to moderate depression.	
Comment	Small number of patients, relatively high drop out rate. In the chapter 'Study medication' placebos are mentioned. However, there is no placebo group in the table of results.	

Study	**HDTSG 2002**	
Indication	Moderately severe major depressive disorder (according to DSM-IV; HAM-D ≥ 20; GAF ≤ 60)	
Duration of use	8 weeks	
Daily dosage	900-1800 mg (3 x 300- 3 x 600 mg)	
Single dosage	300 – 600 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	50-150 mg sertraline
	multicentre	n=12
	number of patients	340
Outcome	HAMD reduction/response rate: Placebo: -9.20/-31;9% LI 160: -8,68/-23;9% Sertraline: -10.53/-24;8% Conclusion: No efficacy of LI 160 and of sertraline in the treatment of moderately severe major depression. Possible reason: Low assay sensitivity.	
Comment	No efficacy despite of increase of dosage during study	

Study	**Montgomery *et al.* 2000**
Indication	Mild to moderate depression (DSM-IV)
Duration of use	12 weeks

Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=18
	number of patients	248
Outcome	Conclusion: There is no statistically significant difference between placebo and LI 160. (HAMD-score after 6 weeks). Negative Outcome	

Study	**Vorbach *et al.* 1997**	
Indication	Severe episode of a major depression according to ICD-10 F 33.2, recurrent, without psychotic symptoms	
Duration of use	6 weeks	
Daily dosage	1800 mg	
Single dosage	600 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	
	reference-controlled	150 mg/d imipramine
	multicentre	n=20
	number of patients	209
Outcome	HAMD (17 items) reduction: LI 160:from 25.3±4.7 to 14.4±6.1 Imipramine: from 26.1±4.8 to 13.4±5.9 Conclusion: Efficacy not statistically equivalent, equivalence only in subgroups with more than 33% and 50% reduction of the HAMD total score. Superiority for LI 160 in adverse events.	

Study	**Wheatley 1997**	
Indication	Mild to moderate major depression (HAMD-17 score: 17-24; according to DSM-IV)	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	75 mg/d amitriptyline
	multicentre	n=19
	number of patients	165
Outcome	HAMD reduction: LI 160: from 20 to 10 Amitriptyline: from 21 to 6 Conclusion: No statistically significant difference between LI 160 and amitriptyline; *Hypericum* is better tolerated.	

Study	**Harrer *et al.* 1994**	
Indication	Moderately severe depressive episodes, according to ICD-10, F 32.1 (HAMD 17-items >- 16)	
Duration of use	4 weeks	
Daily dosage	900 mg/d	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	Maprotiline (3 x 25 mg)
	multicentre	n=6
	number of patients	102
Outcome	HAMD reduction: LI 160: 20.5 -> 12.2, no statistically significant difference compared to maprotiline. Maprotiline: 21.5 -> 10.5 Responder rate: 61% in *Hypericum*, 67% in maprotiline Onset of effects up to the second week of treatment. After 2 weeks of treatment more pronounced effect with maprotiline, after 4 weeks both groups similar.	

Study	**Shelton *et al.* 2001**	
Indication	Major depression (HAMD: ≥ 20 for more than 2 years, according to DSM-IV: major depression disorder, single episode or recurrent, without psychotic features)	
Duration of use	8 weeks	
Daily dosage	900 mg/d for 4 weeks, in case of not adequate response increase to 1200 mg/d	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=11
	number of patients	200
Outcome	Response rate in the ITT-analysis: LI 160: 26.5% (for statistical significance 36.1% is needed) Placebo: 18.6% In the *Hypericum* group there was a significantly greater proportion of remissions. Conclusion: LI160 is not effective in the treatment of major depression; good compliance: only adverse effect: headache.	
Comment	High number of patients with chronic depression. Sponsoring by Pfizer	

Wurglics *et al.* (2002) stated that although no significant difference between placebo and verum was detected, significant differences in the number of remissions and number of responders were observed. Patients included were severely depressed (duration of depression more than 10 years); the acute phase had a mean duration of 2 years. This is a clear difference to the clinical studies preformed in Europe. The authors point out the extremely low responder rate under placebo in this study.

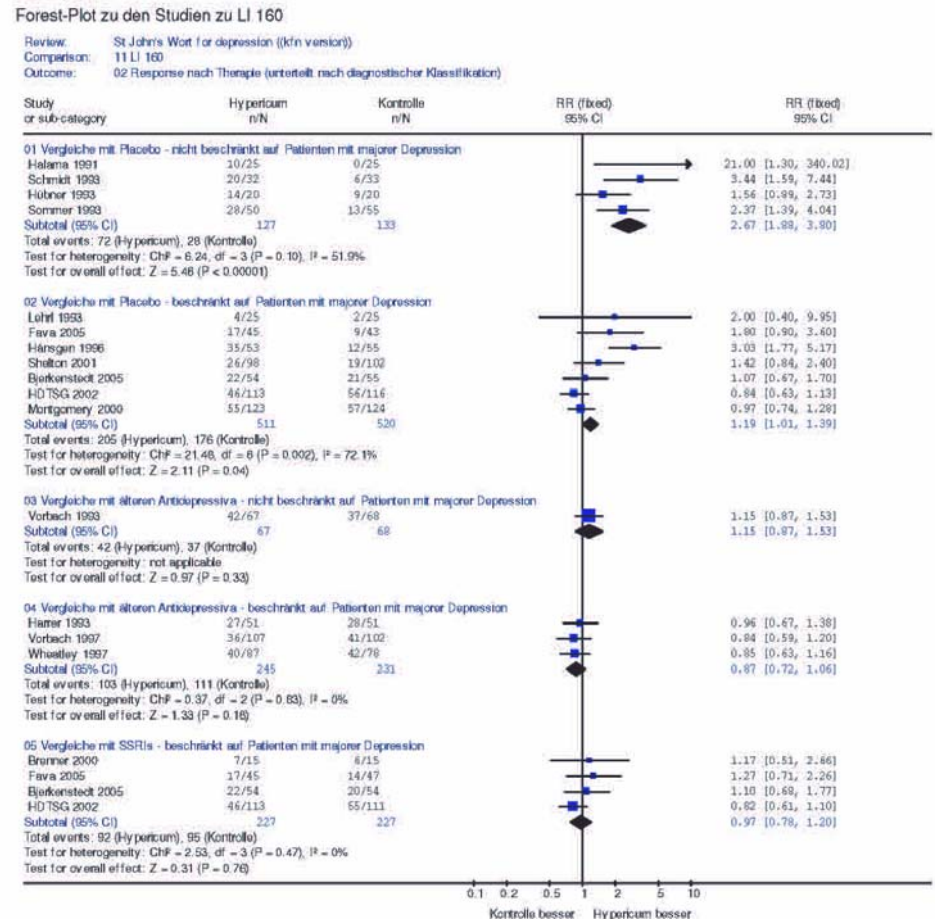
Study	**Hänsgen *et al.*. 1996**	
Indication	Mild to moderate major depression, according to DSM-III-R (HAMD >- 16)	
Duration of use	4 weeks (+2 weeks)	
Daily dosage	900 mg/d	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=17
	number of patients	102
Outcome	HAMD reduction: LI 160: 21.0 -> 8.9, statistically significant compared to placebo. Placebo: 20.4 -> 14.4 Responder rate: 70% in *Hypericum*, 24% in placebo Further 2 weeks of verum-treatment in both groups: Similar improvement in the former placebo-group like in the first 2 weeks of treatment in the verum group.	

Study	**Hänsgen *et al.*. 1994**	
Indication	Mild to moderate major depression, according to DSM-III-R (HAMD >- 16)	
Duration of use	4 weeks (+2 weeks)	
Daily dosage	900 mg/d	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=11
	number of patients	67
Outcome	HAMD reduction: LI 160: 21.8 -> 9.2, statistically significant compared to placebo. Placebo: 20.4 -> 14.7 Responder rate: 81% in *Hypericum*, 26% in placebo Further 2 weeks of verum-treatment in both groups: Similar improvement in the former placebo-group like in the first 2 weeks of treatment in the verum group.	

Study	**Sommer *et al.* 1994**	
Indication	Depressive symptoms according ICD-09 300.4 (neurotic depression) and 309.0 (brief depressive reaction).	
Duration of use	4 weeks	
Daily dosage	900 mg/d	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=3

	number of patients	105
Outcome	Only graphical presentation of data; improvement under *Hypericum* after 4 weeks significant at a 1% level compared to placebo. Responder rate: 67% in *Hypericum*, 28% in placebo	

Meta-analysis of clinical studies with LI 160 (Linde 2007)



Conclusion:
Reference controlled studies: All studies included patients with major depression; similar or insignificantly less efficacy compared to standard antidepressants; in some studies no difference between *Hypericum*, reference medication and placebo. Only one study (Vorbach *et al.* 1997) was designed for proof of equivalence.
Placebo controlled studies: Tendency that in older studies (published before 2000) better outcome for *Hypericum*; modern studies also with negative outcome.
Studies including patients with more severe depressive episodes (daily dosage up to 1800 mg extract) do not show sufficient efficacy.

Extract WS 5570:

Extract	WS 5570
Extraction solvent	80% methanol
DER	3-7:1
Total hypericins	0.12-0.28%
Hyperforin	3-6%
Flavonoids	≥ 6.0%

The extraction solvent and the declared amount of Hypericine of this extract are identical with that of LI 160.

Study	**Anghelescu *et al.* 2006**	
Indication	Moderate to severe depression according to DSM-IV criteria: 296.22, 296.23, 296.32 and 296.33 (HAMD 17-item: ≥ 22)	
Duration of use	6 weeks of acute treatment	
Daily dosage	900 mg or 1800 mg; dose increase in week 2 in patients with HAMD improvement <20%	
Single dosage	300 mg or 600 mg	
Relapse	Patients with a HAM-D total score decrease of >=50% during the 6 weeks of acute treatment were asked to continue the treatment for another 16 weeks (n=133)	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	20/40 mg/d paroxetine; dose increase in week 2 in patients with HAMD improvement <20%
	multicentre	n=21
	number of patients	133
Outcome	HAMD reduction: WS 5570: from 25.3+/-2.5 to 4.3+/-6.2 Paroxetine: from 25.3+/-2.6 to 5.2+/-5.5 During maintenance treatment alone 61.6% of the *Hypericum* group and 54.6% of the paroxetine group showed additional reduction of HAMD score. Remission occurred in 81.6% of the patients in the *Hypericum* group and in 71.4% in the paroxetine group. 3 patients under *Hypericum* and 2 patients under paroxetine showed an increase in HAMD score of >5 during continuation treatment Conclusion: WS 5570 and paroxetine are similarly effective in preventing relapse in a continuation treatment after recovery from an episode of moderate to severe depression.	

Study	**Szegedi *et al.* 2005**	
Indication	Moderate to severe major depression (HAMD 17-item: ≥ 22; DSM-IV: 296.22, 296.23, 296.32, 296.33)	
Duration of use	6 weeks	
Daily dosage	900 mg-1800 mg; dose increase in week 2 in patients with HAMD improvement <20%	
Single dosage	300 mg-600 mg	
Relapse	Responders (decrease in total HAMD score ≥ 50%) were invited to participate in a four month double blind maintenance phase	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	20 mg-40 mg/d paroxetine; dose increase in week 2 in patients with HAMD improvement <20%
	multicentre	n=21
	number of patients	251
Outcome	HAMD recuction/% responder: WS 5570: -14.4 / 71% Paroxetine: -11.4 / 60% Conclusion: WS 5570 is as effective as paroxetin in the treatment of moderate to severe major depression	
Comment	The results of the maintenance phase will be published elsewhere.	

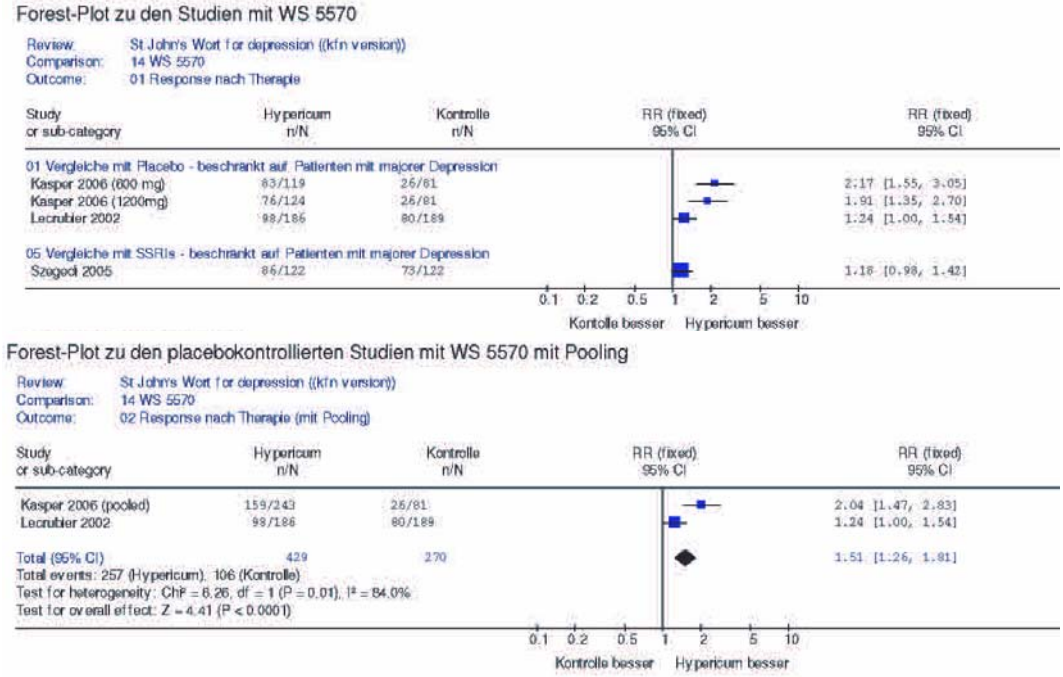
Study	**Lecrubier *et al.* 2002**	
Indication	Mild to moderate major depression (single or recurrent episode, DSM-IV code: 296.21, 296.22, 296.32, HAMD 17-item: 18-25)	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=26
	number of patients	375
Outcome	HAMD reduction/Responders WS 5570: -9.9/52.7% Placebo: -8.1/42.3% (The difference is significant) Conclusion: WS 5570 is safe and more effective than placebo in the treatment of mild to moderate major depression.	

Study	**Kasper *et al.*. 2006**	
Indication	Mild or moderate major depressive episode (single or recurrent episode, DSM-IV criteria: 296.21, 296.31, 296.21, 296.22, 296.31, 296.32; HAMD 17-item: ≥ 18, "depressive mood" ≥ 2)	
Duration of use	6 weeks	
Daily dosage	600-1200 mg	
Single dosage	600 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=16
	number of patients	332
Outcome	More patients in the WS 5570 1200 mg group met the criterion of remission (HAMD: ≤ 7 at treatment end) HAMD reduction: WS 5570 600 mg: -11.6 ± 6,4 WS 5570 1200 mg: -10.8 ± 7.3 Placebo: -6.0 ± 8.1 Conclusion: WS 5570 is safe and more effective than placebo in treatment of mild to moderate depression.	
Continuation study	Kasper *et al.* 2007	
	Those participants with a HAMD total score decrease ≥ 50% during acute treatment were eligible for 4 months of double blind continuation treatment. 69 patients 600 mg/day, 68 patients 1200 mg/day, 24 patients placebo. Additional slight decrease of HAMD in both active groups (0.8 and 0.4 points), deterioration in the placebo group (2.1 points).	

Study	**Kasper *et al.* 2008**
Indication	Recurrent episode of moderate major depression; HAMD 17-item: ≥ 20, ≥ 3 previous episodes in 5 years (ICD-10 F33.0. F33.1, DSM-IV 296.3).

Duration of use	6 weeks single blind acute treatment, then 26 weeks double blind continuation treatment, then 52 weeks double blind maintenance treatment	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	+	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	yes
	number of patients	426
Outcome	Relapse rates: *Hypericum* 18.1%; placebo 25.7% Average time to relapse: *Hypericum* 177 days; placebo 163 days Conclusion: WS 5570 showed a beneficial effect in preventing relapse after recovery from acute depression. Tolerability in continuation and long-term maintenance treatment was on the placebo level.	

Meta-analysis of clinical studies with WS 5570 (Linde 2007)



Conclusion: All studies are well designed. All studies report superiority compared to placebo or non-inferiority compared to standard medication.

Comparison with LI 160:
In contrast to the recent studies published for LI 160 all modern studies for WS 5570 demonstrated a positive outcome for *Hypericum*. Since the extracts LI 160 and WS 5570 are very similar in their key parameters, it seems to be justified to combine the results. It can be concluded that the efficacy of this type of extract in the treatment of mild to moderate severe depression is well documented.

Extract Ze 117:

Extract	Ze 117
Extraction solvent	There are differing informations on the extraction solvent: 50% ethanol (m/m) or ethanol 49% m/m : 2-propanol (97.3:2.7)
DER	4-7:1
Total hypericins	0.2%
Hyperforin	nearly free of hyperforin (e.g. 0.07% Mueller SC 2004)

Information on the refinement of the extract in order to reduce the content of hyperforin is not available.

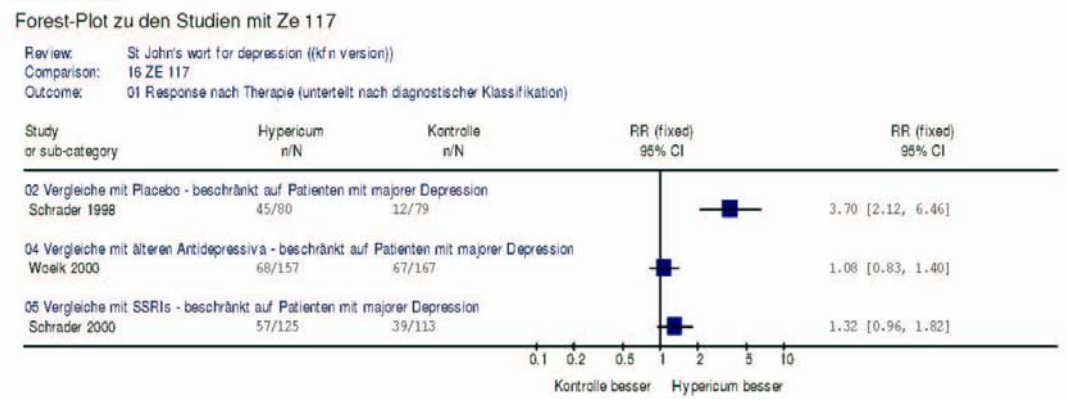
Study	**Schrader 2000 (Friede *et al.* 2001)**	
Indication	Mild to moderate depressive episode / recurrent depressive episode (ICD-10; F 32-0 and F 32-1, HAMD scale (21-item) 16-24)	
Duration of use	6 weeks	
Daily dosage	500 mg	
Single dosage	250 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	20 mg fluoxetine
	multicentre	n=7
	number of patients	240
Outcome	HAMD reduction: Ze 117: from 19.65 to 11.54/-7.25 Fluoxetine: from 19.50 to 12.20/-8.11 Conclusion: *Hypericum* and fluoxetine are equipotent. The safety of Ze 117 was superior to that of fluoxetine.	
Comment	Contact of patients with investigators only at the beginning of the study and after 6 weeks in order to minimize the placebo effect. Nearly identical data in the publication compared to Friede *et al.* 2001. However, no coincidence of the authors and the sponsor.	

Study	**Woelk 2000**	
Indication	Mild to moderate depression (ICD-10 codes F32.0, F33.0, F32.1, F 33.1; HAMD score (17-item) > 17)	
Duration of use	6 weeks	
Daily dosage	500 mg	
Single dosage	250 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	150 mg/d imipramine
	multicentre	n=40
	number of patients	324
Outcome	HAMD reduction: Ze 117: from 22.4 to 12.0 Imipramine: from 22.1 to 12,75 Conclusion: Ze 117 and imipramine are therapeutically equivalent in the treatment of mild to moderate depression. In the treatment of	

	depression with anxiety *Hypericum* has more benefit. There are fewer adverse events in the Ze 117 group.
Comment	The dosage of imipramine is relatively high, which could be the reason for the high number of drop outs in the reference group.

Study	**Schrader *et al.* 1998**	
Indication	Mild to moderate depression (ICD-10; F 32-0 and F 32-1)	
Duration of use	6 weeks	
Daily dosage	500 mg (corresponding to 1 mg hypericin daily)	
Single dosage	250 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=16
	number of patients	162
Outcome	HAMD (21-item) reduction/% responder: Ze 117: from 20.13 to 10.53/56% Placebo: from 18.76 to 17.89/15% Conclusion: ZE 117 is significantly superior compared to placebo and safe in treatment of mild to moderate depression	
Comment	Contact of patients with investigators only at the beginning of the study and after 6 weeks in order to minimize the placebo effect.	

Meta-analysis of clinical studies with ZE 117 (Linde 2007)



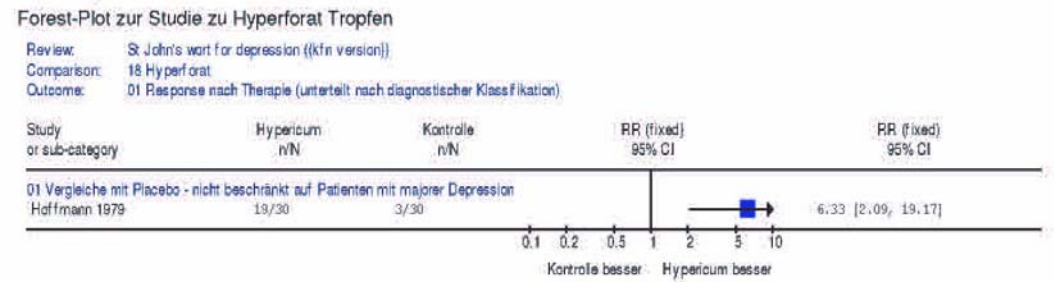
Conclusion: The superiorioty of the extract ZE 117 against placebo and the non-inferiority against imipramine and fluoxetine could be demonstrated. Compared with the results obtained with the extracts LI 160 and WS 5570 it can be concluded that hyperforin is not solely responsible for clinical efficacy. According to the manufacturer the extract is on the market in Germany at least since 1996. Therefore the minimum of 10 years of medicinal use is fulfilled.

Liquid extract

Extract	Hyperforat drops
Extraction solvent	50% ethanol
DER	0.5:1
Total hypericins	2 mg/ml
Hyperforin	not specified

Study	**Hoffmann *et al.* 1979**	
Indication	Mild to severe forms of depression	
Duration of use	6 weeks	
Daily dosage	90 drops (= 3.6 ml = 7.2 mg hypericin)	
Single dosage	30 drops	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	-
	multicentre	-
	number of patients	60
Outcome	Not standardised symptom score with 47 items; improvement under *Hypericum* after 6 weeks 61.4%, in the placebo group 16.8%. Responder: *Hypericum*: 80% Placebo: 33%	
Comment	Lack of statistical evaluation; inadequate study design	

Meta-analysis of clinical studies with Hyperforat drops (Linde 2007)



Conclusion: An old study (inadequate study design) shows superiority against placebo. No data are available on a comparison to synthetic antidepressants.

Extract STW 3

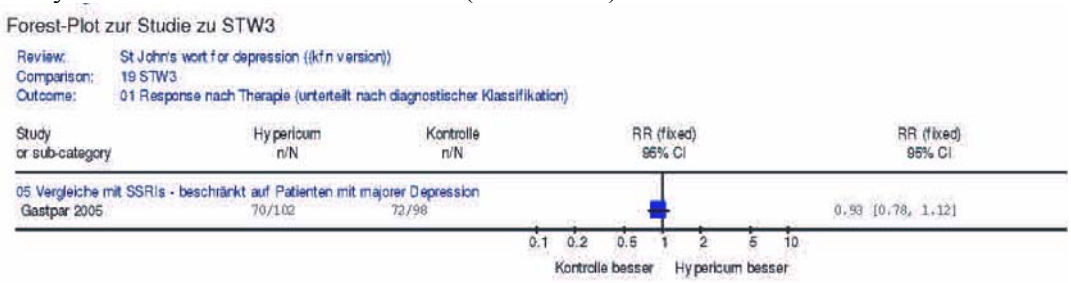
Extract	STW 3
Extraction solvent	50% ethanol
DER	5-8:1
Total hypericins	mean 0.2%
Hyperforin	mean 2%
Flavonoids	mean 9%

Study	**Gastpar *et al.* 2005**	
Indication	Moderate depressive disorder (according to ICD-10 criteria: F32.1 or F33.1; HAMD 17-items: 20-24)	
Duration of use	12 weeks	
Daily dosage	612 mg	
Single dosage	612 mg	
Relapse	after 12 weeks additional treatment for 12 weeks of n=161	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	50 mg sertraline
	multicentre	n=18
	number of patients	241
Outcome	HAMD reduction: (week 12/week 24)	

	STW 3: from 22.0 to 8.3/5.7 Sertraline: from 22.1 to 8.1/7.1 Conclusion: STW 3 is therapeutically equivalent to sertraline in moderate depression and it is well tolerated.
Comment	Single daily dose

Observational study: Demmling *et al.* (2004)
Post marketing observational study in 793 family care units, 4188 patients with psychovegetative disorders, depressive disturbances, anxiety, nervous restlessness were treated with Laif 900 (STW3-VI, DER 3-6:1) once daily for 12 weeks. Diagnosis according ICD-10, measure for assessment was Hamilton Depression scale.
ICD-10 F 32.0: 34.8%
F 33.0: 16.1%
F 32.1: 32.7%
F 33.1: 10.9%
F 34.1: 5.9%
HAMD decreased from an average of 15.8 to 9.5 after 4 weeks and finally to 4.6. The percentage of responders was about 78%, even in the subgroup of patients with an HAMD baseline of ≥ 17 the percentage of responders was about 77%. 0.6% of the patients reported adverse events, severe adverse events were unrelated to the treatment. No drug interactions were reported (7.2% of the patients used oral contraceptives; 0.4% anticoagulants from the coumarin-type; 1.6% digoxin; 0.6% theophylline).

Meta-analysis of clinical studies with STW3 (Linde 2007)



Conclusion: An adequate study which demonstrates non-inferiority compared to sertraline (50 mg).

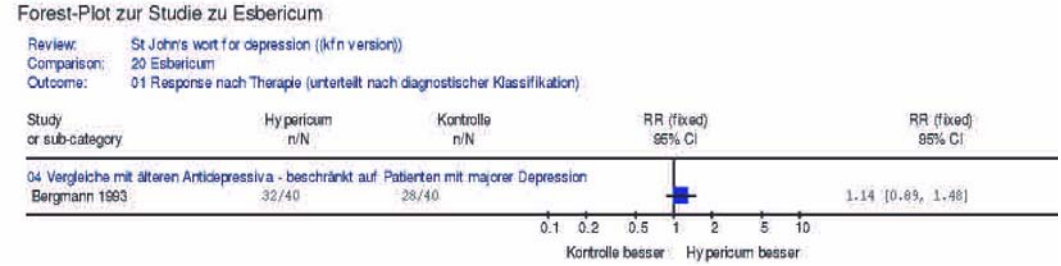
Esbericum capsules:
Daily dosage: 213-252 mg extract;

Extract	Esbericum
Extraction solvent	60% ethanol
DER	2-5.5:1
Total hypericins	0.1%
Hyperforin	not specified
Flavonoids	not specified

Study	**Bergmann *et al.* 1993**	
Indication	Mild to moderate depression (ICD-10 F32.0, F32.1, F33.0, F33.1)	
Duration of use	6 weeks	
Daily dosage	213-252 mg extract preparation (including excipients, = 3 x 60 mg native extract corresponding to 0.75 mg hypericin)	
Single dosage		
Relapse	-	
Study design	*randomized*	yes
	placebo-controlled	no
	reference-controlled	30 mg amitriptyline/day
	multicentre	n=1
	number of patients	80

Outcome	HAMD reduction/% responder: Esbericum: from 15.82 to 6.43/84.2% Amitriptyline: from 15.26 to 6.65/73.7% From the fact that the low dosages of amitriptyline and of *Hypericum* were effective it can be assumed that only patients with mild symptoms were included. This is also reflected by the relatively low starting values of the HAMD scale.
Comment	Low dosage of amitriptyline

Meta-analysis of clinical studies with Esbericum capsules (Linde 2007)



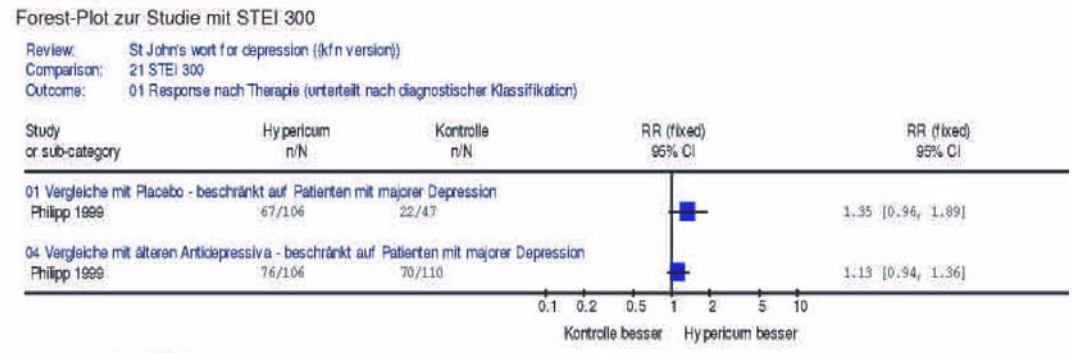
Conclusion: In the context with the results of the other extracts this study contributes to the overall evidence on the use of *Hypericum* extracts for the improvement of depressive symptoms.

Extract STEI 300:

Extract	STEI 300
Extraction solvent	60% ethanol m/m
DER	5-7:1
Total hypericins	0.2-0.3%
Hyperforin	2-3%
Flavonoids	not specified

Study	**Philipp *et al.* 1999**	
Indication	Moderate depression according to ICD-10 (codes F32. 1 and F33.1) (HAMA score > 18)	
Duration of use	8 weeks	
Daily dosage	1050 mg	
Single dosage	350 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	100 mg/d imipramine (titrated within 4 days from 50 mg)
	multicentre	n=18
	number of patients	263
Outcome	HAMD reduction/% responder: STEI 300: 22.7-> 7.3/76% Placebo: 22.7-> 10.6/63% Imipramine: 22.2-> 8.0/66.7% Conclusion: STEI 300 is as effective as imipramine and more effective than placebo in the treatment of moderate depression and it is safe.	
Comment	Study of high methodological quality	

Meta-analysis of clinical studies with STEI300 (Linde 2007)



Conclusion: Superiority against placebo and non-inferiority against imipramine (100 mg) could be demonstrated.

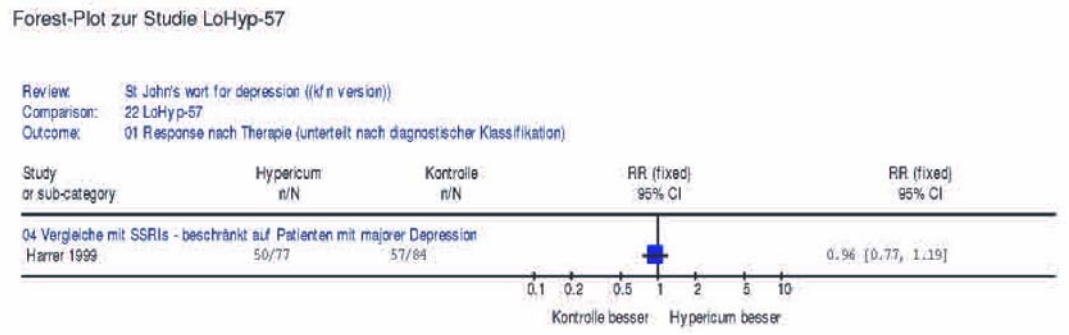
Extract LoHyp-57:

Extract	LoHyp-57
Extraction solvent	60% ethanol
DER	5-7:1
Total hypericins	0.2-0.3%
Hyperforin	2-3%
Flavonoids	not specified

Extract identical to STEI 300, but different dosage form and posology.

Study	**Harrer *et al.* 1999**	
Indication	Mild to moderate major depression according to ICD 10 (F32.0, F32.1)	
Duration of use	6 weeks	
Daily dosage	800 mg	
Single dosage	400 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	20 mg fluoxetine (= 22.4 mg fluoxetine HCl)
	multicentre	n=17
	number of patients	149
Outcome	HAMD (17-items) reduction: LoHyp 57: from 16.60 to 7.91 (mild: from 14.21 to 6.21; moderate: from 18.73 to 9.43) Fluoxetine: from 17.18 to 8.11 (mild: from 15.21 to 7.46; moderate: from 19.10 to 8.75) Responder rate: LoHyp 57: 71.4% (mild subgroup: 81.8%; moderate subgroup: 62.2%) Fluoxetine: 72.2% (mild subgroup: 76.9%; moderate subgroup: 67.5%) Conclusion: LoHyp 57 is equivalent to fluoxetine in the treatment of mild to moderate major depression particularly in elderly patients.	
Comment	No confidence intervals were shown in the publication, therefore the non-inferiority has formally not been demonstrated; the patients were 60-80 years of age.	

Meta-analysis of clinical studies with LoHyp-57 (Linde 2007)



Conclusion: 800 mg of LoHyp-57 is equivalent to 20 mg fluoxetine in the treatment of mild to moderate major depression.

Extract STW3-VI:

Extract	STW3-VI
Extraction solvent	80% ethanol
DER	3-6:1
Total hypericins	mean 0.2%
Hyperforin	mean 2.0%
Flavonoids	mean 9%

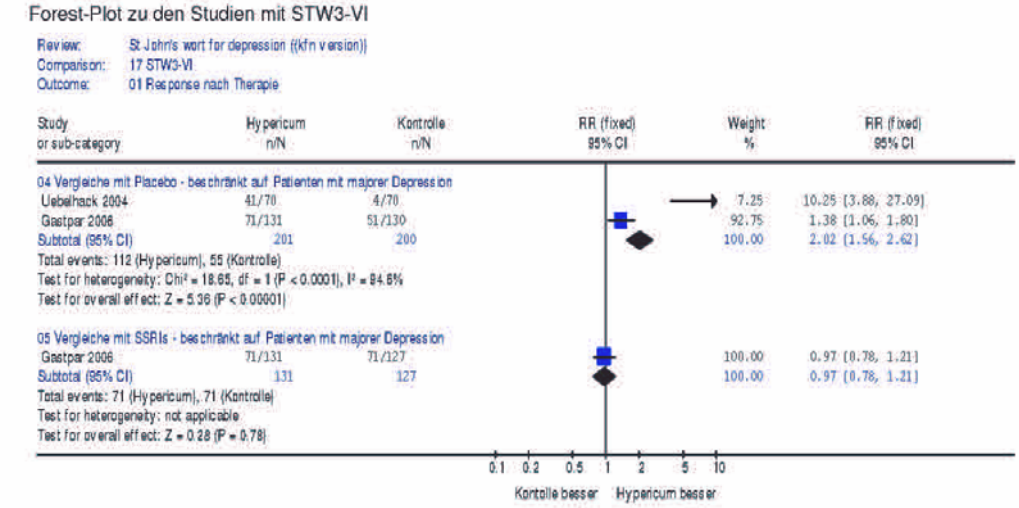
Study	**Gastpar *et al.* 2006**	
Indication	Moderate depression (HAMD 17-items score: 20-24, ICD-10. F32.1, F33.1, according to DSM-IV major depressive episode and recurrent major depression)	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	900 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	20 mg citalopram
	multicentre	n=21
	number of patients	388
Outcome	HAMD reduction/% responder: *Hypericum*: 21.9 -> 10.3/54.2% Citalopram: 21.8-> 10.3/55.9% Placebo: 22.0 -> 13.0/39.2% Conclusion: The *Hypericum* group was statistically non-inferior to citalopram and significantly superior to the placebo.	
Comment	Study of high methodological quality.	

In a retrospective study (Singer *et al.* 2008) 154 responders of the clinical study by Gastpar *et al.* (2006) in patients with moderate depression (HAMD score 20-24) which received STW 3-VI (Laif 900), citalopram or placebo for 6 weeks were observed for 5 years.
In 19.5% of the patients a relapse was observed with the highest ratio in the citalopram group (25.9%), followed by the placebo group (17.4%), the minimal relapse rate was in the *Hypericum* group (14.8%). The severity of the relapse was identical in all three groups.
Relapse + recurrence: *Hypericum* 44.4%, citalopram 48.1%, placebo 52.2%.

Duration until relapse, recurrence: *Hypericum* 1833 days, citalopram 1755, placebo 802 days.
The authors suggest that the prognosis under *Hypericum* is better compared to citalopram.

Study	**Uebelhack *et al.* 2004**	
Indication	Moderate depressive disorders (ICD-10 F32.1, F33.1) and HAMD (17-items) score : 20-24	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	900 mg	
Relapse		
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=1
	number of patients	140
Outcome	HAMD reduction/% responder: STW3-VI: 22.8 -> 11.8/58.6% Placebo: 22.6 -> 19.2/5.7% Conclusion: STW3-VI in a single daily dose is superior to placebo.	
Comment	The low responder rate under placebo is explained by the authors that primarily patients with moderate depression were included, while other studies included also a higher number of patients with mild depression.	

Meta-analysis of clinical studies with STW3-VI (Linde 2007)



Conclusions: Superiority against placebo and non-inferiority against citalopram (20 mg) could be demonstrated.

Extract WS 5572:

Extract	WS 5572
Extraction solvent	60% ethanol
DER	2.5-5:1
Total hypericins	not specified
Hyperforin	4-5% (Rychlik *et al.* 2001, Lackmann *et al.* 1998) 5% (Lemmer *et al.* 1999) 1.5% (Kalb *et al.* 2001)

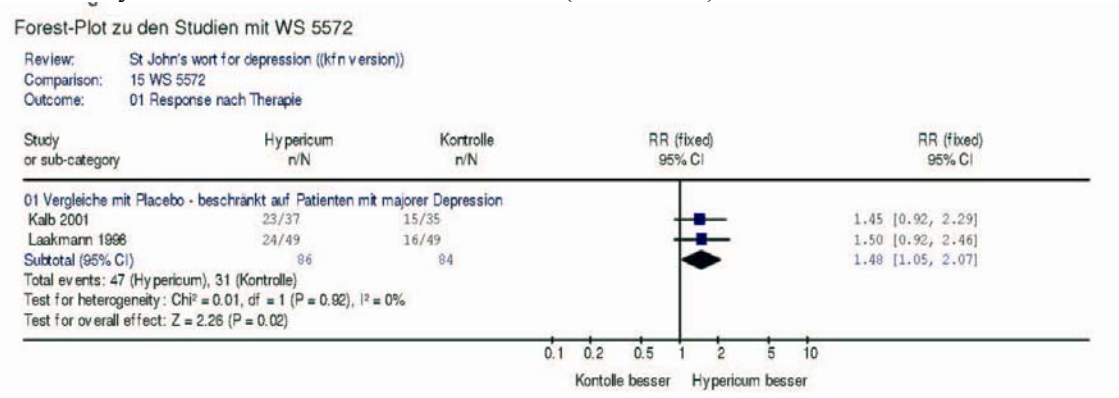
Study	**Rychlik *et al.* 2001**	
Indication	Mild to moderate depression (based on CGI)	
Duration of use	7 weeks	
Daily dosage	600 mg/1200 mg	
Single dosage	600 mg	
Relapse	-	
Study design	*randomized*	no
	double blind	no
	placebo-controlled	no
	reference-controlled	comparison of 600 mg and 1200 mg daily
	multicentre	n=446
	number of patients	2166
Outcome	Responders: 600 mg: 83.7 % 1200 mg: 86.9 % Conclusion: Good effectiveness and tolerability of WS 5572	
Comment	Observational study	

Study	**Kalb *et al.* 2001**	
Indication	Mild to moderate major depressive disorder (according to DSM-IV criteria) (DSM-IV code: 296.21, 296.31, 296.22, 296.32, HAMD (17-items): ≥ 16)	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	no
	multicentre	n=11
	number of patients	72
Outcome	HAMD reduction/% responder: WS 5572: 19.7 -> 8.9/62.2% Placebo: 20.1 -> 14.4/42.9% Conclusion: Superior compared to placebo	
Comment	Efficacy was already statistically significant at day 28 Adaptive 2-stage design	

Study	**Laakmann *et al.* 1998**	
Indication	Mild or moderate depression according to DSM-IV criteria, HAMD ≥ 17	
Duration of use	6 weeks	
Daily dosage	900 mg	
Single dosage	300 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	yes
	reference-controlled	900 mg WS 5573
	multicentre	n=11
	number of patients	147
Outcome	HAMD reduction/% responder: WS 5572: 20.9 -> 10.7/49.0% WS 5573: 20.3 -> 11.8/38.8% Placebo: 21.2 -> 13.3/32.7% Conclusion: WS 5572 (5% hyperforin) was superior to placebo WS 5573 (0.5% hyperforin) and placebo were descriptively comparable The therapeutic effect depends on the content of hyperforin.	
Comment	WS 5572 and WS 5573 are produced with the identical manufacturing process (identical DER, extraction solvent), the only difference between the extracts relates to the content of hyperforin. The fingerprint chromatograms of the two extracts are identical except for hyperforin. It is not mentioned how the differences in the content of hyperforin are achieved. The negative outcome for the extract with low content of hyperforin is in contrast to the positive findings with the extract ZE 117, which is said to be nearly free of hyperforin.	

Observational study: Lemmer *et al.* (1999):
6382 patients with mild to moderate depression were treated with WS 5672. In 59.6% the depression occurred for the first time, 31.5% had a relapse, 8.6% suffered from chronic depressive disorder.
0.7% adverse events, only 0.1% were considered causally related to medication.
Break through bleeding in 0.05% of women below 50 years of age, which is considered as the usual frequency in the untreated population.
No cases of interactions were observed.

Meta-analysis of clinical studies with WS 5572 (Linde 2007)



Conclusion: WS 5572 is superior to placebo in the treatment of mild to moderate major depression.

Extract Calmigen:

Extract	Calmigen
Extraction solvent	not specified
DER	not specified
Total hypericins	0.3%
Hyperforin	not specified

Study	**Behnke *et al.* 2002**	
Indication	Mild to moderate depression (ICD-10 F32), HAMD (17-items) score 16-24	
Duration of use	6 weeks	
Daily dosage	300 mg	
Single dosage	150 mg	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	40 mg fluoxetin
	multicentre	n=446
	number of patients	70
Outcome	HAMD reduction/% responder; Calmigen: 20.0 -> 10.0/55% Fluoxetine: 20.7 -> 8.7/66%	
Comment	Number of patients too small for a comparison of efficacy. Not to be confused with Calmigen capsules (300 mg *Hypericum* extract, extraction solvent methanol 80%, 0.3% hypericin, authorized in DK)	

Extract Hyperiforce:

Extract	Hyperiforce
Extraction solvent	not specified
DER	4-5:1 (shoot tips)
Total hypericins	0.5%
Hyperforin	not specified

Study	**Lenoir *et al.* 1999**	
Indication	Mild to moderate depression (ICD-10)	
Duration of use	6 weeks	
Daily dosage	corresponding to 0.17 mg, 0.33 mg or 1 mg hypericin	
Single dosage		
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	comparison of different dosages
	multicentre	n=38
	number of patients	348
Outcome	Reduction in HAMD score from initially 16-17 to 8-9 in all groups. Responder rate 62%-68%. The extract was effective at all three dosages.	
Comment	No placebo group	

Extract HYP611:

Extract	HYP611
Extraction solvent	ethanol 60%
DER	3.5-6:1
Total hypericins	0.18% (Wurglics *et al.* 2002)
Hyperforin	2.22% (Wurglics *et al.* 2002)

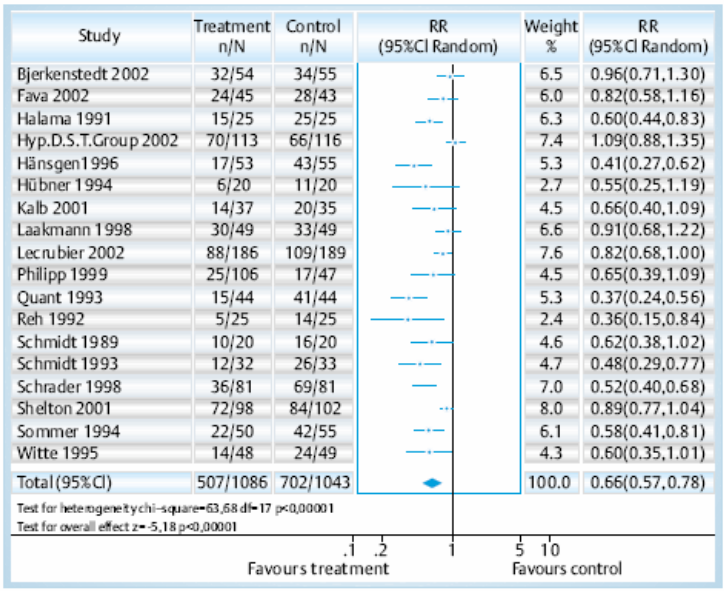
Study	**Bracher 2001**	
Indication	Mild to moderate depression	
Duration of use	6 weeks	
Daily dosage	650 mg extract	
Single dosage	650 mg extract	
Relapse	-	
Study design	*randomized*	yes
	double blind	yes
	placebo-controlled	no
	reference-controlled	comparison of different dosages
	multicentre	n=?
	number of patients	207
Outcome	Reduction in Montgomery-Asberg depression rating scale in verum group 11.5 points, in placebo group 7.8 points; HAMD score decrease in verum group 8.6 points, in placebo group 6.3 points.	
Comment	Number of study centers not given. Publication in a not peer reviewed journal. However, Linde (2008) could retrieve detailed information about the study and included it in the latest Cochrane review.	

The same extract was tested in an observational post-marketing multicenter surveillance study with 607 patients over a period of 6 weeks (Mueller 1998).
Patients received 425 or 850 mg extract per day (no further information)
Indication: Depressive mood disorder.
Assessment of efficacy by using HAMD and van Zerssen Depression Scale (more suitable for emotional disturbances). The author found a clear reduction of symptoms.

Psychotonin® (Liquid extract, DER 1: 5-7, extraction solvent ethanol 50%)
According to Linde (2007) all studies performed with this type of extract are not convincing from the current point of view. The methodology is inadequate, the number of included patients is small, and the drop-out-rate is considerably high. The studies do not fulfil the criteria for well-established use.

Overall meta-analysis
Roder *et al.* (2004) published a meta-analysis of effectiveness and tolerability of treatment of mild to moderate depression with *Hypericum* extracts.
The results demonstrate a significant superiority of *Hypericum* extracts over placebo (mean response: *Hypericum*: 53.3% and placebo: 32.7%). Compared to standard antidepressive *Hypericum* is similarly effective for the treatment of depression (mean response: *Hypericum*: 53.2%, synthetic antidepressive: 51.3%). In the subgroup of mild to moderate depression *Hypericum* showed better results against the standard antidepressive group (mean response: 59.5% / 52.9%) and a better side-effect profile. The fail-safe-N-test indicates that 423 studies with no effect would be needed to negate the presented result for placebo studies.

Relative risk of non-response after treatment with *Hypericum* or placebo (Linde 2007):



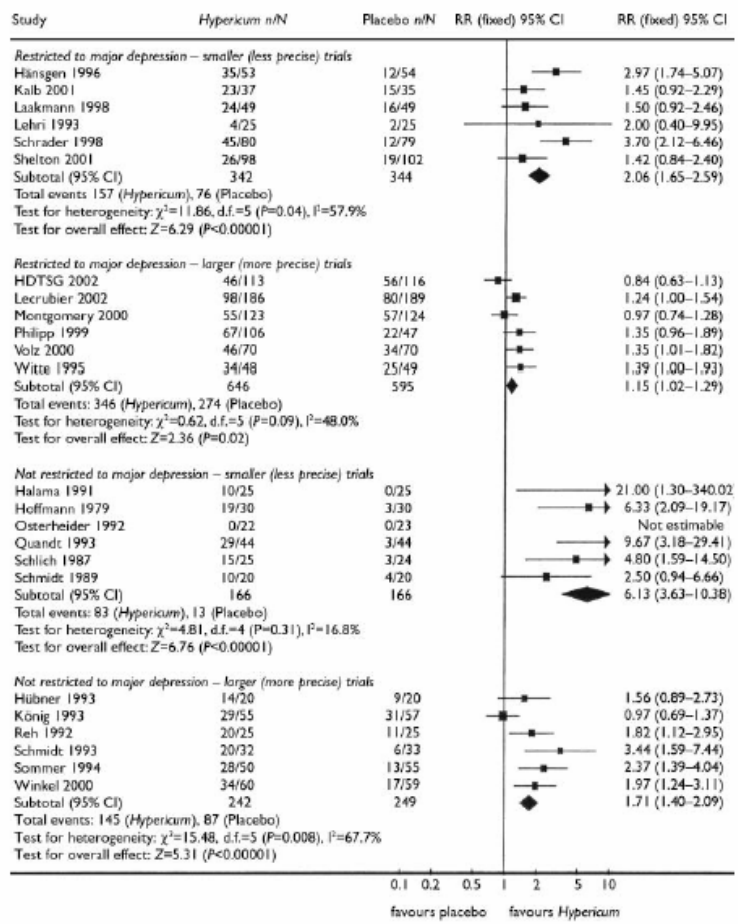
Study	Treatment n/N	Control n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Bjerkenstedt 2002	32/54	34/55		6.5	0.96(0.71,1.30)
Fava 2002	24/45	28/43		6.0	0.82(0.58,1.16)
Halama 1991	15/25	25/25		6.3	0.60(0.44,0.83)
Hyp.D.S.T.Group 2002	70/113	66/116		7.4	1.09(0.88,1.35)
Hänsgen1996	17/53	43/55		5.3	0.41(0.27,0.62)
Hübner 1994	6/20	11/20		2.7	0.55(0.25,1.19)
Kalb 2001	14/37	20/35		4.5	0.66(0.40,1.09)
Laakmann 1998	30/49	33/49		6.6	0.91(0.68,1.22)
Lecrubier 2002	88/186	109/189		7.6	0.82(0.68,1.00)
Philipp 1999	25/106	17/47		4.5	0.65(0.39,1.09)
Quant 1993	15/44	41/44		5.3	0.37(0.24,0.56)
Reh 1992	5/25	14/25		2.4	0.36(0.15,0.84)
Schmidt 1989	10/20	16/20		4.6	0.62(0.38,1.02)
Schmidt 1993	12/32	26/33		4.7	0.48(0.29,0.77)
Schrader 1998	36/81	69/81		7.0	0.52(0.40,0.68)
Shelton 2001	72/98	84/102		8.0	0.89(0.77,1.04)
Sommer 1994	22/50	42/55		6.1	0.58(0.41,0.81)
Witte 1995	14/48	24/49		4.3	0.60(0.35,1.01)
Total (95%CI)	507/1086	702/1043		100.0	0.66(0.57,0.78)

Test for heterogeneity chi-square=63,68 df=17 p<0,00001
Test for overall effect z=-5,18 p<0,00001

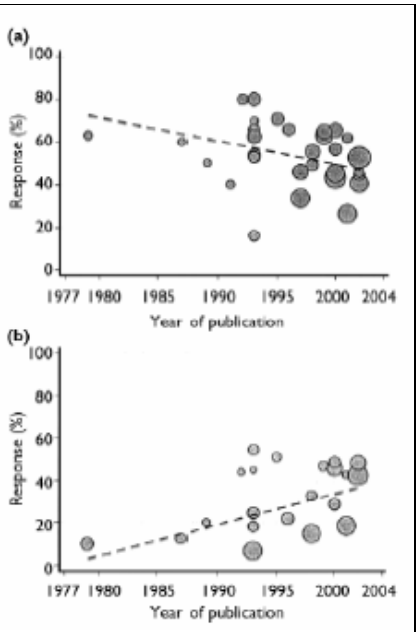
.1 .2 1 5 10
Favours treatment Favours control

Werneke *et al.* (2004) came to similar results. They found that the effect sizes in recent studies were smaller than those resulted form earlier studies.

Linde *et al.* (2005) concluded that the available data for major depression is confusing. While *Hypericum* has minimal beneficial effects over placebo, other trials suggest that *Hypericum* and standard antidepressants have equal efficacy.



Response to *Hypericum* extracts in depression. Results from placebo-controlled trials stratified by type of depression and study size. Studies identified by first author and year, n: number of responders; N: number of patients per group; RR response rate ratio (Linde 2007)



Response rates over time to a) *Hypericum* extracts and b) placebo (Linde 2007)

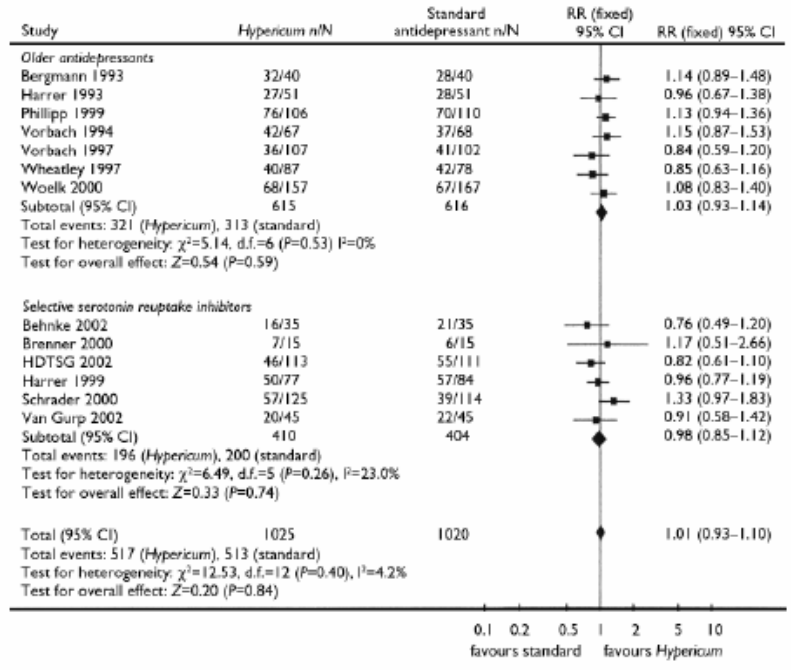


Fig. 5 Response to *Hypericum perforatum* extracts in depression: results from controlled trials stratified by type of comparison drug. Studies identified by first author and year (HDTSG, Hypericum Depression Trial Study Group; *n*, number of responders; *N*, number of patients per group; RR, response rate ratio).

Response to *Hypericum* extracts in depression. Results from controlled trials stratified by type of comparison drug. Studies identified by first author and year, n: number of responders; N: number of patients per group; RR response rate ratio (Linde 2007)

In a further Cochrane review Linde *et al.* (2008) assessed the outcome of studies in which exclusively patients with major depression were included. 29 studies in 5489 patients met the inclusion criteria; the duration of treatment was 4 to 12 weeks.
Overall the *Hypericum* treatment was superior to placebo, similarly effective as standard antidepressants, and had fewer side effects than standard antidepressants. Studies from German speaking countries were more favourable to *Hypericum* compared to studies performed in other countries.
The cumulative evidence now suggests that *Hypericum* extracts have a modest effect over placebo in a similar range as standard antidepressants. An attempt of treating mild to moderate major depression with one of the *Hypericum* preparations positively tested in clinical trials is clearly justified.
However, the differences in the findings from different countries make clear-cut recommendations difficult.

Assessor's conclusion:

Overview of extracts with predominately positive study outcome (Superiority against placebo, equivalence to reference medication):

ICD-10 F32.0: mild depressive episode
ICD-10 F32.1: moderate depressive episode
ICD-10 F33.0: recurrent depressive disorder, current episode mild
ICD-10 F33.1: recurrent depressive disorder, current episode moderate
DSM-IV 296.21: major depressive disorder, single episode, mild
DSM-IV 296.22: major depressive disorder, single episode, moderate
DSM-IV 296.23: major depressive disorder, single episode, severe without psychotic features
DSM-IV 296.31: major depressive disorder, recurrent, mild
DSM-IV 296.32: major depressive disorder, recurrent, moderate
DSM-IV 296.33: major depressive disorder, recurrent, severe without psychotic features

	single episode				recurrent				single	recurrent
	mild		moderate		mild		moderate		severe	severe
	ICD-10 F32.0	DSM-IV 296.21	ICD-10 F32.1	DSM-IV 296.22	ICD-10 F33.0	DSM-IV 296.31	ICD-10 F33.1	DSM-IV 296.32	DSM-IV 296.23	DSM-IV 296.33
LI 160			x			x		x		
WS 5570				x				x	x	x
STW3-VI			x				x			
STEI 300			x				x			
LoHyp-57	x		x							
WS 5572		x		x		x		x		
HYP611		x		x						
STW3			x				x			
ZE 117	x		x		x		x			

	DER	extraction solvent	% hypericins	% hyperforin	% flavonoids	daily dosage	duration
LI 160	3-6:1	methanol 80% v/v	0.12-0.28	approx. 4.5%	approx. 8.3%	900 mg	4-12 weeks
WS 5570	3-7:1	methanol 80% v(v	0.12-0.28	3-6%	≥ 6.0%	600-1800 mg	6/26 weeks relapse +
STW3-VI	3-6:1	ethanol 80% v/v	0.26% (mean)	3.0% (mean)	7.17% (mean)	900 mg	6 weeks relapse +
STEI 300	5-7:1	ethanol 60% m/m	0.2-0.3%	2-3%	not specified	1050 mg	8 weeks
LoHyp-57	5-7:1	ethanol 60% v/v	0.2-0.3%	2-3%	not specified	800 mg	6 weeks
WS 5572	2.5-5:1	ethanol 60% v/v	not specified	4-5%	not specified	600-1200 mg	6-7 weeks
HYP611	3.5-6:1	ethanol 60% v/v	0.1-0.3%	<6%	>6%	650 mg	6 weeks
STW3	5-8:1	ethanol 50% v/v	0.21% (mean)	3.3% (mean)	7.11% (mean)	612 mg	12 weeks
ZE 117	4-7:1	ethanol 50% m/m	0.2%	nearly free	not specified	500 mg	6 weeks
Pharm.Eur.	not specified	ethanol 50-80% v/v methanol 50-80% v/v	0.10-0.30%	< 6.0%	> 6.0%		

Wording of the indication:
According to the 'Note for guidance on clinical investigation of medicinal products in the treatment of depression' several facts should be considered:

Randomised double blind comparisons versus placebo are needed.
Three-arm trials including both a placebo and an active control are recommended.
Generally duration of about 6 weeks should be sufficient.
For licensing it should be shown that a short-term effect can be maintained during the episode. For this a relapse prevention study is probably the best design.
Recurrence prevention is not an obligatory part of a dossier.
Demonstration of an acceptable benefit/risk in moderately ill patients will be considered sufficient for a registration package to get a license for 'Episodes of Major Depression".
A 50% improvement on the usual rating scales is accepted as a clinically relevant response.

Data on relapse prevention are available from extract STW3-VI (DER 3-6:1, extraction solvent ethanol 80% v/v) and extract WS 5570 (DER 3-7:1, extraction solvent methanol 80% v/v). Extract LI 160 is very similar to WS 5570 with respect to DER, extraction solvent and content of major constituents.
Proposal of indication for these extracts:

Herbal medicinal product for the symptomatic treatment of mild to moderate depressive episodes.

Overall the clinical evidence is also positive for the other extracts as reviewed by Linde *et al.* (2008). Due to the lack of data on relapse prevention the indication should be clearly different.
Proposal of indication for the remaining extracts:

Herbal medicinal product for the short term treatment of mild to moderate depressive symptoms.

II.3.2.2.2 Somatoform disorders

Volz *et al.* (2002) conducted a multicentre, randomised, placebo controlled, 6-week trial comparing the efficacy of LI 160 (600 mg/day) and placebo in 151 out-patients suffering from somatisation disorder (ICD-10: F45.0), undifferentiated somatoform disorder (F45.1), or somatoform autonomic dysfunctions (F45.3). The primary outcome measure was the decrease of the Hamilton Anxiety Scale, subfactor somatic anxiety (HAMA-SOM), during the trial period. The *Hypericum* extract was of superior effectiveness concerning the primary outcome criterion HAMA-SOM [decrease from 15.39 (SD 2.68) to 6.64 (4.32) in the *Hypericum* group and from 15.55 (2.94) to 11.97 (5.58) in the placebo group (statistically significant difference, P=0.001)]. This was corroborated by the result of a statistically significant superior efficacy in the outcome criteria additionally used such as Clinical Global Impression, HAMA-total score, HAMA, subscore psychic anxiety, Hamilton Depression Scale, Self-Report Symptom Inventory 90 items - revised (SCL-90-R), and SCL-90-R, subscore somatic anxiety. The efficacy of LI 160 was preserved after splitting the population in those with and those without mild depressive symptoms [corrected]. Tolerability of LI 160 was excellent. The efficacy was independent of an existing depressive mood.

In a prospective, randomized, placebo-controlled double-blind parallel group study, 184 outpatients with somatisation disorder (ICD-10 F45.0), undifferentiated somatoform disorder (F45.1), and somatoform autonomic dysfunction (F45.3), but not major depression, received either 300 mg of *Hypericum* extract LI 160 twice daily or matching placebo for 6 weeks (Muller *et al.* 2004). Six outcome measures were evaluated as a combined measure by means of the Wei Lachin test: Somatoform Disorders Screening Instrument--7 days (SOMS-7), somatic subscore of the HAMA, somatic subscore of the SCL-90-R, subscores "improvement" and "efficacy" of the CGI, and the global judgment of efficacy by the patient. In the intention to treat population (N=173), for each of the six primary efficacy measures as well as for the combined test, statistically significant medium to large-sized superiority of *Hypericum* extract treatment over placebo was demonstrated ($p < .0001$). Of the *Hypericum* extract patients, 45.4% were classified as responders compared with 20.9% with placebo ($p = .0006$). Tolerability of *Hypericum* extract treatment was equivalent to placebo.

II.3.2.2.3 Schizophrenia

Hypericum extract LI 160 has demonstrated a ketamine-antagonising effect. Therefore Murck *et al.* (2006) examined whether LI 160 reverses changes of a low dose ketamine on auditory evoked potentials (AEP) in healthy subjects. The authors performed a double-blind randomized treatment with either 2 x daily 750 mg LI 160 or placebo given for one week, using a crossover design, in 16 healthy subjects. A test-battery including AEPs, the oculodynamic test (ODT) and a cognitive test were performed before and after an infusion with 4 mg of S-ketamine over a period of 1 hour. S-ketamine led to a significant decrease in the N100-P200 peak to peak (ptp) amplitude after the placebo treatment, whereas ptp was significantly increased by S-ketamine infusion in the LI 160 treated subjects. The ODT and the cognitive testing revealed no significant effect of ketamine-infusion and therefore no interaction between treatment groups. Provided that ketamine mimics cognitive deficits in schizophrenia, LI 160 might be effective to treat these symptoms.

II.3.2.2.4 Nootropic effects

A study from Elis *et al.* (2001) aimed to examine whether acute administration of a standardized *Hypericum* extract could exert a nootropic effect in normal human subjects. The study employed a double-blind, crossover, repeated-measures design. Twelve healthy young subjects completed the Cognitive Drug Research (CDR) memory battery, following administration of placebo, 900 mg and 1800 mg *Hypericum* (Blackmore's Hyperiforte). The findings suggested that *Hypericum* does not have an acute nootropic effect in healthy humans at these doses. However, there was some evidence for an impairing effect on accuracy of numeric working memory and delayed picture recognition at the higher dose. This observed impairment could be due to a sensitivity of these specific tasks to modulation by neurotransmitters that have been noted to have memory-impairing effects (e.g. y-aminobutyric acid (GABA), serotonin).

In a randomized, double-blind, cross over study 12 healthy male volunteers received capsules with 255-285 mg St John's wort extract (900 µg hypericin content), 25 mg amitriptyline and placebo three times daily for periods of 14 days each with at least 14 days in between (Siepmann *et al.* 2002). The doses of amitriptyline and St John's wort extract are comparable with respect to their antidepressant activity. Neither St John's wort extract nor amitriptyline had an influence on cognitive performance such as choice reaction, psychomotor coordination, short-term memory and responsiveness to distractive stimuli. Amitriptyline but not St John's wort extract decreased self rated activity ($P < 0.05$). Both drugs caused significant qEEG changes. St John's wort extract increased theta power density. Amitriptyline increased theta as well as fast alpha power density.

II.3.2.2.5 Subacute atopic dermatitis

In a half-side comparison study Schempp *et al.* (2003) assessed the efficacy of a cream containing *Hypericum*: Extract standardised to 1.5% hyperforin (verum) in comparison to the corresponding vehicle (placebo) for the treatment of subacute atopic dermatitis. The study design was a prospective randomised placebo-controlled double-blind monocentric study. In twenty one patients suffering from mild to moderate atopic dermatitis (mean SCORAD 44.5) the treatment with verum or placebo was randomly allocated to the left or right side of the body, respectively. The patients were treated twice daily over a period of four weeks. Eighteen patients completed the study. The severity of the skin lesions on the left and right side was determined by means of a modified SCORAD-index (primary endpoint). The intensity of the eczematous lesions improved on both sides of treatment. However, the *Hypericum*-cream was significantly superior to the vehicle at all clinical visits (days 7, 14, 28) ($p < 0.05$). Skin colonisation with Staphylococcus aureus was reduced by both verum and placebo, showing a trend to better antibacterial activity of the *Hypericum* cream ($p = 0.064$). Skin tolerance and cosmetic acceptability was good or excellent with both the *Hypericum* cream and the vehicle (secondary endpoints).

II.3.2.2.6 Premenstrual syndrome

19 women with premenstrual syndrome who were in otherwise good physical and mental health and not taking other treatments for premenstrual syndrome were investigated in a prospective, open,

uncontrolled, observational pilot study (Stevinson & Ernst 2000). The participants took *Hypericum* tablets for two complete menstrual cycles (1 x 300 mg *Hypericum* extract per day standardised to 900 µg hypericin). Symptoms were rated daily throughout the trial using a validated measure. The Hospital Anxiety and Depression scale and modified Social Adjustment Scale were administered at baseline and after one and two cycles of treatment. There were significant reductions in all outcome measures. The degree of improvement in overall premenstrual syndrome scores between baseline and the end of the trial was 51%, with over two-thirds of the sample demonstrating at least a 50% decrease in symptom severity. Tolerance and compliance with the treatment were encouraging.

Hicks *et al.* (2004) performed a randomized, double-blinded, placebo-controlled trial with two parallel treatment groups. After a no-treatment baseline cycle, volunteers were randomized to either *Hypericum* extract or placebo for a further two menstrual cycles. 169 normally menstruating women who experienced recurrent premenstrual symptoms were recruited onto the study. 125 completed the protocol and were included in the analysis. Study medication: 600 mg of *Hypericum* extract (standardized to contain 1800 µg of hypericin) or placebo (containing lactose and cellulose). A menstrual diary was used to assess changes in premenstrual symptoms. The anxiety-related subgroup of symptoms of this instrument was used as the primary outcome measure. After averaging the effects of treatment over both treatment cycles it was found that there was a trend for *Hypericum* extract to be superior to placebo. However, this finding was not statistically significant.

II.3.2.2.7 Menopausal symptoms

In a drug-monitoring study Grube *et al.* (1999) investigated 12 weeks of treatment with St. John's Wort, one tablet three times daily (900 mg *Hypericum* extract LI 160), in 111 women from a general medical practice. The patients who were between 43 and 65 years old had climacteric symptoms characteristic of the pre- and postmenopausal state. Treatment outcome was evaluated by the Menopause Rating Scale, a self-designed questionnaire for assessing sexuality, and the Clinical Global Impression scale. The incidence and severity of typical psychological, psychosomatic, and vasomotor symptoms were recorded at baseline and after 5, 8, and 12 weeks of treatment. Substantial improvement in psychological and psychosomatic symptoms was observed. Climacteric complaints diminished or disappeared completely in the majority of women (76.4% by patient evaluation and 79.2% by physician evaluation). Of note, sexual well-being also improved after treatment with St. John's Wort extract.

Additionally some clinical trials with fixed combinations are published (e.g., combination *Hypericum* + Cimicifuga racemosa Uebelhack *et al.* 2006, Chung *et al.* 2007). Although the authors report a positive outcome with regard to climacteric complaints, such publications are considered only marginally because the amount of the contribution of each combination partner to the overall efficacy cannot be estimated.

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

Depression in children

Hübner & Kirste (2001) investigated a *Hypericum* extract in children under 12 years with symptoms of depression and psychovegetative disturbances.
Study design: Multi-center, post-marketing surveillance study; n=101 children under 12 years, dosage: 300 to 1800 mg per day.
Based on the data available for analysis, the number of physicians rating effectiveness as 'good' or 'excellent' was 72% after 2 weeks, 97% after 4 weeks and 100% after 6 weeks. The ratings by parents were very similar. There was, however, an increasing amount of missing data at each assessment point with the final evaluation including only 76% of the initial sample. Tolerability was good and no adverse events were reported. The authors suggest that *Hypericum* is a potentially safe and effective treatment for children with symptoms of depression.

Findling *et al.* (2003) conducted an open-label prospective outpatient pilot study of St. John's wort in juvenile depression.

Youths 6 to 16 years of age meeting DSM-IV criteria for major depressive disorder, prospective, open-label, outpatient study; dosage: 3 x 150-300 mg. The extract is not further specified.
33 children with a mean age of 10.5 (2.9) years were enrolled. After 4 weeks of St. John's wort therapy, 22 youths had their dose increased to 900 mg/day. Twenty-five of the patients met response criteria after 8 weeks of treatment. Overall, St. John's wort was well tolerated. The authors conclude that *Hypericum* may be an effective treatment for youths diagnosed with major depressive disorder.

Assessor's comment: The Hypericum extract is characterized improperly.

In an 8 week open-label study on efficacy and safety of 3 x 300 mg *Hypericum* extract (0.3% hypericin, 3% hyperforin) 26 adolescents were enrolled (Simeon *et al.* 2005). In 7 adolescents the symptoms persisted or worsened, 8 of the 26 were noncompliant. Therefore only 11 participants finished the study. In 9 of the 11 patients a significant clinical improvement was observed.

Fegert *et al.* (2006) analyzed the prescription data of antidepressants in Germany in the years 2000-2003. Approximately 280.000 persons under the age of 20 were accessed.
Hypericum and tricyclic antidepressants accounted for more than 80% of antidepressant use.
In all of the 4 years *Hypericum* was the preferably prescribed antidepressant in this age group:
2000: *Hypericum* 55.59%, Imipramine 16.25%
2001: *Hypericum* 52.24%, Imipramine 14.93%
2002: *Hypericum* 50.58%, Imipramine 11.85%
2003: *Hypericum* 40.36%, Omipramol 10.72%

Attention deficit, hyperactivity disorder
In a randomized, double-blind, placebo controlled study (Weber *et al.* 2008) 54 children aged 6 to 17 years received 300 mg *Hypericum* extract (containing 0.3% Hypericin) 3 times daily for 8 weeks. All participants met the diagnostic criteria for ADHD. *Hypericum* did not improve the symptoms.

Assessor's conclusion on the use in the paediatric population:
Although there are no controlled studies with children and adolescents published it can be concluded that there is a widespread documented use of *Hypericum* extracts among adolescents. However, there are no data available on the efficacy and safety in this population. Therefore the use in children and adolescents below 18 years of age is not recommended.

II.3.2.4 Assessor's overall conclusions on clinical efficacy

Dry extracts prepared with ethanol (50-80%) or methanol (50%) demonstrated clinical efficacy in the treatment of depression. Relapse studies have been performed with extracts prepared with 80% ethanol or 80% methanol (v/v) only. Therefore these extracts are suitable for the treatment of mild to moderate depressive episodes. Dry extracts which are prepared with ethanol 50-68% (v/v) should be used for the short term treatment of symptoms of mild depressive disorders only.
There are several new therapeutic approaches (smoking cessation, treatment of alcoholism, menopausal symptoms …) published. However, at the moment the clinical evidence is insufficient in order to be considered in a community monograph.
The clinical data of the hyperforin cream demonstrate a great potential. However, the herbal preparation is less than 10 years in medicinal use; therefore well-established use is impossible in the monograph for the moment.

II.3.3 Clinical Safety/Pharmacovigilance

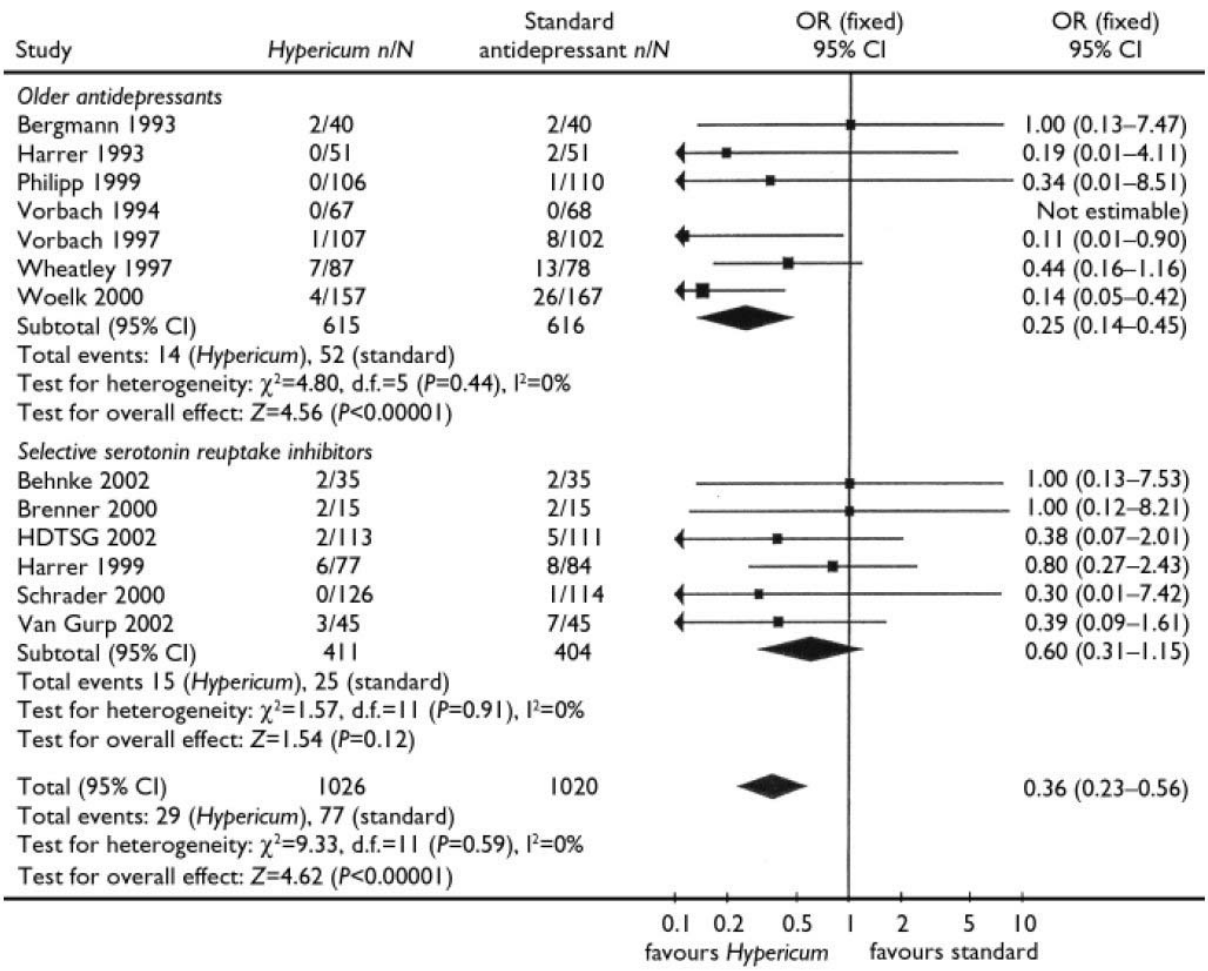
II.3.3.1 Patient exposure

II.3.3.2 Adverse events

A randomized, double-blind, crossover study was performed in healthy male volunteers aged 22 to 31 years (25 +/- 3 years; mean +/- SD) years by Siepmann *et al.* (2004). Subjects orally received capsules with 255 to 285 mg St. John's wort extract (900 µg hypericin content), 25 mg amitriptyline, and placebo 3 times daily for periods of 14 days each with at least 14 days between. Vasoconstrictor responses of cutaneous blood flow (VR) and skin conductance response (SR) following a single deep inspiration were employed as parameters of autonomic function. St. John's wort extract had no effect on VR and SR.

Stevinson & Ernst (2004) reviewed systematically the clinical evidence associating *Hypericum* extract with psychotic events. Seventeen case reports associated the use of *Hypericum* extract with psychotic events. In 12 instances, the diagnosis was mania or hypomania. Causality is in most cases possible. In no case a positive rechallenge has been reported. These case reports raise the possibility that *Hypericum* extract may trigger episodes of mania in vulnerable patients.

Linde performed in his meta-analysis (Linde *et al.* 2005) also an analysis of safety. There was a trend towards lower probability of dropping out because of adverse effects in the *Hypericum* groups compared to standard therapy (see figure below).



Adverse events reported from clinical trials:

Study	Extract	Daily dose	Adverse events
Lecrubier *et al.* (2002)	WS 5570	3 x 300 mg	n=21 of 186 Nausea (4.8%) Headache (1.6%) Dizziness (2.2%) Abdominal pain (1.1%) Insomnia (1.6%)
Kalb *et al.* (2001)	WS 5572	3 x 300 mg	Sinusitis Bronchitis Common cold
Schrader *et al.* (1998)	Ze 117	2 x 250 mg	n=6 of 81 (7.4%) Abdominal pain (2) Moderate Diarrhoea (1) Moderate Melancholia (1) Moderate Acute deterioration (1) Moderate Dry mouth (1) Mild
Schrader (2000)	Ze 117	2 x 250 mg	8% only GI disturbances (5%) with an incidence greater than 2%
Randlov *et al.* (2006)	PM235, (Cederroth International AB, Sweden)	3 x 270 mg	mild, mainly headache, gastrointestinal symptoms
Anghelescu *et al.* (2006)	WS 5570	900 mg or 1800 mg	26.8% of 71 no "typical adverse events (except: 1 allergic reaction to sunlight → early study termination) 0.006 AE/d
Woelk (2000)	Ze 117	2 x 250 mg	62 of 157 (39%) Dry mouth (13) Headache (3) Sweating (2) Asthenia (2) Nausea (1)
Philipp *et al.* (1999)	STEI 300	3 x 350 mg	0.5 events per patient (22%) most frequently reported adverse event: Nausea
Gastpar *et al.* (2005)	STW3	612 mg	9.8% related to study medication Diarrhoea (1) Serious adverse events (3): shoulder blade after falling down the stairs, somatic disorder, cerebral haemorrhage)
Bjerkenstedt *et al.* (2005)	LI 160	3x 300 mg	Adverse events: 38 Patients with adverse events: 35.1% Adverse events possibly related to study medication: 24 Body as a whole (13) Gastro-intestinal system disorders (6) Autonomic nervous system disorders (10) Central & peripheral nervous system disorders (10) Skin and appendages disorders (9) Psychiatric disorders (2) Others (5)
Kasper *et al.* (2006)	WS 570	600 mg or 1200 mg (2 x 600 mg)	All adverse events. 49 (39.8%) Serious events 1 (tendon rupture attributable to accidental injury) Ear and labyrinth disorders 3 (2.4%) Gastrointestinal disorders 24 (19.5%) General disorders and administration site

			conditions 2 (1.6%) Infection and infestations 7 (5.7%) Injury, poisoning and procedural complications 1 (0.8%) Investigations 1 (0.8%) Metabolism and nutrition disorders 1 (0.8%) Musculoskeletal and connective tissue disorder 1 (0.8%) Nervous system disorder 6 (4.9%) Psychiatric disorders 2 (1.6%) Renal and urinary disorders 1 (0.8%) Reproductive system and breast disorders 1 (0.8 %) Respiratory, thoracic and mediastinal disorders 4 (3.3%) Skin and subcutaneous disorders4 (3.3%) Vascular disorders 1 (0.8%)
Fava *et al.* (2005)	LI 160	3 x 300 mg	n=90 Most common adverse events. Headache (42%) Dry mouth (22%) Nausea (20%) Gastrointestinal upset (20%) Sleepiness (18%)
Shelton *et al.* (2001)	LI 160	900 mg/d for 4 weeks, after this period no adequat response, new dose 1200 mg/d	Headache (41%) Abdominal pain (≥ 10%)
Hypericum Depression Trial Study Group (2002)	LI 160	900 to 1500 mg (3-5 x 300 mg)	Diarrhoea (21%) Nausea (19%) Anorgasmia (25%) Forgetfulness (25%) Frequent urination (27%) Sweating (18%) Swelling (19%)
Szegedi *et al.* (2005)	WS 5570	900 mg (3 x 300 mg) – 1800 mg (3 x 600 mg)	Adverse events per day WS 5570 900 mg (0.029) WS 5570 1800 mg (0.039) Upper abdominal pain (9.6%) Diarrhoea (9.6%) Dry mouth (12.8%) Nausea (7.2%) Fatigue (11.2%) Dizziness (7.2%) Headache (10.4%) Sleep disorder (4%) Increased sweating (7.2%) Highest incidence: Gastrointestinal disorders (59 events in 42 patients) Nervous system disorders (35 events in 29 patients) 2 serious adverse events (psychic decompensation attributable to social problems, hypertensive crisis), both not caused by *Hypericum*
van Gurp *et al.* (2002)	?	900 to 1800 mg/d	Sleep disturbance (54.8%) Anxiety (42.9%) Sexual problems (11.9%)

			Headaches (42.9%) Dizziness (11.9%) Tremor (19.1%) Sweating (16.7%) Dry mouth (38.1%) Muscle spasms (11.9%) Muscle or joint stiffness (19.1%) Urinary problems (16.7%) Difficulty digesting (19.1%) Nausea or vomiting (9.5%) Diarrhoea (23.8%) Lack of appetite (23.8%) Heart palpitations (9.5%) Fatigue (45.2%) Pain (11.9%) Blurred vision (14.3%) 1 serious adverse reaction (acute manic reaction)
Laakmann *et al.* 1998	WS 5573 WS 5572	3 x 300 mg	WS 5573 (28.6% of 49 patients) WS 5572 (28.6% of 49 patients) Bronchitis (3/1) Influenza-like symptoms (2/0) Cough (2/0) Infection (1/0)
Schrader 2000	Ze 117	2 x 250 mg	8 % *Hypericum* GI disturbances (5%)
Lenoir *et al.* 1999	Hyperiforce (provided by Bioforce AG, Roggwil, Switzerland)	3 x 1 tablet (standardised to either 0.17 mg, 0.33 mg, or 1 mg total hypericin per day)	There is no difference in AE with possible or probable causality in the three treatment-groups. Probable/Possible relation to study medication: Skin (0/3) Nerves (2/5) Psyche (1/1) Gastrointestinal tract (4/0) Organism as a whole (0/2)
Harrer *et al.* 1999	LoHyp 57	2 x 400 mg	n=12 (For this reason withdrawn: 6)
Gastpar *et al.* 2006	STW3-VI	900 mg	17.2% Total AEs. 58 Related: 10 Gastrointestinal disorders (6) Ear and labyrinth disorders (1) Skin and subcutaneous tissue disorders (1)
Wheatley 1997	LI 160	3 x 300 mg	37 % of the patients Dry mouth (5%) Drowsiness (1%) Sleepiness (2%) Dizziness (1%) Lethargy (1%) Nausea/Vomiting (7%) Headache (7%) Constipation (5%) Pruritus (2%)
Vorbach *et al.* 1997	LI 160	3 x 600 mg	23% of the patients n=37 Dry mouth (3) Gastric symptoms (5) tiredness/sedation (5) Restlessness (6) Tremor (2)

			Dizziness (5) Allergic skin reaction (1)
Rychlik *et al.* 2001	WS 5572	600 mg/1200 mg	17 patients n=21 (13 with relation to *Hypericum*) AEs frequency < 1% Skin irritation, pruritus Allergic exanthema Nervousness, restlessness Gastrointestinal disorders (4) Diarrhea Insomnia

According to the review by Greeson *et al.* (2001) the overall incidence of ADR is in the range of 2%. The most commonly reported side effects were gastrointestinal irritations (0.6%), allergic reactions (0.5%), fatigue (0.4%) and restlessness (0.3%). In comparison, the overall ADR incidence for SSRIs is between 20% and 50%, including more serious side effects.

Additional case reports:

A case of acute neuropathy after taking 500 mg of *Hypericum* powder per day and exposure to sunlight was reported (Bove 1998).

O'Breasail & Argouarch (1998) published two cases where *Hypericum* (no details of the product) may be linked to the development of hypomania.

During the year 2001, poison control centres in US were contacted regarding 356 exposures involving *Hypericum* (Gryzlak *et al.* 2007). Only a minority (39) resulted in adverse events. 21% reported exposures were coded as intentional, 13% were reported as 'suspected suicidal'.
Most of the reported exposures occurred among children of 5 years or younger. For patients ≥ 20 years of age exposures were more likely to be associated with adverse effects.

II.3.3.3 Serious adverse events and deaths

Several case reports document psychotic adverse reactions like mania and psychosis (review in Hammerness *et al.* 2003). The majority of the affected persons had histories of affected illness, in most cases *Hypericum* was combined with other psychopharmaceuticals. The symptoms remitted after discontinuation of the medication. As a precaution *Hypericum* extracts should not be taken by persons with a history of mania or psychosis. Seizures are reported after overdose only (Karalapillai & Bellomo 2007).

II.3.3.4 Laboratory findings

II.3.3.4.1 Phototoxicity

Hypericin

Schempp *et al.* (1999) describe the HPLC detection of hypericin and semiquantitative detection of pseudohypericin in human serum and skin blister fluid after oral single-dose (1 x 6 tablets) or steady-state (3 x 1 tablet/day, for 7 days) administration of the *Hypericum* extract LI 160 in healthy volunteers (n = 12). Serum levels of hypericin and pseudohypericin were always significantly higher than skin levels (p </= 0.01). After oral single-dose administration of *Hypericum* extract the mean serum level of total hypericin (hypericin + pseudohypericin) was 43 ng/ml and the mean skin blister fluid level was 5.3 ng/ml. After steady-state administration the mean serum level of total hypericin was 12.5 ng/ml and the mean skin blister fluid level was 2.8 ng/ml. These skin levels are far below hypericin skin levels that are estimated to be phototoxic (>100 ng/ml).

Dry extracts

In a prospective randomized study Schempp *et al.* (2003) investigated the effect of the *Hypericum* extract LI 160 on skin sensitivity to ultraviolet B (UVB), ultraviolet A (UVA), visible light (VIS) and solar simulated radiation (SIM). Seventy two volunteers of skin types II and III were included and were divided into six groups, each consisting of 12 volunteers. In the single-dose study the volunteers (n = 48) received 6 or 12 coated tablets (5400 or 10800 mg hypericin). In the steady-state study the

volunteers (n = 24) received an initial dose of 6 tablets (5400 mg hypericin), and subsequently 3 x 1 tablets (2700 mg hypericin) per day for 7 days. Photo testing was performed on the volar forearms prior to medication and 6 h after the last administration of *Hypericum* extract. The erythema-index and melanin-index were evaluated photometrically using a mexameter. After both single-dose and steady-state administration, no significant influence on the erythema-index or melanin-index could be detected, with the exception of a marginal influence on UVB induced pigmentation (p = 0.0471) in the single-dose study. The results do not provide evidence for a phototoxic potential of the *Hypericum* extract LI 160 in humans when administered orally in typical clinical doses up to 1800 mg daily. This is in accordance with previous pharmacokinetic studies that found hypericin serum and skin levels after oral ingestion of *Hypericum* extract always to be lower than the assumed phototoxic hypericin threshold level of 1000 ng/ml.

The objective of a study by Schulz *et al.* (2006a) was to investigate the effect of two different *Hypericum* extracts (STW 3, STW 3-VI) on photosensitivity with respect to minimal erythema dose (MED) after 14 days treatment. Both open, multiple-dose, one-phase studies were conducted in 20 healthy men, receiving one tablet per day. MED values were determined prior to *Hypericum* extract administration (baseline) and after 14 days of treatment using an erythema tester emitting a light very similar to sun light (main emission spectrum: 285-350 nm). Skin reactions with respect to MED were evaluated 12 h, 24 h (primary endpoint), 48 h and 7 days after irradiation. All volunteers reached steady-state of hypericin/pseudohypericin plasma concentrations before study day 14, when the irradiation under treatment conditions took place. In all subjects MED was measurable under baseline and under *Hypericum* treatment conditions. With respect to the primary endpoint, in both studies, mean MED (24 h) were not significantly different between baseline and after 14 days of *Hypericum* treatment. However, the individual photosensitivity of the skin could increase under the treatment conditions, just as well photosensitivity could decrease or remain unchanged. There were no clinically relevant changes in the laboratory parameters, the vital signs, physical findings and other observations related to safety during the examinations. In one study (STW 3), two adverse events were reported, both described as hypersensitivity to light in mild intensity. The two studies showed that treatment with the two *Hypericum* extracts under steady state and under prescribed conditions were safe medications without significant increases of photosensitivity.

Köppel *et al.* (2008) investigated the effect of a dry extract (DER 3.5-6:1, Ethanol 60% v/v, Esbericum capsules, 60 mg, 3 capsules twice daily for 2 weeks) on photosensitivity. The results of the study revealed that in the presence of a stable plasma concentration of hypericin (6.72 ng/ml) the MED (minimal erythema dose) values did not change significantly.

***Hypericum* oil**

Schempp *et al.* (2000) investigated the effects of *Hypericum* oil (hypericin 110 mg/ml) and *Hypericum* ointment (hypericin 30 mg/ml) on skin sensitivity to solar simulated radiation. Sixteen volunteers of the skin types II and III were tested on their volar forearms with solar simulated radiation for photosensitizing effects of *Hypericum* oil (n=8) and *Hypericum* ointment (n=8). The minimal erythema dose (MED) was determined by visual assessment, and skin erythema was evaluated photometrically. With the visual erythema score, no change of the MED could be detected after application of either *Hypericum* oil or *Hypericum* ointment (P>0.05). With the more sensitive photometric measurement, an increase of the erythema-index after treatment with the *Hypericum* oil could be detected (P< or =0.01). The results do not provide evidence for a severe phototoxic potential of *Hypericum* oil and *Hypericum* ointment, detectable by the clinically relevant visual erythema score. However, the trend towards increased photosensitivity detected with the more sensitive photometric measurement could become relevant in fair-skinned individuals, in diseased skin or after extended solar irradiation.

Assessor's comment:
The mentioned content of hypericin is in contrast to investigations from Maisenbacher et al (1992), these authors found only artefacts of hypericin.
From traditional use of Hypericum oil it is known that the exposure to sunlight of treated parts of the skin would lead to skin irritations. In traditional medicine it is recommended to protect treated skin from sunlight.

II.3.3.4.2 Limited liver function

Johne *et al.* (2002) investigated the influence of impaired liver function on the pharmacokinetic data of major constituents of *Hypericum*. 8 Patients with mild and 8 with moderate liver cirrhosis received a single dose of the extract LI 160 (900 mg) and for 12 days 3 x 300 mg of this extract. The data were compared to 8 healthy volunteers. The authors conclude that moderate liver cirrhosis may increase plasma levels of hypericin, pseudohypericin and hyperforin.

Assessor's comment:
Although statistically significant (testing for significance using data from such a small population should be questioned), the very broad ranges overlap for all constituents and groups with the exception of pseudohypericin in patients with moderate liver cirrhosis. It is common knowledge that impaired liver function alters the metabolism of the majority of drug substances. Nevertheless it is unusual to mention this in the SPC. Since the proposed indication for well-established use of Hypericum needs medical supervision a special statement regarding limited liver function is unnecessary.

II.3.3.5 Safety in special populations and situations

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

Fegert *et al.* (2006) analyzed the prescription data of antidepressants in Germany in the years 2000-2003. Approximately 280.000 persons under the age of 20 were assessed.
Hypericum and tricyclic antidepressants accounted for more than 80% of antidepressant use.
In all of the 4 years *Hypericum* was the preferably prescribed antidepressant in this age group:
2000: *Hypericum* 55.59%, Imipramine 16.25%
2001: *Hypericum* 52.24%, Imipramine 14.93%
2002: *Hypericum* 50.58%, Imipramine 11.85%
2003: *Hypericum* 40.36%, Omipramol 10.72%

Assessor's comment: From this data it can be concluded that there is a documented widespread use of Hypericum extracts among adolescents. However, there are no data available on the efficacy and safety in this population. Therefore the use in children and adolescents below 18 years of age is not recommended.

Kaye *et al.* (2000) evaluated data from 1017 hospital patients. 30% used *Hypericum*. The authors propose that pseudoephedrine, MAOIs and SSRIs should be avoided in these patients.
Larkin (1999) proposes to stop herbal supplements 2 weeks before elective surgery. *Hypericum* should be stopped 5 days before, because it may prolong the effects of some narcotics and anaesthetics (Larkin 2001).

Assessor's comment: The mentioned interaction with narcotics and anaesthetics is hypothetical, there are no reports published.

II.3.3.5.2 Drug interactions

The extent of induction of CYP3A varies among St. John's wort products and depends on hyperforin dose (Mueller SC *et al.* 2006, Gutmann *et al.* 2006). Products that do not contain substantial amounts of hyperforin (<1%) have not been shown to produce clinically relevant enzyme induction (Madabushi *et al.* 2006). Hypericin may be assumed to be the P-glycoprotein inducing compound, although the available evidence is less convincing (Mannel 2004).
Several meta-analyses are published on the pharmacokinetic interactions of *Hypericum* with the cytochrome-P450 enzyme complex and P-glycoprotein (Pal & Mitra 2006, Madabushi *et al.* 2006, Whitten *et al.* 2006, Zhou *et al.* 2004, Mills *et al.* 2004, Henderson *et al.* 2002, Izzo & Ernst 2009).

Volz & Zeller. (2000) report from a observational trial (11.296 patients receiving STW3-VI, Laif 600, DER 5-8:1, per tablet 2 mg hypericin, 30 mg flavonoids, 11 mg hyperforin; 612 mg extract per tablet. The mean period was 65 days. No reports of interactions were received although 10% of the patients

used ß-blockers, 10% ACE-inhibitors, 6% diuretics, 7.8% thyroid hormones, 4.2% oral contraceptives and 3.8% estrogens.

The causality of some of the published interactions is questioned by Schulz (2006b), particularly the combinations with serotonin reuptake inhibitors and digoxin.
The elevated activity of CYP3A returns to basal level approximately 1 week after termination of *Hypericum* administration (Imai *et al.* 2008). This should be considered when in the case of elective surgery substances will be used which may be influenced.

Interactions with benzodiazepines:
Moody *et al.* (2004) states that P450 3A4 is extensively involved in many pathways of oxidative metabolism of benzodiazepines.

Assessor's comment: This statement supports the proposal to include benzodiazepines in general to the interaction section.

20 healthy male volunteers received low hyperforin extract for 2 weeks (Mueller *et al.* 2009). Midazolam plasma concentration time profiles were analyzed on the day before and on day 14 of *Hypericum* medication.
Study medication: 2 x 500 mg *Hypericum* powder per day. Content per capsule: 0.06 mg hyperforin, 0.6 mg hypericin, 17.77 mg flavonoids. No significant changes were observed.

Assessor's comment: Low-dose hyperforin preparations do not seem to have an influence on the metabolism of midazolam.

Interactions with oral contraceptives:
Hypericum has been also reported to cause bleeding and unwanted pregnancies when concomitantly administered with oral contraceptives.

Hall *et al.* (2003) studied the interactions between an oral contraceptive (Ortho-Novum 1/35 (1 mg norethindrone and 0.035 mg ethinylestradiol)) and a *Hypericum* extract (food supplement, 900 mg per day). Ortho-Novum 1/35 was given for 3 cycles. During the second and third cycles the volunteers received *Hypericum* extract. Midazolam was given on days 22 and 23 orally or intravenously.
Concomitant use resulted in a significant increase of oral clearance of norethindrone (8.2 ± 2.7 L/h to 9.5 ± 3.4 L/h, P = 0.42) and a significant reduction in the half-life of ethinylestradiol (23.4 ± 19.5 hours to 12.2 ± 7.1 hours, P = 0.23). The oral clearance of midazolam was significantly increased, the systemic clearance remained unchanged. Serum concentrations of follicle-stimulating hormone, luteinizing hormone and progesterone were not significantly affected. Breakthrough bleeding occurred in 2 of 12 women in the control phase compared to 7 of 12 women in the *Hypericum* phase.
No ovulation was found. Therefore an increase of breakthrough bleeding is not necessarily associated with a loss of contraceptive efficacy. The authors interpret the changes in pharmacokinetics of norethindrone and ethinylestradiol as 'modest'.

Murphy *et al.* (2005) studied the interactions between a low dose oral contraceptive and *Hypericum*. 16 healthy women received an oral contraceptive (20 µg ethinyl estradiol and 1 mg norethindrone) for two consecutive cycles; treatment with *Hypericum* extract (3 x 300 mg, *Hypericum* Byuers Club, alcoholic extract, 0.3% hypericin, 3.7% hyperforin) was added for two additional cycles.
Results: The authors observed a significant 13-15% reduction in the dose exposure. Breakthrough bleeding increased, and there was evidence of follicle growth and probable ovulation.

Pharmacokinetic data of ethinyl estradiol:

	control	under *Hypericum*
Cmax (pg/ml):	90	84
Tmax (h):	2.0	2.0
AUC (pg . h/ml):	994	854

Author's conclusion: Women taking oral contraceptives should be cautioned that the use of *Hypericum* might reduce the effectiveness of their birth control method.

Pfrunder *et al.* (2003) studied the interaction between *Hypericum* and low-dose oral contraceptives in a randomised controlled trial. 18 healthy females were treated with a low-dose oral contraceptive (0.02 mg ethinyl estradiol, 0.150 mg desogestrel) alone or combined with 2 x 300 mg or 3 x 300 mg *Hypericum* extract daily (LI 160) for 2 menstrual cycles.
No change in follicle maturation, serum estradiol or progesterone concentrations were found.
Significantly more subjects reported intracyclic bleeding, the AUC and Cmax of ethinyl estradiol remained unchanged, whereas the AUC and Cmax of 3-ketodesogestrel decreased significantly.
There was no evidence of ovulation, but intracyclic bleeding episodes may adversely affect compliance to oral contraceptives. The decrease in serum 3-ketodesogestrel may enhance the risk of unintended pregnancies.

The low-hyperforin extract Ze 117 was tested in women taking a low-dose oral contraceptive (*Hypericum*: 250 mg extract 2 x daily, 20% total hypericin, < 0.2% hyperforin; oral contraceptive: Lovelle, Low-dose, 0.020 mg ethinyl estradiol, 0.150 mg desogestrel)(Will-Shahab *et al.* 2001). In the abstract of a symposium presentation no data were presented. The authors conclude that after 2 weeks of *Hypericum* extract the plasma concentrations remained within the 80%-125% range as defined for bioequivalence studies.

Assessor's comment: The amount of hypericin in the extract must be questioned. The duration of treatment seems to be too short compared with the usual duration of use of Hypericum.

Interaction with SSRIs:
When combined with serotonin reuptake inhibitors, antidepressants (e.g. sertaline, paroxetine, nefazodone) or buspirone, *Hypericum* extracts can cause a serotonergic syndrome.

Gordon (1998) published a case report of a complication: A female patient (50 years old) stopped taking paroxetine 40 mg and started taking *Hypericum* powder 600 mg per day. After 10 days she took 20 mg paroxetine additionally. She was found to be incoherent, groggy, slow-moving and almost unable to get out of bed. Next day the signs returned to normal.
This case was classified by the author as an interaction between the SSRI paroxetine and the MAO inhibitor *Hypericum*.

Assessor's comment: The role of Hypericum as MAO inhibitor is discussed controversially. Butterweck et al 2003 summarize that MAO inhibitors are present in Hypericum. Their relatively high inhibition concentrations do not suggest any relevance of MAO-A or –B inhibition to the antidepressant effect.

Five cases of clinically diagnosed central serotonergic syndrome among elderly patients who combined prescription antidepressants with St. John's wort are described by Lantz *et al.* (1999).
Cases 1, 3, 4: 50 mg sertraline, 900 mg *Hypericum*
Case 2: 75 mg sertraline, 900 mg *Hypericum*
Case 5: 200 mg nefazodone, 900 mg *Hypericum*

Assessor's comment: The Hypericum preparations are not properly characterized. In view of the problems associated with the diagnosis of serotonergic syndrome the cases are very poorly described.

Bonetto *et al.* (2007) report a case of a suspected serotonin syndrome. The *Hypericum* preparation is not mentioned (self-prescribed pills). This indicates the use of a food supplement and not of a medicinal product with definite composition.
A 28 year old woman was on fluoxetine 60 mg/day for 1 year (bulimia), eletriptan 40 mg/day previous 3 days (migraine), and on *Hypericum* for one month.
Symptoms: Epileptic fit with clonic convulsions, mental slowness, tremor of fingers, slightly elevated temperature, diffuse myalgia. Highly elevated levels of creatine kinase and D-dimer. The medication was stopped. After 10 days the blood examination was returned to normal values.

Evans (2008) replied to the findings by Bonetto *et al.* (2007). In the opinion of Evans the authors did not rule out other possible reasons for the presented symptoms. In the opinion of Evans the symptoms would fit much better to an infectious aetiology than to a serotonin syndrome.
The author revised all cases reported from the FDA on serotonin syndrome. Out of the alleged 29 cases only 7 cases met the Sternbach criteria for serotonin syndrome, but no case met the Hunter criteria. In the opinion of Evans it is premature to give a warning when more than 1 million patients have been exposed to the drug combinations (triptans and SSRI) with only 7 cases meeting just one set of criteria.

Assessor's comment: Bonetto is of the opinion that Hypericum is an inhibitor of CYP3A4 like fluoxetine. This wrong fact is used by Bonetto to make the serotonin syndrome more plausible. In fact Hypericum should counteract the inhibition of CYP3A4 by fluoxetine.

Waksman *et al.* 2000 published a case report of an assumed serotonin syndrome. The patient took *Hypericum* 600 mg/day (no further details), discontinued 3 days prior to presentation and paroxetine 20 mg on the day of presentation. Symptoms: restlessness, uncontrollable movements of all four extremities. These symptoms were classified as serotonin syndrome.

Assessor's comment: It is more than doubtful that after discontinuation of Hypericum such symptoms are causally related to Hypericum. The mentioned adverse reactions are known for paroxetine too.

Based on the original descriptions of serotonin syndrome (fatal reactions to serotonergic compounds) in animal studies and fatal human cases with interactions between MAO inhibitors and serotonergic compounds Fischer (1995) proposes to use the term 'serotonergic reaction' for such cases and reserve the term 'serotonin syndrome' for the most severe life-threatening cases of the spectrum of serotonergic reactions.

The interpretation of the results of drug-drug-interaction studies is discussed controversially. With respect to FDA guidelines pharmaceutical industry proposes to classify a decrease in the midazolam AUC by less than 50% as a weak interaction, a decrease more than 50% as a strong interaction (Bjornsson *et al.* 2003).

Interactions with voriconazole
In a controlled, open-label study Rengelshausen *et al.* (2005) investigated effects caused by short-term and long-term intake of *Hypericum* extract. 16 healthy men stratified for CYP2C19 genotype received *Hypericum* extract LI 160 (3 x 300 mg / day) for 15 days. Single oral doses of 400 mg voriconazole were given before treatment (control), on day 1 and on day 15.
Day 1: Short-term clinically irrelevant increase in voriconazole parameters. This is limited to the absorption phase of voriconazole.
Day 15: Extensive reduction of voriconazole exposure

Interactions with methadone
Eich-Höchli *et al.* (2003) report about 4 patients in methadone maintenance treatment. After 14-47 days of treatment with *Hypericum* extract (LI160, 900 mg/day) the methadone concentration was reduced to 19-60% of the original concentration. 2 patients reported symptoms that suggested a withdrawal syndrome.

Interactions with digoxin:
Johne *et al.* (1999) performed a single blind, placebo controlled parallel study.
After achievement of a steady state for digoxin healthy volunteers received 0.25 mg digoxin per day either with placebo (n = 12) or combined with 900 mg *Hypericum* extract (LI 160, n = 13) for further 10 days.
10 days of *Hypericum* treatment resulted in a decrease of digoxin AUC by 25%. After multiple dosing a reduction in trough concentration (33%) and C_{max} (26%) was observed, the effects were time-dependent.

Mueller SC *et al.* (2004) studied the pharmacokinetics of digoxin determined in 96 healthy volunteers before comedication and after 14 days of comedication with *Hypericum*.
Medication, per day:

LI 160: 28.9 mg hyperforin, 2.5 mg hypericin, 95.4 mg flavonoids
Hyperforin-containing powder:
4 g per day: 21.1 mg hyperforin, 4.8 mg hypericin, 117.8 mg flavonoids
Hypericum oil: 3 x 2 capsules containing 200 mg oil extract each. 0.13 mg hyperforin, 0.016 mg hypericin, 0.007 mg flavonoids per day.
Tea (prepared from 1.75 g): 2 x 1 cup. 0.04 mg hyperforin, 0.6 mg hypericin, 71 mg flavonoids per day.
Hyperforin-reduced powder:
2 g per day: 0.3 mg hyperforin, 2.4 mg hypericin, 58.9 mg flavonoids
Fresh plant juice: 2 x 10 ml. 3.56 mg hyperforin, 0.58 mg hypericin, 93.6 mg flavonoids per day.
Ze117: 0.38 mg hyperforin, 0.34 mg hypericin, 55.8 mg flavonoids

Results:
Comedication with 2 g powder without hyperforin, tea, juice, oil extract, hyperforin-free extract (Ze 117), 1g or 0.5 g hyperforin-containing powder: No significant interaction
Comedication with LI 160: reduction of AUC -24.8%, Cmax -37%, Ctrough -19%.
Comedication with 4 g hyperforin-containing powder: Similar interaction compared to LI 106.

Interactions with theophylline:
Nebel *et al.* (1999) report a case of a 42 year old women who was stabilized to 2 x 300 mg theophylline daily. After some time the dosage was increased to 800 mg bid because the plasma concentrations were lower than desired. She took several other drugs, but the only change was the new addition of *Hypericum* extract (300 mg/day). After stopping *Hypericum* the plasma concentration of theophylline increased about 100% after 7 days.

As a consequence of this report Morimoto *et al.* (2004) investigated 12 Japanese male volunteers who received 3 x 300 mg *Hypericum* extract (TruNature), labelled as containing 0.3% hypericin. After 14 days they received a single oral dose of 400 mg theophylline. The treatment of *Hypericum* produced no significant difference compared to the control group.

Assessor's comment: Theophylline is metabolized via CYP1A2, which is not influenced by Hypericum (Wang et al 2001). There is no rationale for a pharmacokinetic interaction between Hypericum and theophylline.

Interaction with finasteride
Lundahl *et al.* (2009) investigated the influence of *Hypericum* extract (300 mg, bid, hyperforin content 4%) given for 2 weeks on the pharmacokinetic profile of finasteride. *Hypericum* lowered the Cmax to 42%, the AUC to 66% and the elimination half-life to 54% compared to values before *Hypericum* treatment. The hyperforin concentration in the plasma was 21±7 ng/ml after the last dose of *Hypericum*.

Interaction of the herbal tea
Alscher & Klotz (2003) published a case report that drinking of a herbal tea containing *Hypericum* resulted in a significant decrease of the blood level of cyclosporine in a kidney transplant patient. Five days after stopping tea intake the blood levels returned to previous levels.

Assessor's comment: No data are provided on the composition of the herbal tea and the dosage frequency. The data are in contradiction to other publications on the interaction potential of Hypericum tea.

An 80-year old man, previously on long-term digoxin treatment, started consuming *Hypericum* tea (2 litres per day). After cessation of consuming the tea digoxin poisoning developed (nodal bradycardia, bigeminy) (Andelic 2003).

II.3.3.5.3 Use in pregnancy and lactation

Grush *et al.* (1998) report of two pregnant women taking *Hypericum* extract (not more characterized, 900 mg/day). No signs of toxicity or other harmful effects are reported. Nonetheless the authors are concerned about the use of *Hypericum* instead of an established effective treatment because safety of *Hypericum* in pregnancy and lactation has not been established.

Klier *et al.* (2002) report from a mother with post-natal depression. She took 3 x 300 mg *Hypericum* extract (LI 160). Four breast milk samples were analysed. Only hyperforin is excreted into breast milk at a low level, hyperforin and hypericin were below the detection limit in the infant's plasma. No side effects were seen in mother or infant.

Lee *et al.* (2003) conducted a prospective, observational cohort study. 33 breastfeeding women received *Hypericum* (704.9 ± 463.6 mg/day, no further characterization) compared with 101 disease matched and 33 age and parity-matched nondisease controls.
No statistically significant differences in milk production, maternal adverse events and infant weight over the first year of life were observed.

Five mothers who were taking 300 mg of *Hypericum* extract (LI 160) 3 times daily and their breastfed infants were assessed by Klier at al (2006). Thirty-six breast milk samples (foremilk and hindmilk collected during an 18-hour period) and 5 mothers' and 2 infants' plasma samples were analyzed for hyperforin levels. Hyperforin is excreted into breast milk at low levels. However, the compound was at the limit of quantification in the 2 infants' plasma samples (0.1 ng/ml). Milk/plasma ratios ranged from 0.04 to 0.13. The relative infant doses of 0.9% to 2.5% indicate that infant exposure to hyperforin through milk is comparable to levels reported in most studies assessing anti-depressants or neuroleptics. No side effects were seen in the mothers or infants. The authors conclude that these results add to the evidence of the relative safety of St. John's wort while breast-feeding which was found in previous observational studies.

In a review Dugoua *et al.* (2006) searched 7 electronic databases and compiled data according to the grade of evidence found. The authors found very weak scientific evidence based on a case report that St Johns wort is of minimal risk when taken during pregnancy. There is *in vitro* evidence from animal studies that St John's wort during pregnancy does not affect cognitive development nor cause long-term behavioural defects, but may lower offspring birth weight. There is weak scientific evidence that the use of St. John's wort during lactation does not affect maternal milk production nor affect infant weight, but, in a few cases, may cause colic, drowsiness or lethargy. There is weak scientific evidence that St John's wort induces CYP450 enzymes, which may lower serum medication levels below therapeutic range; this may be of concern when administering medications during pregnancy and lactation. Caution is warranted with the use of St John's wort during pregnancy until further high quality human research is conducted in order to determine its safety. The use of St John's wort during lactation appears to be of minimal risk, but may cause side effects. Caution is warranted when using medications along with St John's wort.

Moretti *et al.* (2009):
In Canada 54 women who were exposed to *Hypericum* preparations during pregnancy were observed and the data compared to 108 women in 2 control groups (other medication for depression and healthy women). No difference in the rates of major malformations compared to the general population was observed (Moretti *et al.* 2009). No data on the type of the preparations and the posology are available.

Assessor's comment:
The data are not sufficient to recommend Hypericum during pregnancy.

II.3.3.5.4 Overdose

Karalapillai & Bellomo (2007) reported a case of overdose in suicidal intention of a 16-year-old girl. It has been reported that the girl had taken up to 15 tablets per day for 2 weeks and 50 tablets just before hospitalisation. Seizures and confusion were diagnosed, after 6 days the EEG was normal, no further seizures occurred in the following 6 months. The published data on the composition of the tablets are not clear ('300 µg tablets').

Assessor's comment:
In a personal communication the author confirmed that there is a typing error in the publication. The product contained 300 mg extract per tablet. These symptoms occurred therefore after ingestion of 4500 mg extract per day over a period of 2 weeks (approximately the 5-fold therapeutic dose) and an additional dose of 15000 mg extract (approximately the 17-fold therapeutic dose).

II.3.3.5.5 Drug abuse

II.3.3.5.6 Withdrawal and rebound

Beckman *et al.* (2000) conducted a telephone survey of 43 subjects who had taken *Hypericum* extract to assess demographics, psychiatric and medical conditions, dosage, duration of use, reason for use, side effects, concomitant drugs, professional consultation, effectiveness, relapse, and withdrawal effects. Most subjects reported taking *Hypericum* extract for depression, and 74% did not seek medical advice. Mean dosage was 475.6+/-360 mg/day (range 300-1200 mg/day) and mean duration of therapy was 7.3+/-10.1 weeks (range 1 day-5 yrs). Among 36 (84%) reporting improvement, 18 (50%) had a psychiatric diagnosis. Twenty (47%) reported side effects, resulting in discontinuation in five (12%) and one emergency room visit. Two consumers experienced symptoms of serotonin syndrome and three reported food-drug interactions. Thirteen consumers experienced withdrawal symptoms and two had a depressive relapse. These data suggest the need for greater consumer and provider awareness of the potential risks of *Hypericum* extract in self-care of depression and related syndromes.

Assessor's comment:
Details on the type of products used are missing. Data from a telephone survey should be assessed reluctantly.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

Friede *et al.* (1998) studied potential sedative effects of *Hypericum* in a placebo-controlled clinical study in cross-over design on 19 healthy persons over a period of 15 days.
Study medication: Ze117, 250 mg per coated tablet 2 times daily.
Ze 117 was shown to have no sedative effect in mental performance and reaction time tests under controlled conditions, so no impairment of the ability to drive vehicles or operate machinery is anticipated. In addition, cognition was not further impaired when *Hypericum* was administered concomitantly with alcohol (0.5‰ blood alcohol level).
Schmidt (1991) found in a placebo-controlled study (verum 17 paients, placebo 15 patients) that four week treatment with *Hypericum* extract LI 160 (900 mg daily) did not impair coordination, concentration and attention of patients.
In a double-blind randomized three-way cross-over trial with 18 volunteers Herberg (1994) studied the influence of Aristoforat (1 capsule contains *Hypericum* extract with 0.25 mg total hypericines, 3 capsules daily, 10 days) combined with alcohol (blood alcohol level of 0.57‰) on mental capability. Tests studied optical orientation, permanent concentration, acoustic reaction time, coordination of motor functions.
The authors did not find differences between placebo and verum.

Schmidt *et al.* (1993) investigated in a placebo-controlled double-blind study in 32 healthy volunteers the influence of alcohol intake and *Hypericum* extract on mental performance.
Group 1: 3 x 300 mg LI160 per day for 7 days; then 7 days placebo
Group 2: first placebo, then active treatment

After consumption of alcohol (blood alcohol concentration between 0.045 and 0.08%) psychometric tests were performed on day 7 and on day 14. Interactions between *Hypericum* and alcohol on the level of psychomotor and mental performance can be ruled out. The authors suggest that *Hypericum* can be used safely when driving or using machines.

Assessor's comment: The conclusions are only partly correct. The data suggest that additionally to alcohol there is no impairment on mental performance. Only the studies of Friede et al (1998) and Schmidt (1991) studied the influence of Hypericum alone.Considering the small number of treated persons and the findings on sedation in animals of Girzu et al (1997) it can be concluded that adequate studies in order to clarify this aspect are missing.

II.3.3.6 Assessor's overall conclusions on clinical safety

The adverse events observed in clinical trials which are most probably linked to the study medication are in general mild, the frequency is considerably lower in comparison to synthetic antidepressants. The induction of CYP3A4 is well documented; the amount is directly correlated with the content of hyperforin in the herbal preparation. Pharmacokinetic interactions are documented for several drug substances metabolised via CYP3A4 having with a narrow therapeutic range. *Hypericum* extracts should not be used concomitantly with these substances. Adequate studies with extracts with low hyperforin content which could justify exemptions in the wording of contraindications, special warnings and in the interactions section of the monograph are missing. Nevertheless, the risk / benefit assessment favours the benefits of the *Hypericum* dry extracts.
The induction of the CYP3A4 is reversible within approximately 1 week after stopping ingestion of *Hypericum* extracts.
No influence on the mental performance at least in case of low-hyperforin extracts was observed. *Hypericum* extracts do not additionally impair mental capability in persons after alcohol intake.
The only risk of the cutaneous application of *Hypericum* oil seems to be the phototoxicity when treated skin is exposed to intense sunlight. A special warning should inform the patient.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Dry extracts of *H. perforatum* demonstrated superiority over placebo and non inferiority against standard medication in mild to moderate major depression in several controlled clinical trials. Therefore these types of extracts are proposed for 'well-established use'. The herbal tea and other mostly liquid extracts orally applied have a long tradition in folk medicine for the treatment of low mood, anxiety, to 'strenghten the nerves'. Provided that the duration of use is restricted to several days the traditional use of such herbal preparations can be granted. The cutaneous application of oil preparations is plausible based on pharmacological tests.

Benefit – Risk – Assessment
Well-established use:
Numerous clinical trials have shown the efficacy of herbal preparations containing *Hypericum* in the respective indications. A comparison with therapeutic alternatives reveals that for many herbal preparations containing *Hypericum* a non-inferiority compared to synthethic antidepressants could be demonstrated.
Hyperforin, which may be present in the herbal preparations, is responsible for interactions with other drug substances which are metabolized by certain CYP450 isoenzymes. Nevertheless, the rate and severity of adverse effects was clearly lower for *Hypericum* than for synthetic antidepressants (Schulz 2006c). Therefore the well-established use can be recommended for the herbal preparations, indications and posologies given in the monograph.

Traditional use:
At least in the alpine regions of Central Europe *H. perforatum* is the most important and most frequently used herb in traditional medicine.

Oral administration:
The considerable appreciation of *Hypericum* in traditional medicine and pharmacological data make the use in the proposed indication plausible.
Possible risks with the oral administration of preparations of *Hypericum* are related with pharmacokinetic interactions which are caused by the constituent hyperforin. The extent of the induction of the metabolic enzymes is dose-dependent and time-dependent. The oral use for the traditional preparations is limited with 2 weeks. This duration of use may be sufficient for the induction of the activity of the CYP-enzymes in the case of high-hyperforin preparations.

Interaction studies with digoxin (e.g. Mueller SC *et al.* 2004) revealed that a daily intake of less than about 5 mg hyperforin did not induce the enzyme activity significantly. The amounts of hyperforin administered with the herbal tea, the expressed juice or the powdered herbal substance are clearly below this limit.

Herbal preparation	DER	Max. daily dosage	Daily intake of hyperforin (according to published data (Müller at al 2004))
C (oil extract)	1:13	600 mg	0.65 mg
H (expressed juice	1:75	30 ml	5.34 mg
I (tea)		corresp. 6 g herbal substance	0.07 mg
J (powder)	Herbal substance	1000 mg	5.3 mg

The liquid extracts and tinctures are prepared with ethanol 50% (v/v). With this extraction solvent only about 20% of the hyperforin present in the herbal substance can be extracted (Meier 1999). The usual content of hyperforin in the herbal substance is about 0.5%, however amounts up to 4% are published. The calculation in the table below indicates that in the case of 20% extraction rate the daily intake of hyperforin is clearly below 5.3 mg when a typical herbal substance is used for extraction. But even in the worst case (4% hyperforin in the herbal substance) the amounts are only slightly above the limit. In this calculation the poor stability of hyperforin in liquid extracts is not considered. Therefore the actual amounts will be clearly lower.

Herbal preparation	DER	Max. daily dosage	Daily intake of hyperforin (0.5% in herbal substance = real case)	Daily intake of hyperforin (4% in herbal substance = worst case)
D	1:10	12 ml	1.12 mg	9.6 mg
E	1:5	4.5 ml	0.9 mg	7.2 mg
F	1:2	3.6 ml	1.8 mg	14.4 mg
G	1:6	4 ml	0.66 mg	5.3 mg

It is known that extracts prepared with ethanol 50% (v/v) contain less than 1% of hyperforin (Blaschek *et al.* 2008). With the extraction solvent ethanol 38% (m/m) (= ethanol 45% v/v) not more hyperforin should be expected in the traditional herbal preparation A. At the maximum daily dosage of 360 mg an amount of 3.6 mg hyperforin will be administered.

Herbal preparation	DER	Max. daily dosage	Hyperforin content extract	Daily intake of hyperforin
A	4-7:1	360 mg	max. approx. 1.6%	3.6 mg

For comparison: With a typical daily dose of 900 mg of hyperforin containing dry extracts approximately 27 mg of hyperforin are administered.

It can be concluded that the daily intake of hyperforin of all herbal preparations listed under traditional use are unlikely to induce enzyme activity when administered in the proposed posology and not longer than 2 weeks. However, a safety margin should be considered. Therefore the daily uptake of hyperforin with traditional herbal medicinal products should be limited to a maximum of 1 mg. With the low intake of hyperforin combined with the short duration of use clinically relevant interactions

are not likely to occur based on the current scientific knowledge. Under these circumstances the risk associated with traditional herbal preparations is acceptable.

Cutaneous administration:
The use of liquid *Hypericum* preparations in the mentioned indication is documented for a long period. Based on pharmacological data the use in the indication is plausible. Beside the risk of increased photosensitivity of the treated skin areas no concerns are known. The risk is at an acceptable level for traditional herbal medicinal products.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPHS ON *HYPERICUM PERFORATUM* L. HERBA[4,5]

III.2 LITERATURE REFERENCES

[4] According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2)

[5] According to the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2)