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**OVERVIEW OF COMMENTS RECEIVED ON
COMMUNITY HERBAL MONOGRAPH ON
HYPERICUM PERFORATUM L., HERBA
(EMA/HMPC/101304/2008)**

This document was valid from 12 November 2009 until 23 November 2022.

Table 1: Organisations and/or individuals that commented on the draft 'Community herbal monograph on *Hypericum perforatum* L., herba' as released for public consultation on 6 November 2008 until 15 March 2009.

Organisation
1 Willmar Schwabe GmbH & Co KG, D-76227 Karlsruhe, Germany (Schwabe)
2 AFSSAPS (French Health Products Agency)
3 Gesellschaft f. Phytotherapie e.V. Prof. Volker Schulz (Schulz)
4 ARKOPHARMA Laboratories, Lid de Carros le Broc, 1ère avenue, 2709m, 06510 Carros, France (Arkopharma)
5 Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicines Agency)
6 R&D PHARMA S. A. M., MC-98000 Monaco (R&D)
7 Farmedica d.o.o., Leskoskova 12, 1000 Slovenia (Farmedica)
8 Belgian Federal Agency for Medicinal and Health Products (Belgian Medicines Agency)
9 National Agency for Medicines Finland (NAM)
10 Polish Medicines Agency
11 Aykler (MCM Klosterfrau), Gerlach
12 Kooperation Phytopharmaka, Plittersdorfer Str. 218, 53173 Bonn (Koop Phyto)
13 AESGP, 7, Avenue de Tervuren, BE-1040 Brussels
14 Association of Natural Medicine in Europe (ANME), D-61137 Schöneck, Germany
15 ESCOP (European Scientific Cooperative on Phytotherapy), Argyle House, Gandy Street, Exeter, Devon EX4 3LS, United Kingdom
16 NCA Hungary

Table 2: Discussion of comments

GENERAL COMMENTS	
Comment and Rationale	Outcome
<p>We are of the opinion that published data could only support a traditional use and that provided scientific data are currently insufficient to recognize SJW preparations as well-established herbal preparations. In particular, efficacy of SJW in major depressive episode (MDE) is insufficiently demonstrated.</p> <p>The arguments are the followings:</p> <p>Heterogeneity of methodological approaches, in particular regarding inclusion criteria, sample size, difference in doses tested without satisfactory dose range study make difficult the assessment of results from meta-analysis (Linde 2007).</p> <p>Heterogeneity in results and in effect size is not clearly explained, and some well-conducted studies with sufficient number of patients failed to demonstrate statistically significant difference (HDTSG, 2002; Montgomery and al., 2000), when other (Lecrubier and al. 2002) only showed minimal difference.</p> <p>Validity of results is questionable in some positive studies due to a minimal or absent placebo response (Schrader and al. 1998), while the placebo response is generally high in studies in MDE.</p> <p>The efficacy / safety balance in the elderly has not been satisfactorily addressed.</p> <p>In case of positive opinion dealing with a well-established use status, we have some proposals of important changes for the monograph text.</p>	<p>In the opinion of the HMPC the criteria for well-established use are fulfilled for several extracts of Hypericum. Although the coherence of scientific assessment may be questioned, the overall evidence as published in the meta-analysis of Linde (Linde 2008) supports well-established use in the proposed indication.</p> <p>The proposed changes for the part of the well-established use in the monograph will be considered.</p>
<p>Introduction:</p> <p>According to a not yet published database, which was the database of a doctors theses 2008 by Gerlach, mentioned a several times in this draft – the „Volksmed“ Database, which comprises widespread the traditional use of plants, their indications, the mode of use etc. of Austrian rural population – Hyperici herba is the most important used medicinal remedy of Austrian traditional medicine. The contents of this database was collected by Austrian students between 1983 and 1995 in rural parts of Austria in order to save knowledge of the traditional medicine.</p> <p>So far to explain the following complaint.</p> <p>Function of HMPC-Monographs</p> <p>To our understanding a draft to a HMPC-monograph (traditional use) should collect data which support the traditional use of a plant and the evidence to be used longer than 30</p>	<p>It is not the primary aim of a community monograph to save knowledge on the traditional use of herbal medicines. Community monographs are based on the long standing medicinal use of clearly defined herbal preparations. During the consultation phase everybody is encouraged to submit details on herbal preparations and indications which have not yet been included in the monograph. All preparations and indications fulfilling the criteria laid down in the legislation will be considered.</p> <p>The traditional use of Hypericum oil in myalgia and rheumatism is already recognised from literature.</p>

years. The data must not contain a specific amount or quality. Though, the indications and traditional uses should be documented to be obtained and preserved for past and further preparations and generations.

To be clear: Traditional medicine is mostly orally passed on knowledge. The contents depend on circumstances like landscape, climate, economic conditions, distance from cities etc and vanishes. Moreover The National Agency for the Intangible Cultural Heritage/UNESCO is considering traditional medicine worth of protection worldwide!

Therefore it seems appropriate to the HMPC-monograph to collect and save the medicinal knowledge in accordance with the advice and efforts of the UNESCO. Traditional medicine which is in most of the cases older than centuries must be protected and handed it on to next generations as one of the most important basics of narrative medicine which is the counterbalance to evidence based medicine special in cases of paediatric use. It cannot be that knowledge of centuries and generations should be ignored in the future forcing thousands of children in clinical studies under the criteria of evidence based!

Indications - Improper abbreviations

Furthermore in the present draft indications are roughly abbreviated – without given reasons.

Patient groups are reduced to adults although there is evidence that the plant and preparations were used in children, pregnant women and while breastfeeding too.

Hypericum is traditionally used not only to cure depression (to correct Länger) but also to „calm nerves“ (not to confuse with neuropathie), insomnia and tranquilization (Länger:

‘Weak nerves’, vegetative dystonia)

All other indications in oral therapy for example like gastrointestinal disorders, hepatobiliary and renal disorders, urinary disorders or endocrine disorders have to be seen in this context – they are all described for decades well documented in the references of the current monograph.

By the way, the most important application in Austrian traditional medicine is the external use of Hyperici oleum and not only in the proposed indications of this monograph for the treatment of minor inflammations and healing of minor wounds but also in the traditional indications of myalgia, rheumatism, lumbago, ischialgia neuralgia and orally in abdominal pain.

However, for traditional use in the sense of the EU legislation a plausibility of the effects has to be given. Based on the published data on the constituents of Hypericum oil there is no rationale for the use in myalgia or rheumatism.

The use in children will be discussed at the relevant section in this document.

This in the literature established wordings does not mean that in accordance with the NtA, volume 2A, chapter 1, point 3.4 it might be not possible to change them in such a way that the products will claim the OTC-status

Its simply true that mode of actions are mostly not known till now and that there is a lack of praeclinical and clinical data but this is not the aim of this monograph for prove traditional use and beyond is not in accordance with the NtA, volume 2A, chapter 1, point 3.4 which clearly lays down, that “long tradition makes it possible to reduce the need for clinical data, in far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience as testified by bibliography or expert evidence. Claimed indications must be exclusively appropriate to traditional herbal medicinal products, which by virtue of their composition and purpose, are intended and designed fur use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.”

Further on “.....Another major task of the HMPC is to establish community herbal monographs for the application of both the traditional and well-established use provisions and to serve as a basis for simplified registration or bibliographical marketing authorisation applications.”

To annihilate all other indications and ways of applications means to vaste possible resources, disregard the intentions of the UNESCO in a very brute manner.

Scientific studies established in the last years mainly concentrated on depression for the time giving as mentioned in this monograph. This might be fundamental for well-established use and full applications but not for traditional use in the light of narrative based medicine as accomplished above.

Implementing this draft will cause the completely lost of ancient knowledge and experiences forcing pharmaceutical industry to claim only the accepted indications and patient groups by new applications in the future, reducing established and well-known products on this new way or in worth cases, loosing active marketing authorisations by not fulfilling these criterias.

Conclusio

So the authors urgently request the scientific board in accordance with the Nta, volume 2A, the advices of the UNESCO to protect all the described indications orally as well as topical, including the application in the paediatric population by this monograph now

<p>and for further generations furthermore the current wide variability of herbal medicinal products in the EU memberstates.</p>	
<p>In general, it has to be remarked with respect to the well-established use, that clinical data support the use in the treatment of mild to moderate depressive episodes. The fact, that the vast majority of clinical studies has been conducted not in patients with mild, but with mild to moderate or moderate depression, and that efficacy was comparable with standard antidepressants authorized for the treatment of major depression, including moderate depression, leads to the conclusion, that moderate depressive episodes are a necessary part of the therapeutic indication.</p> <p>With respect to the qualitative and quantitative composition, a limitation of well established use to preparations with hyperforin contents of at least 2 % seems to be not justified. This would be in contrast to the specification in the Ph Eur extract monograph on Hyperici herba (07/2008:1438), and is not backed by published data on hyperforin contents of several extracts with clinically proven efficacy in the above mentioned indication, as they have mean contents of hyperforin in the range of or below 2 %.</p> <p>With respect to the interactions it has to be emphasized, that interactions are mainly a function of the daily hyperforin dose applied. As a number of preparations in traditional use contain low drug equivalents and hyperforin amounts per daily dose, preparations with a content of 1 g herbal drug equivalent or below should be exempted from all contraindications or warnings based on an interaction potential of the drug.</p> <p>The assessment report, which is highly appreciated, in particular that it has been published simultaneously with the monograph, will be commented separately.</p>	<p>The mentioned issues will be discussed at the relevant section of this document.</p>
<p>The National Competent Authority of Hungary insists on the opinion that neither the proposed indication (mild to moderate depressive episode) nor reference to well-established use is acceptable.</p> <p>Hypericum extracts are not proven to be effective in relapse prevention longer than one decade.</p>	<p>Not endorsed.</p> <p>The time over which the dry extracts have been used in the proposed indication for well-established use is clearly longer than 10 years.</p>

SPECIFIC COMMENTS ON TEXT Well-established use		
Section number and heading	Comment and Rationale	Outcome
<p>2. Qualitative and quantitative composition</p> <p>Well-established use</p>	<p>Comments:</p> <p>In the list of herbal preparations, the extract WSPP® 5570 is not covered. This extract is approved in 10 EU countries.</p> <p>WS® 5570 is a hypericum extract with DER 3-7:1, 0.10-0.30% hypericin, 3.0-6.0% hyperforin and not less than 6.0% flavonoids (not less than 1.5% rutin), extraction solvent methanol 80% (v/v). It complies with the recently published Ph. Eur. monograph "<i>St. John's wort dry extract, quantified</i>". A distinguishing feature of this extract is the addition of ascorbic acid during production, as a protectant for certain sensitive constituents.</p> <p>We request the inclusion of this herbal preparation in the monograph under „well established use“. A separate listing of this herbal preparation appears to be of special importance, as it is the only extract for which the indication „mild to moderate depressive episodes“ is justified (please refer to the comments on 4.1.).</p> <p>Proposed change:</p> <p>We propose to add</p> <p>as “Herbal preparation C”:</p> <p>Dry extract (DER 3-7:1), extraction solvent methanol (80% v/v), hypericin: 0.10-0.30%, hyperforin: 3.0-6.0%, flavonoids: minimum 6.0 % (rutin: not less than 1.5%), produced by adding ascorbic acid “.</p> <p>The consecutive numbering of the other herbal preparations would have to be adapted accordingly.</p>	<p>The mentioned extract is extract B) under well-established use in the draft monograph. The slight difference in the DER is caused by different data from literature and will be corrected.</p> <p>The clinical data to this extract are already considered and evaluated in the assessment report.</p>

<p>2</p>	<p>In paragraph II.1.1.2 Herbal preparation(s) of the Draft Assessment Report on “Community Herbal Monograph on <i>Hypericum perforatum</i> L., Herba” (Doc. Ref.: EMEA/HMPC/101303/2008), the statement regarding the <u>Influence of the extraction solvent on the composition of the extract</u> (page 9/65) indicates that the alcoholic degree of the solvent and the hyperforin and adhyperforin extraction are correlated, the higher the alcoholic degree is, the higher the hyperforin and adhyperforin contents are.</p> <p>According to this statement, there are no reasons not to include the Herbal preparation B [Dry Extract (DER 3.5-6:1), extraction solvent Ethanol 60% (m/m)] of the Traditional use section in the Well-Established use section, knowing that alcoholimetric tables from European Pharmacopoeiae indicate that 60 % (m/m) corresponds to 67.7 % (V/V) and therefore that an extraction with Ethanol 60 % (m/m) will extract at least as much hyperforin and adhyperforin as the same extraction with Ethanol 60 % (V/V).</p> <p>Providing that this extract [Ethanol 60 % (m/m)] has the same ranges of tracers [hypericin 0.10-0.30 %, hyperforin > 2 %, flavonoids > 6 %], its posology should be the same as the Herbal preparation F of the section Well-Established use which is the following:</p> <p>Single dose : 300 to 600 mg Dosage frequency: 2-3 times daily Daily dose : 600 to 1200 mg</p> <p>Comments: According to the above mentioned general comment</p> <p>Proposed change :</p> <p>Addition in the Well-Established use column of paragraph 2. QUALITATIVE AND QUANTITATIVE COMPOSITION</p> <p>ii) Herbal preparation</p> <p>H) Dry extract (DER 3.5-6:1), extraction solvent ethanol (60% m/m), hypericin 0.10-0.30%, hyperforine > 2 %, flavonoids > 6 %</p>	<p>Endorsed.</p> <p>The respective extract will be deleted from traditional side. The list of extracts on the well-established use side will be shortened, similar extracts will be combined. Therefore the mentioned extract will be combined with the other extracts prepared with ethanol 60%.</p>
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2	<p>We suggest to adjust the limit for Hyperforin to the Eu.Phr.monograph, “< 6%”. Limit value is documented by several publications.</p>	<p>As criticised by several interested parties the mentioned limits of active markers and analytical markers will be deleted.</p>
2	<p><u>Well-established use</u></p> <p>The proposed classification of the existing preparations gives a good overview, but in some parts is not yet in accordance with the available data for the preparations on the market. We suggest a modification of the text as follows, giving two alternative comments.</p> <p>Comment, version No. 1, relates to the actual outline of the preparations, given in the monograph draft (A to G) and the respective outline in the assessment report (A to I). Instead of this outline we clearly prefer a simplified outline, which would better comply to the fact, that the preparations A to H are differing mainly regarding the extraction solvent containing methanol or ethanol, but are otherwise essentially similar with respect to their composition as well as to the proof of efficacy in clinical studies. Such a simplified outline is given in version No. 2 of our comment.</p> <p>Comment, Version 1:</p> <p>A) Dry extract (DER 3-6:1), extraction solvent methanol (80 % v/v), total hypericins 0.10-0.30 %, hyperforin SS $\geq 2\% < 6\%$, flavonoids >6.0 %</p> <p>B) Dry extract (DER 4-7:1), extraction solvent methanol (80 % v/v), total hypericins 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %</p> <p>C) Dry extract (DER 3-6:1), extraction solvent ethanol (80 % v/v), total hypericins 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %</p> <p>D) Dry extract (DER 5-7:1), extraction solvent ethanol (60 % v/v w/m), total hypericins 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %</p> <p>E) Dry extract (DER 5-7:1), extraction solvent ethanol (60 % v/v),</p>	<p>Partly endorsed.</p> <p>The dry extracts prepared with ethanol differ in the DER, the strength of the extraction solvent and in the posology. Therefore not all ethanolic extracts will be combined.</p> <p>Preparation type H and I will be included.</p>

- total hypericins 0.10-0.30 % , hyperforin $\geq 2\%$ < 6 % , flavonoids >6.0 %**
- F) Dry extract (DER 2.5-5:1), extraction solvent ethanol (60 % v/v),
total hypericins 0.10-0.30 % , hyperforin $\geq 2\%$ < 6 % , flavonoids >6.0 %
- G) Dry extract (DER 5-8:1), extraction solvent ethanol (50 % v/v),
total hypericins 0.10-0.30 % , hyperforin $\geq 2\%$ < 6 % , flavonoids >6.0 %
- H) **Dry extract (DER 4-7:1), extraction solvent ethanol (50 % v/v),
total hypericins 0.10-0.30 % , hyperforin < 6 % , flavonoids >6.0 %**
- I) **Dry extract (DER 3.5-6:1), extraction solvent ethanol (60 % v/v),
total hypericins 0.10-0.30 % , hyperforin < 6 % , flavonoids >6.0 %**

Rationale:

For several of the extracts mentioned above, published data do not support a lower limit of hyperforin of 2 %. This applies to the extracts C) and G), as documented in the publications of Melzer et al. 1998, Wurglics et al. 2001a, Wurglics et al. 2001b, Volz and Zeller 2000) which mention hyperforin contents between 1.5 and 2.4 %, and also to the extract H), for which data in the assessment report document a hyperforin content even below even 0.1 %. All these extracts have been successfully studied in clinical trials supporting a well established use.

This is reflected in the new monograph on St. John´s wort dry extract, quantified, Ph Eur 07/2008:1874, corr. 6.3. In case of the flavonoids and hypericin, the HMPC monograph is already adapted to this new Ph Eur monograph. In case of hyperforin the limits should therefore be adapted to this monograph, too, as a deviation is scientifically not justified, and as Ph Eur is even legally binding. We therefore propose to give a maximum concentration of 6 % should be given for hyperforin and to delete the minimum concentration of > 2 %. This

takes into account the properties of the extracts clinically tested and the known properties of hyperforin as an inductor of dose dependent drug interactions. In addition we propose to use the term “total hypericin” instead of “hypericin”, thereby adapting the terminology to that of the the Ph Eur monograph. The use of the term “total hypericin” makes apparent, that the component pseudohypericin is also subsumed in the declarations of the respective preparations.

Extract H, which is already listed in the assessment report, should not be excluded from the extracts listed under well established use. In contrast to the reasons for exclusion given in the assessment report, information on the extraction solvent (50 % ethanol) is consistent, based on information authorized by swissmedic and freely available from the manufacturer.

Extract I is contained in several products on the market with a single dose of 425 mg and a daily dose of 850 mg, as e.g. in Felis 425 Hartkapseln, or with a single daily dose of 650 mg as e.g. in Felis 650 Filmtabletten, for which a clinical study (Bracher et al. 2001) proves efficacy. This study was also included in the recently published Cochrane analysis (Linde et al. 2008).

In conclusion, for each of the extracts included in the list above, studies are existing which prove efficacy in mild to moderate or in moderate depressive episodes, thus supporting its well established use in these indications.

Comment, Version 2

Rather than splitting the preparations to a number of categories which do not differ in a pharmaceutically or clinically meaningful way, we prefer merging them to two larger groups:

Dry extract (DER native 3-6:1), extraction solvent methanol (80 % v/v) containing hypericin 0.10-0.30 %, hyperforin < 6 %, flavonoids >6.0 %, or

	<p>dry extract (DER native 2.5-8.1), extraction solvent ethanol (50-80 % v/v), containing hypericin 0.10-0.30 %, hyperforin < 6 %, flavonoids >6.0 %</p> <p>Rationale: The herbal preparations A-G and additionally the herbal preparations H and I from our comment, version 1, as the active substances of the respective herbal medicinal products are all essentially similar with respect to their pharmaceutical quality (Gaedcke 2003, Pharm Unserer Zeit 32, 192-201).</p> <p>The pharmaceutical quality is defined by the Ph Eur monographs on the herbal drug (01/2008:1438) and the herbal drug extract (07/2008:1874), so that the range of extracts complying to them is in accordance to the range of extracts with well established use. Furthermore, the DER should refer to the native extracts.</p> <p>The quality of the different herbal preparations of well established use in the indication mild to moderate depressive episodes is sufficiently similar, so allowing to merge them. The assessment report is based on the analysis of Linde (2007), which showed efficacy for each of the preparations A to F separately. Now Linde et al have published a Cochrane report pooling the evidence for all extracts in well established use including A-I (Linde et al. 2008). They have shown now, that there are no differences in the efficacy of these preparations. The logical consequence is to reclassify these extracts together and to characterize the groups by extraction solvents and ranges of DER native, following the comparison of pharmaceutical equivalence of Gaedcke (2003).</p>	
2	<p>General comments: In case a preparation proposed for the well-established medicinal use is not accepted for this category it should in any case be included under traditional use.</p>	See above.

<p><u>Well-established use</u></p> <p>ii) Herbal preparations</p> <p>Instead of listing different extracts A) to G) (or H), respectively), we suggest to summarize the existing extracts in two groups:</p> <p>The extracts should comply with the Ph. Eur. monograph "St. John's wort dry extract, quantified" (ref. 07/2008:1874 corrected 6.3).</p> <p>A) Dry extracts, extraction solvent methanol (80 % v/v), range of DER 3-7:1*, hypericin 0.10-0.30 %, hyperforin < 6 %, flavonoids > 6.0 %</p> <p>B) Dry extracts (DER 2.5-8:1), extraction solvent ethanol (50 - 80 % v/v) or ethanol (50 – 80 % m/m), hypericin 0.10-0.30 %, hyperforin < 6 %, flavonoids > 6.0 %</p> <p>and delete the rest.</p> <p>*) This ratio also comprises a DER of 4.1-7.1:1 which was expressly required by the German health authority for the preparation TEXX 300.</p> <p><u>Rational:</u> Upon closer inspection of the extract compositions, the phytochemical properties and the comparison with the dose regimens it becomes clear that the detailed list proposed in the draft monograph is not too helpful. E.g., the well-established preparations D and E are apparently</p>	<p>Due to inconsistent information on the content of hypericin, hyperforin and flavonoids the limits will be omitted in the monograph.</p> <p>The fact that in a member state a product has been authorized under well-established use, does not necessarily mean that this product has to be included in the well-established use part of the monograph. The clinical data for all extracts have to be evaluated according to current guidelines. Only extracts with sufficient evidence of efficacy can be included.</p> <p>The proposed combination of herbal preparations in the well-established use part of the monograph includes the mentioned preparations.</p> <p>The extract Ze 117 complies with the definition in the monograph of the European Pharmacopoeia and will be included. As mentioned in section 6 of the monograph the amount of hyperforin has to be declared for all extracts.</p>
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¹ – Cesradyston 425 (DER 3.0-6.0:1)
– Felis 425/650 (3.5-6.0:1; applied in the above-mentioned clinical studies)
– Hewepsychon uno (DER 3.5-6:1)
– Hyperforat 250 (3.5-6:1)
– Johanniskraut 650 1A (3.5-6:1)
– Johanniskraut AL (3.5-6:1)
– Johanniskraut CT (3.5-6:1)
– Johanniskraut ratiopharm 425 (3.5-6:1)
– Johanniskraut Sandoz 425 (3.5-6:1)
– Neurovegetalin 425 (3.5-6:1)
– Spilan 425 mg Kapseln (3.5-6:1)
– Tonizin 425 (3.5-6:1).

identical, and the difference can only be seen when the dose scheme is taken into account. This problem should be mended by giving a dose range. Furthermore, efficacy of St. John's wort has been demonstrated with a wide range of preparations, including some which are listed in the draft as "traditional". It does not appear appropriate to state in a monograph that an extract with the solvents ethanol 60 and 80 % and a DER covering a range of 3-7:1 has an acceptable level of efficacy, but an extract with 70 % ethanol and the same DER is attached to the traditional use. In addition, the "traditional" preparation B is in fact well-established with the dose of 3x300 mg.

We therefore propose to summarize all extracts with proven efficacy based on scientific literature data and distinguish only according to the used extraction solvent (methanol or ethanol, respectively) between the two preparations A (including former preparations A and B) and B (including former preparations C-G, plus the former "traditional" preparation B as well as the preparations H and I not included so far (see also comments on the draft Assessment Report pp 40/65, 53/65 for further details).

Furthermore, the limits for hypericin, hyperforin and flavonoids are not based on bibliographic evidence and, in case of hyperforin, partly contradicts the valid version of the monograph on *Hyperici herba* of the European Pharmacopoeia (EP) (ref. 07/2008:1438), where the contents of "total hypericins, expressed as hypericin (..): 0.10 per cent to 0,30 per cent (dried extract); flavonoids, expressed as rutin (..) minimum 6.0 per cent (dried extract); hyperforin (..): maximum 6.0 per cent (dried extract)" are given. However, some of the clinical studies mention flavonoid or hyperforin contents, in case of the latter including some in the range of, or even below 2 %. The definition of well-established use must necessarily be made based on literature data, not on the specifications of the EP, as this may have changed since the studies were made with given preparations. With a reference to the EP especially the levels of hypericin and flavonoids will not require any further definition. For hyperforin, it is sufficient to give a maximum content of hyperforin in the extract (e.g. < 6.0 %).

In case the HMPC prefers a detailed list of existing preparations, the following approach seems to be acceptable, based on the subdivision

in herbal preparations A-G originally given in the draft. Then, at least for the extracts C) and G) the hyperforin concentration should be given as < 6 % (instead of > 2 %, which does not comply with analytical properties of the extract (see *comments on the draft assessment report* for further explanations). However, it would be more consistent in general to adapt the hyperforin content for all preparations to the EP monograph for St. John's wort dry extract, quantified (ref. 07/2008:1874 corrected 6.3):

- A) Dry extract (DER 3-7:1), extraction solvent methanol (80 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- B) Dry extract (DER 4-7:1)*, extraction solvent methanol (80 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- C) Dry extract (DER 3-6:1), extraction solvent ethanol (80 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- D) Dry extract (DER 5-7:1), extraction solvent ethanol (60 % m/m), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- E) Dry extract (DER 5-7:1), extraction solvent ethanol (60 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- F) Dry extract (DER 2.5-5:1), extraction solvent ethanol (60 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- G) Dry extract (DER 5-8:1), extraction solvent ethanol (50 % v/v), hypericin 0.10-0.30 %, hyperforin $\geq 2\% < 6\%$, flavonoids >6.0 %
- H) Dry extract (DER 4-7:1), extraction solvent ethanol (50 % m/m), hypericin 0.1 - 0.3 %, hyperforin < 6 %, flavonoids >6.0 %**
- I) Dry extract (DER 3.5-6:1), extraction solvent ethanol (60 % m/m), hypericin 0.1 - 0.3 %, hyperforin < 6 %, flavonoids > 6 %**

***) This ratio also comprises a DER of 4.1-7.1:1 which was expressly required by the German health authority for the preparation TEXX 300.**

Note: It should read "total hypericin" instead of "hypericin" according to the EP.

In addition, we would like to add the following explanation:

An analysis of the extract definitions given in the clinical trials reveals the following facts for the original proposition in the draft monograph:

Well-established use

- **Preparation A** (methanol 80 %, DER 3-7:1) corresponds to the extract LI 160 (Jarsin) for solvent, solvent concentration and DER. However, the quantity of >6.0 % of flavonoids cannot be substantiated by published data regarding the studies. In addition, a hyperforin content of ≥ 2 % is mentioned in only two clinical trials (Barnes et al. 2006; Hypericum Depression Trial Study Group 2002), although the value is confirmed in analytical studies (Melzer et al. 1998; Wurglics et al. 2001a; Wurglics et al. 2001b).

Preparation A also partly corresponds to the extract WS 5570 (DER 3-7:1, methanol 80 % v/v as in Neuroplant aktiv and SE Hypericum N) as indicated in some clinical trials (Kasper et al. 2006; Kasper et al. 2007). Hyperforin contents are indicated with 3-6 %.

In summary, the definition for preparation A seems to be correct where it relates to LI 160 and extract WS 5570. If the composition of preparation A is in fact correct, the two extracts are identical and do not require further differentiation.

- **Preparation B** (methanol 80 %, DER 4-7:1) corresponds to TEXX 300 (official declaration 4.1-7.1:1) and Neuroplant 300 N – the latter containing a different extract than Neuroplant 300 = WS 5572.

- The published study for TEXX 300 (Sepehrmanesh 1999) does not give values for hyperforin or flavonoids. Melzer et al. (1998) measured 2.53 % hyperforin, whereas Wurglics et al. (2001a, 2001b) found a range of 1.17 to 3.17 % hyperforin. The definition of >2 % hyperforin in the extract would therefore potentially exclude a well-established preparation by creating an artificial limit which is not based on clinical findings and which also introduces a new element not included in the dry extract monograph of the EP, where only an upper limit of hyperforin (6 %) is defined.

Preparation B also corresponds to LI 160 (Jarsin) according to indications given in one clinical trial (Mueller et al. 2004a) and analytical studies (Wurglics et al. 2001a; Wurglics et al. 2001b).

Preparation C (ethanol 80 %, DER 3-6:1) corresponds to the extract STW 3-VI (as in Laif 900). A hyperforin dose has not been specified in the clinical trial publications (Demling et al. 2004; Gastpar et al. 2005; Gastpar et al. 2006; Uebelhack et al. 2004). The definition of 2 % as a lower limit is not justified by scientific data (see *comments on the draft Assessment Report, page 46/65* for further explanations)

- **Preparation D** (ethanol 60 %, DER 5-7:1) corresponds to the preparation "Lo-Hyp" used in one study (Harrer et al. 1999). It also corresponds to the extract STEI 300 which was tested in a clinical trial (Philipp et al. 1999). No data is available supporting a limit for hyperforin and flavonoids. For preparation D, the extraction solvent has to be corrected from ethanol (60% v/v) to ethanol (60% m/m).

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Preparation E (ethanol 60 %, DER 5-7:1): A similar extract with ethanol 60 % v/v and a DER of 3-6:1) was not mentioned on the "well-established side" of the draft Community Herbal Monograph on *Hyperici herba*. This extract was positively tested in at least one double-blind clinical trial (Bracher 2001) and one open observational study (Müller 1998). The efficacy was confirmed by the most recent meta-analysis on the clinical trials with *Hypericum* in mild to moderate depression (Linde et al. 2008). The extract with a DER of 3-6:1 corresponds to many commercially available preparations¹. According to Melzer et al. (1998) the hyperforin content of corresponding preparations ranges from 2.3 % to 5.9 %. Wurglics et al. (2001) give values ranging from 0.91 % to 3.89 %.

- **Preparation F** (ethanol 60 %, DER 2.5-5:1) corresponds to the extract WS 5572. The comparison of hyperforin contents with data from the clinical trials shows inconsistencies: The older studies do not mention hyperforin at all (Reh et al. 1992). One study states 1.5 % of hyperforin (Kalb et al. 2001), other studies claim 5 % (Laakmann et al. 1998a; Laakmann et al. 1998b; Lemmer et al. 1999). The extract composition of WS 5572, may have changed over time regarding the hyperforin content.
- **Preparation G** (ethanol 50 %, DER 5-8:1) corresponds to the extract STW 3 (as in Laif 600 or Psychotonin Hartkapseln). Hyperforin contents are mentioned in one observational study with STW 3 (Volz and Zeller 2000; Zeller 2000), where a content of 1.8 % is stated (see *comments on the assessment report draft*, p 46/65, for further explanations).
- **Newly added: Preparation H:** Dry extract (ethanol 50 % m/m corresponding to *58 % v/v, DER 4-7:1). This preparation corresponds to the extract Ze 117, for which the efficacy has been demonstrated in clinical double-blind trials (Schrader et al. 1998; Schrader 2000; Woelk 2000). The hyperforin content of the extract has been in all studies < 1 %. In summary, Ze 117 fulfils the requirements of well-established use (> 10 years of commercial availability, efficacy clearly demonstrated in clinical trials).

* Details regarding the different declarations of the extract ZE 117, please see comments to the corresponding sections of the assessment report.

- **Newly added: Preparation I:** Dry extract (DER 3.5-6:1), extraction solvent ethanol 60 % m/m, hypericin 0.1 – 0.3 %, hyperforin < 6 %, flavonoids > 6 %. This dry extract (DER 3.5-6 : 1) is contained in many finished products in Germany with a Marketing Authorisation granted under Well-established use since more than 10 years. One example is "Felis 425" from HEXAL company. Further examples are "Johanniskraut Sandoz 425 mg" from Sandoz Pharmaceuticals GmbH and "Johanniskraut 650 – 1 A Pharma" from 1 A Pharma AG. The same extract is contained in "Deprim forte" from company LEK in Ljubljana which got a MA under Well-established use in Slovenia in 1998. Additionally the identical extract is contained in "Dr. Böhm Johanniskraut 425 mg Kapseln" in Austria. This is a well-established use MA granted to company Apomedica, Graz (see original German text below).

Suchergebnis: 1 bis 1 von 1.Dr. Böhm Johanniskraut 425 mg – Kapseln. Zulassungsnummer 1-23802. Zulassungsinhaber Apomedica Pharmazeutische Produkte GmbH, Roseggerkai 3,AT - 8011 Graz. Zulassungsdatum 05.10.2000. Verwendung Human. Packungen 30 Stück, Laufzeit: 36 Monate, 60 Stück, Laufzeit: 36 Monate, 90 Stück, Laufzeit: 36 Monate. Wirkstoffe Herba Hyperici (Auszug). ATC-Codes N06AX: Other antidepressants.

The products Felis[®] 425, Felis[®] 650, Johanniskraut Sandoz 425 mg and Johanniskraut 650 – 1 A Pharma contain dry extract, (DER 3.5-6:1), extraction solvent ethanol 60 % (m/m). Daily doses are 850 mg (Felis[®] 425, Johanniskraut Sandoz 425 mg) and 650 mg (Felis[®] 650, Johanniskraut 650 – 1 A Pharma). Felis[®] 425 and Felis[®] 650 as well as Johanniskraut Sandoz 425 mg and Johanniskraut 650 - 1 A Pharma available in the German market. Marketing authorisation of all products is based on a "well-established use" submission. The efficacy of this extract as a "well-established" preparation was already

	<p>confirmed at the time of registration. The indication and daily dose comply with the requirements of a "well-established" preparation and not with the requirements of a traditional use. The extracts listed in the monograph vary in their qualitative and quantitative composition depending on the polarity and selectivity of the extraction solvent used. Methanol 80 % as well as ethanol 60 % are as polar, unspecified solvents appropriate to dissolve the substances, required for efficacy. Their elution potency is comparable. The attached figure clearly shows that the extraction with different solvents leads to the same spectrum of substances (Enclosure 1).</p> <p>Based on these facts, there is no reason to classify the dry extract (DER 3.5-6:1), extraction solvent ethanol 60 % (m/m) as "traditional use", if others such as dry extract (DER 3-6:1), extraction solvent methanol 80 % (v/v) are included under "well-established use". The quality of this extract is based on the EP requirements.</p> <p>Conclusion: Taking into account that the elution potency of methanol 80 % v/v and ethanol 60 % v/v is comparable, and the fact that the dry extract (DER 3.5-6:1), extraction solvent ethanol 60 % (m/m), is used for products which are already registered as "well-established" products and correspond to the EP requirements, we propose to classify the dry extract (DER 3.5-6:1), extraction solvent ethanol 60 % (m/m), as "well-established use".</p>	
2	<p>a) Phytochemical definitions</p> <p>The draft monograph explicitly refers to the definitions given in the European Pharmacopoeia in the monograph "St. John's wort dry extract, quantified". This Ph. Eur. monograph defines extracts from <i>Hyperici herba</i> as follows:</p> <ul style="list-style-type: none"> -Extracts produced from the herbal drug by a suitable procedure using ethanol (50-80 percent V/V) or methanol (50-80 percent V/V). -0.1 to 0.3 percent total hypericins 	<p>Endorsed.</p> <p>The limits for hypericin, hyperforin and flavonoids will be omitted from the monograph.</p> <p>Similar extracts will be combined.</p>

- Min. 6.0 percent flavonoids, expressed as rutin.
- Maximum 6.0 percent hyperforin and not more than the content stated on the label.

Labelling of hyperforin is mandatory.

Since the draft monograph of the HMPC makes explicit reference to the monograph of the European Pharmacopoeia, the further definitions of the draft community monograph for well-established preparations do not add clarity, and partly even contradict the pharmacopoeial definitions.

There is no reason to define and repeat limits for hypericin, a constituent which is already regulated by the pharmacopoeial monograph, and which – for the same reason – does not even require explicit labelling. All references to hypericin levels can therefore be omitted in section 1 of the draft community monograph. There is no need for the repetition since the content of hypericin is already a precondition for acceptability, as defined by footnote 1 in the headline of this section. In addition, the pharmacopoeial monograph speaks of “total hypericins” – this distinction is not made by the draft community monograph. This contradiction is likely to cause regulatory problems, as manufacturers could not be compliant with both, the pharmacopoeial and the community monograph at the same time.

There is no reason to define and repeat limits for flavonoids. A content of >6.0 percent flavonoids is already part of the pharmacopoeial definition on which the community draft monograph is based. According to the European Pharmacopoeia quantified dry extracts do not even require labelling of flavonoids. The pharmacopoeial monograph does not define an assay on flavonoids. In addition, there is no bibliographic database for flavonoids contents in preparation for well-established use. Flavonoids are not mentioned in the available clinical trials from which well-established use is derived. Since the definition of flavonoids contents in the single preparations suggested by the draft community monograph is obviously not based on bibliographic data, it does not appear justified to put extra emphasis on the flavonoids in addition to the reference made to the European Pharmacopoeia in the headline. The definition

of >6.0 % flavonoids should be omitted in the draft community monograph as it does not add additional information.

Finally, the definitions of the draft community monograph made for hyperforin contradict the pharmacopoeial specification, and the realities of the available products. The European Pharmacopoeia limits hyperforin contents to maximum 6.0 percent, and requires a labelling of the values determined by an assay. Consequently, producers already have to state the hyperforin contents. This labelling is a necessary measure for the assessment of product safety – with the background of elevated hyperforin levels being responsible for the herb-drug interaction phenomena with *Hypericum*. The limit of >2 percent of hyperforin in all preparations defined as well-established in the draft community monograph is not consistent with the available bibliographic data. For many products hyperforin contents in the range between 1.5 and 2.5 percent have been found. The definitions of the draft community monograph could potentially lead an exclusion of products otherwise eligible for well-established use by the application of a too strictly defined criterion.

E.g., the following analytical results on hyperforin contents have been published for German-registered *Hypericum* products (Melzer et al. 1998; Wurglics et al. 2001a; Wurglics et al. 2001b):

Bardo H: 1.5 %
Helarium (DER 4.5-6.7:1, ethanol 60 %): 2.5 %
Hypericum Stada (DER 3.5-6:1): 1.9 %
Johanniskraut-Dragees SN (DER 4-6:1, ethanol 60 %): 2.3 %
Neurovegetalin 425 (DER 3.5-6:1, ethanol 60 %): 2.5 %
Texx 300 (DER 4.1-7.1 :1, methanol 80 %): 1.7-3.2 %
Tonizin forte (DER 3-6:1, ethanol 80 %): 1.7%.

While the compositions should fulfil the criteria of well-established use, these products might no longer be eligible for registration under the rules of well-established use if the definition of > 2 percent of hyperforin were made.

We recommend that the overly exact definition of hypericin, flavonoids and hyperforin contents be removed from the definitions. The reference to the European Pharmacopoeia is sufficient.

b) Extract definitions

The definitions of the extracts in both sections appear overly detailed. The most recent metaanalysis of the Cochrane collaboration has clearly demonstrated that efficacy may be expected from a wide range of extract compositions (Linde et al. 2008). This is also supported by the acceptance of extracts produced with 80 percent methanol, 50, 60 and 80 percent ethanol as a solvent. Correspondingly it is difficult to comprehend that similar preparations produced with 60 and 70 percent ethanol, respectively (preparations B and C in the section of traditional use) should not be acceptable as well-established, although there is clinical data demonstrating the applicability of such preparations against mild to moderate depression (Bracher 2001; Müller 1998). The study of Müller is not a double-blind trial, but since efficacy of similar preparations is amply demonstrated, there is no reason to expect a different outcome with this specific preparation, as confirmed by the positive double-blind study of Bracher.

The extract Ze 117 is missing in the list of well-established preparations, although clinical studies exist. Ze 117 is an extract practically devoid of hyperforin, produced with 50 % ethanol and with a DER of 4-7:1 (Schrader et al. 1998; Schrader 2000; Woelk 2000).

In addition to the question of comparability of extraction solvents, the details defined for the drug-extract ratios are also unrealistically narrow. E.g., preparations A and B (wellestablished) differ only in the drug extract ratio, which is 3-6:1 in case of preparation A, and 4-7:1 in case of preparation B. As the drug-extract ratio is predominantly a function of the plant material, very similar ratios must be expected with the same extraction solvent and the same type of plant material. The exact range indicated in drug registration is usually based on experience, and gives leeway to both sides to cover for biological variation. In the present case, the extracts of preparations A and B would have to be considered practically identical. It would therefore be sufficient to combine the two preparations into one statement: extracts produced with 80 % methanol, having a drug-extract ratio in a range from 3 to 7:1.

	<p>Preparations C and D have exactly the same definition. We finally realized that the separate mentioning refers to different dose schemes of two separate commercial preparations. However, section 2 refers to the qualitative and quantitative composition, not to dose schemes, which are displayed only in section 4.2. The duplicate entry does therefore not make sense. Section 4.2 specifically refers to dose schemes of preparations described in section 2. It would therefore be sufficient to refer to the same qualitative extract composition with two different dose schemes in section 4.2.</p>	
2	<p>Proposed change:</p> <p>We propose to add as “Herbal preparation C”: Dry extract (DER 3-7:1), extraction solvent methanol (80% v/v), hypericin 0.10-0.30%, hyperforin 3-6%.”</p> <p>The numeration of the other herbal preparations would have to be adopted accordingly.</p>	<p>This type of extract is now included.</p>
4.1. Therapeutic indications	<p>Comments:</p> <p>In the draft monograph, the indication is generally limited to “symptomatic treatment of mild depressive episodes”.</p> <p>For Hypericum extract WS[®] 5570, however, sufficient clinical data for the indication “mild <u>and moderate</u> depressive episodes” are available and have been recognised as a proof of efficacy for treatment of mild to moderate depressive episodes. Based on these clinical data, several marketing authorisations have been granted in Europe.</p> <p>WS[®] 5570 is a dry hypericum extract characterised as follows: DER 3-7:1, extraction solvent methanol (80% v/v), hypericin: 0.10-0.30%, hyperforin: 3.0-6.0%, flavonoids: minimum 6.0 % (rutin: minimum 1.5 %), produced by adding ascorbic acid.</p> <p>It is proposed to be added as a separate „Herbal Preparation C“ in chapter ,2. <i>Qualitative and quantitative composition</i>“ (see above).</p>	<p>Following the guidance given for the evidence necessary for marketing authorization of antidepressants studies on relapse prevention are necessary.</p> <p>Only 2 herbal preparations fulfil this criterion: WS 5570 (DER 3-7:1, extraction solvent methanol 80% v/v) and STW3-VI (DER 3-6:1, extraction solvent ethanol 80% v/v). The extract LI 160 is very similar to WS 5570 with regard to DER, extraction solvent and the published data on the contents of the major constituents and therefore both extracts should be considered together.</p> <p>For these extracts the indication ‘Herbal medicinal product for the symptomatic treatment of mild to moderate depressive episodes’ is acceptable according to the guideline.</p> <p>All other extracts mentioned under well-established use in the monograph demonstrate adequate efficacy in the short term treatment of depressive symptoms.</p>

We propose to add, as a second indication, “symptomatic treatment of mild and moderate depressive episodes”, limited to the Herbal Preparation C.

The efficacy of Hypericum Extract WS[®] 5570 (“Herbal Preparation C”) in patients with moderate depressive episodes was demonstrated in four recently conducted, randomised double-blind controlled clinical trials, which showed superiority of WS[®] 5570 as compared to placebo as well as non-inferiority in comparison to an active comparator.

The data resulting from these studies clearly show a statistically significant, as well as clinically relevant antidepressant efficacy of Hypericum extract WS[®] 5570 in patients with moderate depressive episodes. Beyond the positive efficacy data, WS[®] 5570 has a favourable safety profile compared to synthetic antidepressants in terms of frequency, type and severity of adverse drug reactions, up to a daily dose of 1800 mg.

Taking into account all presented clinical data, the results of biometrical evaluation including those of a cross-study analysis for the subgroup of patients with moderate depressive episodes, as well as the favourable safety profile of WS[®] 5570 compared to synthetic antidepressants, the indication “symptomatic treatment of mild and moderate depressive episodes“ appears to be scientifically justified and clinically reasonable for this specific herbal preparation.

A detailed statement on the clinical data justifying the indication “Mild to moderate depressive episodes” may be found in attachment I.

Proposed change:

We propose to change

„Herbal medicinal product for the symptomatic treatment of mild depressive episodes“

	<p>into</p> <p>Indication 1: Herbal preparations A, B, D-H: „Herbal medicinal product for the symptomatic treatment of mild depressive episodes”</p> <p>Indication 2: Herbal preparation C*: „Herbal medicinal product for the symptomatic treatment of mild and <u>moderate</u> depressive episodes“</p> <hr/> <p>* <i>The consecutive numbers refer to the numbering amended as proposed in Chapter „2. Qualitative and quantitative composition” (see above).</i></p>	
<p>4.1</p>	<p>Comments: We do not support the proposed wording of indication for well-established use (“for treatment of mild depressive episodes”). The efficacy in major depressive episodes (MDE, as defined in DSM IV) is not sufficiently demonstrated for SJW. Moreover, diagnosis of MDE is based on careful medical evaluation after exclusion of moderate and severe episodes.</p> <p>Proposed change</p> <p>Well-established use Herbal medicinal product for the symptomatic treatment of mild depressive episodes symptoms present for less than 2 weeks.</p> <p>Traditional use, indication 1 Traditional herbal medicinal product for the relief of mild and transient depressive-like symptoms</p>	<p>Partly endorsed. See above.</p>

4.1.

Therapeutic indications: “Herbal medicinal product for the symptomatic treatment of mild depressive episodes.”

In clinical practice, there are no sharp borders between “mild” and “moderate” depressive episodes. The diagnostic differentiation in controlled clinical studies is mainly based on the Hamilton depression scale, where initial score values below 20 are grouped under the classification „mild“ and score values between 20 and about 26 are classified as classification „moderate depressive episode“. When taking this into account while evaluating all currently available studies with *Hypericum* extracts in the treatment of major depression, where the average of the initial HAMD-Scores is given (Linde et al., 2008; see also table attached), it becomes evident, that the average of the initial score values was below 20 in only 7 of 29 studies (24%). This allows the conclusion, that in the vast majority of the studies, efficacy was tested only in patients with „moderate” but not with „mild“ depressive episodes.

However, it is generally accepted by health professionals that proofs of efficacy in depression of higher severity may be transferred also to depression of lower severity. In contrast, a limitation of the indication to „mild depressive episodes“ cannot be derived from the available pool of data.

There are actually at least seven European countries where *Hypericum* preparations with studies showing the efficacy in the treatment of mild to moderate depressive symptoms are authorized also for the treatment of patients with „moderate depressive episodes“, on the basis of the studies included and evaluated in the present assessment report. This approach is absolutely adequate with respect to the proof of efficacy and may therefore not be excluded in finding the wording for the indication in this HMPC-Monograph for *Hypericum perforatum*.

Not endorsed. See above.

	<p>Proposed Change:</p> <p>Herbal medicinal product for the symptomatic treatment of mild to moderate depressive episodes.</p>	
<p>4.1.</p>	<p>The Spanish Agency is of the opinion that the proposed indication (“symptomatic treatment of mild depressive episodes”) in the well-established use part of the monograph cannot be acceptable for the following reasons:</p> <p>a. –Although the Applicant has submitted numerous studies on the treatment of depression, including patients with mild, moderate and severe major Depression, no studies specifically conducted in the target population (mild MD) are included.</p> <p>b. - There are reasonable doubts if pharmacological treatment (antidepressants) should be recommended for the treatment of mild depression.</p> <p>c. - According to the “Note for Guidance on clinical investigation of medicinal product in the treatment of depression” for the claim of “depressive episode” indication, short and long term efficacy and safety should be demonstrated.</p> <p>Short term: As the Belgium Agency has already commented the preferable design to demonstrate efficacy is a placebo-controlled three-arm study. However, three of the four three-arm studies discussed in the assessment report had a negative outcome.</p> <p>It should be shown that the short term effect can be maintained. The prevention of the deterioration during the index episode (relapse prevention) should be documented. Duration of at least 6 months is required.</p> <p>However, in the submitted documentation there was no positive long-term clinical trial, so the duration of the response could not be demonstrated.</p>	<p>Partly endorsed. See above.</p>

	<p>Nevertheless, based on the assessment of the studies as discussed in the assessment report the hypericum preparations included in the well established use part of the monograph could be considered efficacious for <u>the short term treatment of mild depressive symptoms</u>.</p>	
<p>4.1.</p>	<p>On request of the Belgian Commission for Herbal Medicinal Products, I would like to discuss following issues regarding the formulation of the indication in the Community herbal monograph on <i>Hypericum perforatum</i>, as proposed in the well-established use part of the monograph.</p> <p>We are of the opinion that the indication of “mild to moderate depressive episodes” is not acceptable for the following two reasons.</p> <p>1. For the claim of “depressive episode”, short and long term efficacy and safety should be demonstrated in patients with mild, moderate and severe depressive episode, including patients with recurrent depressive episode. It is thus a major problem that only patients with mild or moderate depressive episode are included in the clinical studies, as this undermines the extrapolation of the study results to patients with severe depressive episode. Specific claims for only mild or moderate depressive episode are not acceptable, as they are not in accordance with the “Note for Guidance on clinical investigation of medicinal products in the treatment of depression.” (CPMP/EWP/518/97, Rev.1).</p> <p>2. Based on the available data, the indication “mild to moderate depressive episode” is not approvable for <i>Hypericum perforatum</i> as short-term and long-term efficacy for the treatment of “depressive episode” is not unequivocally proven. For the claim of “depressive episode”, <u>short</u> and <u>long</u> term efficacy and safety should be demonstrated in patients with mild, moderate and severe depressive episode.</p> <p>For the <u>short-term efficacy</u>, the preferable design to demonstrate efficacy is a placebo-controlled three-arm study. When looking at the three-arm studies discussed in the assessment report, three of the four three arm studies had a negative outcome.</p>	<p>Endorsed.</p>

	<p>For <u>long-term efficacy</u>, the preferable design to demonstrate efficacy is a relapse prevention study. There is one well-conducted long term relapse prevention trial with WS 5570 containing Hypericum, which we assessed carefully in the context of a full application where the indication “depressive episode” was claimed. In this trial long-term efficacy could not be demonstrated, as there was no statistically significant difference between WS 5570 and placebo in time to relapse during continuation treatment. Based on post hoc analyses, the applicant claimed maintenance of effect. However, post-hoc analyses are not acceptable and this study should be considered as a negative study.</p> <p>For the claim of “depressive episode”, short and long term efficacy and safety should be demonstrated in patients with mild, moderate and severe depressive episode, including patients with recurrent depressive episode.</p> <p>Based on the available data the indication “mild to moderate depressive episode” is not approvable for Hypericum, as short term and long term efficacy for the treatment of “depressive episode” is not unequivocally proven.</p> <p>However based on the assessment of the studies as discussed in the assessment report, it can be concluded that Hypericum is efficacious for the short-term treatment of mild to moderate <u>depressive symptoms</u>, but not for the full indication “<u>depressive episode</u>”</p> <p>In our view, following wording of the indication could be acceptable: “Hypericum is indicated for the <u>short term</u> treatment of mild to moderate depressive <u>symptoms</u>”.</p>	
<p>4.1.</p>	<p><u>Well-established use:</u></p> <p>Herbal medicinal product for the symptomatic treatment of mild to moderate depressive episodes.</p> <p>Rationale:</p>	<p>Not endorsed. See above.</p>

The clinical studies showing the efficacy have been conducted almost without any exception in patients with mild to moderate depressive diseases or even with moderate depressive diseases only. Studies comparing Hypericum preparation to chemically defined antidepressants, which are authorized for the indication “major depressive disorder” according to DSM-IV-TR 296.2x resp. 296.3x, did show the non-inferiority of the Hypericum preparations, thereby allowing the conclusion that they are equally efficient also in moderate depression.

As documented in a considerable number of large non-interventional trials, the therapeutic safety is documented by a high responder rate, a very good tolerability and the lack of cases of therapeutic failure. Therefore, there are no safety reasons justifying the exclusion of patients with moderate depressive episodes from therapy with the effective and safe Hypericum preparations in well established use.

Furthermore a considerable number of regulatory agencies from the EU (to our knowledge at least seven, with several more authorization procedures still ongoing) has by now authorized well established use for Hypericum preparations with indications including moderate depressive episodes (see also Comments on the draft assessment report, paragraph I, Regulatory status overview).

The efficacy of these preparations also in moderately depressive patients has now, in addition to the preparation-specific meta analysis cited by the assessment report, been shown by the recent Cochrane report (Linde et al, 2008) with the conclusion, that “an attempt of treating mild to moderate major depression with one of the Hypericum preparations positively tested in clinical trials is clearly justified”. This applies to all preparations listed in this monograph for well established use (including the preparations H and I) separately.

As there are no hints pointing to differences in clinical efficacy between all these preparations, it would be, also from a clinical point of view, be justified, to merge all these preparations to one group, as is proposed in section 2, comment version 2.

4.1

Well-established use

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

Comments: The wording "Herbal medicinal product for the symptomatic treatment of mild depressive episodes" is not consistent with the draft assessment report (page 53) where the indication is proposed as "mild to moderate depressive episodes". Therefore, the rapporteur's proposal should be reflected in the monograph.

The efficacy of St. John's wort preparations included as well-established has been tested in patients suffering from mild to moderate depression according to ICD-10 or DSM-IV criteria. For all these extracts there are studies available and have been considered by the rapporteur, which enrolled moderate depressive patients (see draft assessment report, p. 52/53). Efficacy in moderate depressive patients is even more evident herein than for mild depressive patients. It might be justifiable to deduce proven efficacy for treating a more severe degree of illness to a less severe degree, but a limitation to this less severe degree alone is not at all legitimated.

Furthermore, according to the most recent meta-analysis of clinical trials with St. John's wort extracts, which has not yet been included into the assessment for this monograph draft, "*an attempt of treating mild to moderate major depression with one of the Hypericum preparations positively tested in clinical trials is clearly justified*" (Linde et al. 2008).

The authors stressed in their major conclusions that the tested Hypericum extracts were superior to placebo in patients with major depression and similarly effective as standard antidepressants. Of the 29 studies included, in 19 the severity of depression of the enrolled patients is given with "mild to moderate" and in 9 even with "moderate to severe" (only one study did not distinguish between grades of severity). Many of the studies evaluated herein have also been taken into consideration by the rapporteur. The few studies that were included by Linde et al. (2008), but not by the rapporteur, were e.g.

Not endorsed. See above.

	<p>Bracher et al. (2001) (see also Comments on the draft assessment report II.3.2.2.1). In total, the overall evidence for the efficacy of St. John's wort extracts in this indication is much broader than that of any chemically defined preparation used in this field. Together with the fact that respective preparations have been licensed for this indication by the regulatory agencies of a significant number of European countries, inclusion of this indication into this monograph is justified. Potential considerations that the prescription status of preparations indicated for treatment of moderate depression should be prescription-only are not relevant here, as they can not influence the evaluation of efficacy and safety based on clinical trials and post-marketing surveillance data.</p>	
<p>4.1.</p>	<p>Saint John's wort preparations are well-accepted in the treatment of mild to moderate depression. Many studies have even shown more pronounced effect in moderately depressed patients than in mild depression. The applicability in moderate depression is explicitly and positively mentioned in the most recent metaanalysis of the Cochrane collaboration (Linde et al. 2008) and in monographs on <i>Hypericum perforatum</i>.</p> <p>The argument was heard that a restriction to mild depression should be made because there is no control for over-the-counter medication by physicians. This concern is reflected by the recent change of prescription status in Germany: Preparations claiming the treatment of mild to moderate depression are now available by prescription only, whereas the very same preparation labelled with "mild depression" is OTC. The goal of creating a community list of accepted well-established and traditional use must, however, be seen with the background of the EU Directive 2001/83/EC, as amended by Directive 2004/24/EC, and thus with the facilitation of drug registration. The community list is therefore devised to avoid duplicate work and to provide answers to the question whether the use of a given preparation may be accepted as well-established or traditional. If the bibliographic data supports the well-established use of <i>Hypericum</i> in the indication of mild to moderate depression – as confirmed by the assessment report and, most importantly, by the bibliographic data – this indication should be stated in the monograph. We feel that the question whether the use in moderate depression is</p>	<p>Partly endorsed. See above.</p>

	<p>politically acceptable is not within the scope of the community monograph.</p> <p>Clearly the use of St. John's wort extracts in the indication "mild to moderate depression" fulfils the pre-conditions for the definition as a well-established preparation. This is also accepted by the HMPC assessment report. Consequently, the word "moderate" cannot simply be omitted.</p>	
4.1.	<p>Proposed change:</p> <p>We propose to add: "...to moderate..." to the text. "Herbal medicinal product for the symptomatic treatment of mild depressive episodes"</p> <p>Comment:</p> <p>For well-established use St. John's Wort (SJW) products, sufficient clinical data exist which underline that these products are indicated for mild to moderate depressions. Among recent individual clinical studies which clearly confirm the effectiveness of SJW on mild to moderate depressions, recent reviews have assessed these studies and come to the overall conclusion that SJW products are effective not only for mild but also for moderate depressions (Linde [2008], Pilkington [2006], Rahimi [2009])</p> <p>A most recent clinical study manifests these judgement further (Kasper [2008])</p>	See above.
4.2. Posology and method of administration Well-established use	<p>Comments:</p> <p>The posology which applies for the extract WS® 5570 is the one given under "Herbal preparation B":</p> <p>Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg</p>	<p>Endorsed.</p> <p>Dosage now under herbal preparation A.</p>

	<p>Proposed change:</p> <p>We propose to change</p> <p>Herbal preparation B: Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg</p> <p>into:</p> <p>Herbal preparations B and C*: Single dose: 300-600 mg Dosage frequency: 1-3 times daily Daily dose: 600-1800 mg</p> <hr/> <p>* <i>The consecutive numbers refer to the numbering amended as proposed in Chapter „2. Qualitative and quantitative composition” (see above).</i></p>	
4.2	<p>Well established use</p> <p>Comments:</p> <p><i>In published data, efficacy is generally assessed at week 4 of treatment, or sometimes later. However, some effect might be expected at week 2 o week 3 of treatment. Then time to effect is not established.</i></p> <p>Proposed change:</p> <p>Only short term treatment is recommended.</p> <p>In case of unsatisfactory response within 2 weeks, or in case of worsening, a doctor should be consulted</p>	<p>Partly endorsed</p> <p>The onset of the effect can be later than the proposed 2 weeks, but medical supervision should guarantee that with a continuation of the medication no risk is associated.</p> <p>Proposal:</p> <p>The onset of the effect can be expected within 4 weeks of treatment. If the symptoms persist during the use of the medicinal product, a doctor should be consulted.</p>

<p>4.2</p>	<p>Comments: According to the above mentioned general comment</p> <p>Proposed change :</p> <p>Addition in the Well-Established column of paragraph 4.2 Posology and method of administration</p> <p>Herbal preparation H:</p> <p style="padding-left: 40px;">Single dose: 300-600 mg</p> <p style="padding-left: 40px;">Dosage frequency: 2-3 times daily</p> <p style="padding-left: 40px;">Daily dose: 900-1200 mg</p>	<p>See above.</p>
<p>4.2</p>	<p>The use of Hypericum medicines has shown to be safe also for the patients below the suggested age limit of 18 years. We suggest the lower age limit with 12 years, which corresponds to MA for different Hypericum medicines in several European countries.</p>	<p>Endorsed. See rational below.</p>
<p>4.2.</p>	<p>Comment: no reportet traditional view mentions „depression“ or „vegetative dystonia“ in children and young adolescents. That may contribute to the fact, that children weren´t depressiv in older days or the wording was different or the „desease“ wasn´t part of the vocabulary because depression historically has been underdiagnosed in children.</p> <p>When the U.S. Food and Drug Administration declared in 2004 that certain antidepressants are linked to an increased risk of suicide in adolescents, there was surprisingly little data about how depression was being treated in young patients. Now new research from the Stanford University School of Medicine provides critical documentation of the potential misuse of these medications in the years leading up to the FDA’s decision to issue the so-called “black-box” warnings. To date, the FDA has approved only fluoxetine for patients under the age of 18. (http://med.stanford.edu/news_releases/2005/november/teen-depression.html, 11.1.2009)</p> <p>In Austria no single antidepressant is approved for children under the</p>	<p>Use in adolescents not endorsed.</p> <p>Rationale:</p> <p>It is according to the data evaluated by Fegert et al (2006) correct that Hypericum preparations were in Germany by far the most prescribed antidepressant in persons below 20 years of age.</p> <p>However, there are neither concrete data on the actual use in a defined age group nor sufficient data on efficacy and safety available. Therefore the use in adolescents cannot be supported.</p>

age of 18. So all medical therapies for children are off-label. (http://www.meduniwien.ac.at/neuropsychiatrie/docs/ssri_ckak2005np.pdf, 11.1.2009)

To our opinion it doesn't seem appropriate under these circumstances to forget about Hypericum and to negate and annihilate a possibly good working drug without noteworthy side-effects and known interactions.

3.1.) To determine the efficacy and safety of *H. perforatum* for the treatment of ADHD in children a randomized, double-blind, placebo-controlled trial conducted between March 2005 and August 2006 at Bastyr University, Kenmore, Washington, among a volunteer sample of 54 children aged 6 to 17 years who met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for ADHD by structured interview was performed.

ADHD is not part of the traditional use of Hypericum/extracts. But no difference between groups was found in the number of participants who experienced adverse effects during the study period (*H. perforatum*, 40.7%; 95% CI, 22.4%-61.2% vs placebo, 44.4%; 95% CI, 25.5%-64.7%; $P = .78$)

That means that this extract was safe while used in children. (Weber W, Vander Stoep A, McCarty RL, Weiss NS, Biederman J, McClellan J.

JAMA. 2008 Jun 11;299(22):2633-41)

3.2.) LI160: A multicentre post-marketing surveillance study was conducted in 2002. 101 children aged between 1 and 12 years were treated with a standardized hypericum extract 300-1200g/d. (Hübner WD, Kirste T., *Phytother Res.* 2001 Jun;15(4):367-70.

As reported in the draft the safety of a potential use is given. But there is no reason for the conclusion that the efficacy is not proven! In the contrary: After a minimum of 4 weeks treatment 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.

As it is out of question to claim for double-blind, randomized, prospective multi-center studies when it's about children in special and depression in detail post-marketing surveillance studies or

	<p>observational studies seem to be appropriate.</p> <p>- at least to support the safety of a traditional use.</p> <p>The Kooperation Phytopharmaka was founded in 1982 and is a "Gesellschaft bürgerlichen Rechts" (private company under civic law) with scientific tasks. It was founded by the four organisations: Bundesverband der Arzneimittel-Hersteller e.V. (BAH) Bundesverband der Pharm. Industrie e.V. (BPI) Verband der Reformwaren-Hersteller e.V. (VRH) Gesellschaft für Phytotherapie e.V. (GPhy)</p> <p>This Kooperation Phytopharmaka has a working Group "Dosage in Children". The task of the working group is: Preparation and publication of empiric data on investigations on the dosage of selected herbal medicinal products (HMP) in children.</p> <p>They recoment hyperici herba and products e.g. extracts for the use in children as follows: 2-4g drug daily or 0,2-1,0mg Hypericin in adequate preparations daily.</p> <p>(Kinderdosierungen von Phytopharmaka 2002)</p>	
4.2.	<p><u>Well-established use</u></p> <p>Posology</p> <p>Comments:</p> <p>Following to our Comments to section 2, Version 1, only minor changes and additions are necessary:</p> <p>Herbal preparation D: Single dose: 350 mg Dosage frequency: 2-3 times daily Daily dose: 700-1050 mg</p> <p>Herbal preparation H: Single dose: 250 mg Dosage frequency: 2 times daily Daily dose: 500 mg</p>	<p>Endorsed.</p> <p>Dosages are included now.</p> <p>Use in adolescents: see above.</p>

Herbal preparation I:
Single dose: 325-425 mg
Dosage frequency: 2 times daily
Daily dose: 650-950 mg

Rationale:

Preparation D (STEI 300) is used 2-3 times daily, resulting in a daily dose of 700-1050 mg. Preparations H and I had not been previously included in the monograph draft but as they are well established use preparations, too, they must be included here.

Following our Comments to section 2, Version 2, results in the merger of preparations A to I (listing of these preparations has to be deleted then) under two following declarations:

Herbal preparation A
Single dose: 300-750 mg and
Dosage frequency 1-3 times daily and
Daily dose 600-1800 mg

Herbal preparation B
Single dose: 250-900 mg and
Dosage frequency 1-3 times daily and
Daily dose 500-1200 mg

Each of the three preconditions (regarding single dose, dosage frequency and daily dose) has to be met by the respective preparations.

Rationale:

As the extracts within each of the proposed groups A and B are similar from a qualitative point of view (see section 2), a joint posology for each group is justified.

Comment on age group:

Children and adolescents:

The use in children ~~and adolescents~~ under ~~12-18~~ years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

Rationale:

Products having marketing authorisations in the EU may be used from 12 years on. The safe use of Hypericum in this age group is documented in several post-marketing trials, as is also reflected in the assessment report. That the study published by Hübner has not been using the HAMD-score, as is criticised in the assessment report, is justified by the fact, that this score has not been validated in children. The score used is simpler than the HAMD score, it is recommended e.g. by Hazell et al. 2003 for scores used in children. Taking this into account, the results are not only showing safety, but also efficacy of the treatment. The same is the case with the studies of Findling et al. (2003) and Simeon et al. (2005), which, though small in size, show efficacy of the treatment by validated scores. Besides these studies, there are data from further non-interventional studies (Demling et al., 2004; Rudolf and Zeller, 2004), which included also 30 patients from the age group between 12 and 18, for which efficacy (HAMD, SF 12) and safety was comparable to that in adults, as a reanalysis showed (Müller et al. 2009).

Moreover the guideline of a scientific society (German society of paediatric and adolescent psychiatry (Dt. Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie, 2007) mentions Hypericum preparations and recommends its use in mild to moderate depressive children and adolescents. Hypericum preparations are widely used in children and adolescents and are the most important group of antidepressants in that age group, accounting e.g. for more than 80% of antidepressant use in Germany's children (Potter et al. 2009), as studies using questionnaires (Cala et al. 2003) and large scale analyses of prescription patterns in Germany (Fegert et al. 2006) show. Not in any instance hints on problems with pharmacovigilance were obtained. This is underlined also by a recent review (Potter et al. 2009), despite this publication is otherwise not free from some flaws. Unquestionable the most important therapeutic

	<p>alternative, the tricyclic antidepressants (TCAs), have a clearly less favourable safety profile compared to Hypericum.</p> <p>Duration of use No comment.</p> <p>Method of administration No comment.</p>	
4.2.	<p><u>Well-established use</u></p> <p>Posology <i>Adults and elderly:</i></p> <p>1. Proposal to summarise the preparations</p> <p>Herbal preparation A: Single dose: 300-750 mg and Dosage frequency: 1-3 times daily and Daily dose: 600-1800 mg</p> <p>Herbal preparation B: Single dose: 250-900 mg and Dosage frequency: 1-3 times daily and Daily dose: 500-1200 mg</p> <p>and delete the rest. Please add:</p> <p>For each preparation subsumed under A or B all three respective preconditions (single dose, dosage frequency and daily dose) listed here have to be clearly fulfilled to qualify for a well-established use.</p> <p>Comments: Data on dosage has to be adapted to the respective changes in section 2, where for well established use, grouping in two groups of herbal</p>	See above.

preparations is suggested for replacing the large number of groups A-G. Also the grouping of the preparations for traditional use has to be adapted to section 2.

2. Alternative proposal

Herbal preparation A:

Single dose: 300 mg

Dosage frequency: 3 times daily

Daily dose: 900 mg

Herbal preparation B:

Single dose: 300-600 mg

Dosage frequency: 1-3 times daily

Daily dose: 600-1800 mg

Herbal preparation C:

Single dose: 900 mg

Dosage frequency: 1 single daily dose

Daily dose: 900 mg

Herbal preparation D:

~~Single dose: 350 mg~~

~~Dosage frequency: 3 times daily~~

~~Daily dose: 1050 mg~~

Single dose: 350 mg

Dosage frequency: 2-3 times daily

Daily dose: 700 – 1050 mg

Herbal preparation E:

Single dose: 400 mg

Dosage frequency: 2 times daily

Daily dose: 800 mg

Herbal preparation F:

Single dose: 300-600 mg

Dosage frequency: 2-3 times daily

Daily dose: 900-1200 mg

Herbal preparation G:
a) Single dose: 612 mg
Dosage frequency: 1 single daily dose
Daily dose: 612 mg
b) **Single dose: 306 mg**
Dosage frequency: 2 times daily
Daily dose: 612 mg

Herbal preparation H:
Single dose: 250 mg
Dosage frequency: 2 times daily
Daily dose: 500 mg

Herbal preparation I:
Single dose: 325-650 mg
Dosage frequency: 1-2 times daily
Daily dose: 650-950 mg

Comments: For the corrected herbal preparation D (see above), the posology has been adapted to the posology of the respective product. The dosages of preparations H and I are those proposed for inclusion under chapter 2 and correspond to the preparations mentioned there.

Children and adolescents:
The use in children ~~and adolescents~~ under 12-18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

Comments: An age restriction to a minimum of 12 years is reflected in the national SPCs of well-established preparations with marketing authorizations, and St. John's wort is doubtlessly also in the age group 12-18 years in well established use. This is also supported by the following facts. There is no specific data pointing to differences in pharmacokinetic or pharmacodynamic parameters between children and adults after application of SJW extracts. The use of St. John's wort preparations had up to now not been restricted to adults only. In several post-marketing studies children and adolescents were included.

The re-analysis of two non-interventional studies (Demling et al., 2004; Rudolf and Zeller, 2004) revealed about 30 adolescent patients (range < 18 years) treated with 900 mg SJW daily for about 12 weeks. No specific risks or adverse effects could be identified, and the response rate and the clinical outcomes (HAM-D, SF 12, respectively) were comparable to those of adult patients.

It has to be considered that a considerable number of such NIS may never have been analyzed for this subgroup.

Cala et al. (2003) used a caregiver-report questionnaire and found that 15% of 117 children treated for a psychiatric disorder (ADHD or depression) had been administered herbal products by their primary caregivers within the past year. It can therefore be expected that the use of SJW has reached a much broader extent in practice yet, which is also indicated by the guidelines of e.g. the German society of paediatric and adolescent psychiatry (Dt. Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie, 2007), where the use of SJW is recommended for mild to moderate depressive children and adolescents because of its efficacy and few side effects. A study analyzing the prescription patterns of antidepressants for youths in Germany for the years 2000-2003 emphasized the importance of herbal prescription (here: SJW) in the treatment of children and adolescents (Fegert et al., 2006). The findings are based on prescription data from a health insurance organization (GEK) with 1.4 million members per year across Germany, of whom approximately 280,000 were under 20 years of age (enrolled: youths 0-19 years, insurance members of the whole year). Prevalence was defined as the dispensing of one or more prescriptions for an antidepressant per calendar year per 1000 enrolled youth and varied over the years between 3.37 and 3.74, with a clear predominance in the subgroup of adolescent girls (15-19 years). The percentage of prescriptions of *Hypericum* varied only between 40,4 and 55,6 % over the four years investigated. *Hypericum* therefore was the medication with the highest prescription rate for this age group; together with TCAs they accounted for more than 80% of antidepressant use. And, as the authors stated, this may only reflect the tip of the iceberg, because the data include only prescriptions of SJW preparations reimbursed by the

health insurance companies without regarding the self-medication market.

Altogether this data shows that the use of SJW is indeed broad and well-established also in youths, especially among especially adolescents. Restrictions to adults only may make sense in new substances with unclear risks and benefits for youths, but not for herbal preparations used for decades in this age group. Furthermore, since SJW products have a very broad safe dose range, and since the specific problem of herb-drug interactions is expected to be potentially relevant only for multimorbid patients, but not in children without regular intake of other drugs, no specific problem is expected from the intake of SJW preparations by children and adolescents. In the contrary, data from controlled trials allow the expectation of a significantly better safety of application as compared with alternative medications such as SSRI or TCA. And it has to be stated that after banning the SSRIs and SNRIs as a whole group except fluoxetine (Doc. Ref. EMEA/CHMP/128918/2005 corr.; Doc. Ref. EMEA/202554/2006), TCAs seem to be the only alternative pharmacotherapy for use in children and adolescents left, substances that received only historic labeling based on criteria that no longer apply, well-known for a high potential of adverse effects and small dose range. The consequence might be more untreated depressive children and adolescents. However, untreated and undiagnosed depression undermines social and school functioning, generates severe family stress, prompts significant use of mental health services (Clarke et al. 2003), and is linked to increased risk of other psychiatric disorders such as drug use and suicide (Gould et al. 1998).

In summary, the effectiveness of SJW is sufficiently supported by empirical data for the treatment of major depression in adults (Linde et al., 2008). By comparing adolescents and adults, there is neither relevantly different pharmacodynamics or pharmacokinetics of SJW nor relevantly different clinical symptoms to be considered. Symptoms of major depression in adolescents are approaching the criteria developed for adults (Dt. Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie, 2007). Furthermore, there is enough data derived from NIS and practical use to justify a recommendation regarding SJW as a safe and effective medication.

	<p>Duration of use The onset of the effect can be expected within 4 weeks of treatment. If the symptoms persist despite the use of the medicinal product, a doctor should be consulted.</p> <p>Method of administration Oral use.</p>	
4.2.	<p>The details on dosing appear overly complicated. With efficacy having been proven with different types of extract and, within the same extract definition, different dose schemes (e.g., once daily versus b.i.d. or t.i.d), there is no reason to restrict the list to selected preparations applied in selected dose schemes. In fact, such a restriction appears to contradict the intention of the EU directive, which was not obviously meant to protect the market shares of already existing medicinal products, but to facilitate the registration of similar preparations as medicinal products – preparations which are otherwise marketed as food supplements. It would therefore be sufficient to indicate a daily dose of 600-1050 mg for the well-established preparations – including the ones to be shifted from the traditional use table –, and a dose of 500 mg for the extract with 50 % ethanol (DER 4-7:1, no hyperforin). Single doses can be omitted, as there are identical preparations with double-dose galenical forms (once-a-day preparations). Every single available form would have to be listed with the present concept, which will necessarily lead to an incomplete list.</p> <p>The section on well-established use restricts the application to adults (> 18 years). There is no justification for such a limitation, especially as children were treated in some clinical trials without any treatment-emerging concerns. The restriction to adults would deprive therapy of an efficacious preparation, which has frequently been shown to be much safer than alternative chemically defined medications in the same indication. Due to the increased risk of suicide committed by adolescents the SSRI are no longer recommended in children, whereas the tolerability of the tricyclic antidepressants clearly puts this group of antidepressants at a disadvantage when they are</p>	<p>Endorsed: herbal preparations are combined. Use in adolescents: see above.</p>

	<p>compared with St. John's wort extracts. We suggest that the age limit is changed to 12 years, as with traditional use.</p>	
4.3	<p>Wellestablished use and traditional use, indication 1</p> <p>Comments :</p> <p>The proposed wording raised some public health concerns, due to the safety profile of <i>Hypericum perforatum</i> in relation with numerous interactions with non herbal medicinal products</p> <p>Proposed change :</p> <p>Hypersensitivity to the active substance.</p> <p>Hypericum dry extract must not be used concomitantly with oral anticlotting agents, metabolised antiepileptic agents, estroprogestative contraceptive agents, progestative contraceptive agents, immunosuppressive agents (cyclosporine, sirolimus, tacrolimus), digoxin, amprenavir, indinavir and other protease-inhibitors, tyrosine kinase inhibitors, irinotecan and other cytostatic agents, theophyllin.</p>	<p>Not endorsed.</p> <p>The wording should be not more restrictive than for other substances which induce metabolic enzymes.</p>
4.3.	<p>Cotraindications: "Hypericum dry extract must not be used concomitantly with cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents."</p> <p>These contraindications are based on the induction of specific mechanisms of detoxification by <i>Hypericum perforatum</i> in the liver and intestine with subsequent decrease of the blood level of the drug substances mentioned above. Selecting these drug substances the following facts have to be considered: The activity of the cytochrom P450 enzymes and p-glycoprotein in the body are subject to daily adaptation due to ingested xenobiotics and foodstuffs. The application of pharmaceutical drugs therefore has always to take place on the background of unpredictable fluctuations of the concentrations of the effective substances in the body. Intervals of about $\pm 20\%$ (confidence</p>	<p>Endorsed.</p>

	<p>intervals in proof of bioequivalence) are to be tolerated. In the human pharmacological studies of Johnne et al (1999) and Müller et al (2004) which apparently have been consulted here, the mean change of digoxin levels under co-medication of <i>Hypericum</i> was 25 %, with a fluctuation in the control group between -15 and +8%. These changes are no acute risk for patients in case of digoxin. In accordance with this, no reports are existing on a deterioration of the cardiac function of digitalized patients with cardiac insufficiency under co-medication with <i>Hypericum</i> (Linde et al., 2005). Digoxin therefore should not be listed under contraindications but under warnings.</p> <p>Proposed Change:</p> <p>Same text without digoxin.</p>	
<p>4.3.</p>	<p><u>Well-established use</u></p> <p>Hypersensitivity to the active substance. Hypericum dry extract must not be used concomitantly with cyclosporine, tacrolimus for internal use, digoxin, amprenavir, indinavir and other protease inhibitors, irinotecan and other similar cytostatic agents.</p> <p>Rationale: We suggest to delete digoxin in “4.3 Contraindications” and to list it under “4.4 Special warnings and precautions for use” instead. It holds true that Johnne et al. (1999) and Müller et al. (2004) found a 25% net difference in digoxin AUC (0-24) after 10 to 14 days of concomitant use with SJW’s extract. The authors hypothesize an influence by induction of p-glycoprotein after multiple-dose treatment with hypericum extract. In contrast, Arold et al. (2005) found no statistically significant differences in digoxin levels between the Hypericum group and the placebo group. Uehlecke et al. (2000) found a clear dose dependency: By administration of either 900 mg of a high-dose-extract-formulation or different amounts of encapsulated powder of St. John’s wort, they found a reduction of 24h-AUC of</p>	<p>Endorsed.</p> <p>The external use of tacrolimus for the treatment of eczemas should not be contraindicated.</p> <p>The inclusion of all cytostatic agents in the section contraindications is not justified by literature.</p>

	<p>digoxin for the product and the highest dose (4g) of about 25 or 27%, respectively. For the 2g-dose, reduction was less pronounced (17,6%), and for the lower doses negligible.</p> <p>Furthermore, differences of 20 % in bioavailability have to be tolerated even between two pharmaceuticals containing an identical active agent. There are differences in the resorption rate of digoxin to be considered that are well-known for the pharmacokinetics of digoxin even without comedication (Mutschler et al., 2001). The most important point however is that possible interactions do not result in an intoxication of the patients. The possible interaction results in a reduction of digoxin levels, though without remarkable clinical relevance, not in an increase.</p>	
4.3.	<p><u>Well-established use</u></p> <p>Hypersensitivity to the active substance. Hypericum dry extract may lead to a decrease of serum levels of must not be used concomitantly with cyclosporine, tacrolimus for internal use, digoxin, amprenavir, indinavir and other protease inhibitors, irinotecan and othersimilar cytostatic agents. Concomitant use should be avoided.</p> <p>Comments: see chapter 4.5</p>	<p>Not endorsed.</p> <p>The remaining substances are used in critical circumstances. Additional risks should be avoided.</p>
4.3.	<p><u>Proposed change:</u> <u>Well established use</u></p> <p>Hypericum dry extract with a daily dose of 4 mg (or more) of hyperforin must not be used concomitantly with cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents.</p>	<p>Not endorsed.</p> <p>Published interaction studies with low-hyperforin extracts cover only short term treatment (2 weeks).</p>

	<p>Comment:</p> <p>For SJW products a differentiation has to be made between products having different content of hyperforin. Based on literature data Arold [2005], [Whitten 2006], [Mai 2004], [Mueller 2006] and risk assessments by the health authorities FDA [1997, 2006], EMEA and BfArM, it is justified to set a limit and to establish safety measures in the community monograph which will allow to remove the contra-indications and special warnings related to the interaction potential of SJW for those products which comply with these requirements.</p> <p>The interaction of St. John's wort preparations with concomitantly applied drugs is a well-known phenomenon. It is entirely attributable to the activation of Cytochrome P450 3A4/2C19 and, by the same basic mechanism of binding the steroid X-receptor (which in turn activates both systems), the activation of the p-glycoprotein transporter system (Chen [2004], Moore [2000], Wentworth [2000]). The identification of hyperforin as a strong and selective activator of the PXR system, and thus of drug excretion by PGP, CYP 3A4, 2C9 and 2C19, is confirmed by all clinical evidence, without exception.</p>	
<p>4.3.</p>	<p>The absolute contraindications cited in this section of the draft monograph are not justified by the bibliographically available data. Basically, the risk of interactions is related to the content of hyperforin, a fact which is by now well-known, and which should be reflected in the phrasing. As explained below, the dependency of the interaction potential from the dose of hyperforin should be reflected in the phrasing of the monograph, especially with preparations where – based on hyperforin contents – a clinically relevant interaction is not to be expected.</p> <p>In addition, the place for the discussion of contraindications is section 4.5, otherwise there would be a duplicity of warnings based on the same facts. In this case the very same mechanism of action, hyperforin-induced pharmacokinetic interactions, is the background for warnings in sections 4.3, 4.4 and 4.5. For reasons of simplicity the matter shall be treated in this place.</p>	<p>Not endorsed.</p> <p>According to the SPC guideline other medicines, which must not be used concomitantly should be stated in 4.3. If applicable a cross reference to 4.5 should be given.</p> <p>The mentioned substances are used in serious conditions where the concomitant use of hypericum may cause life threatening situations.</p> <p>The fact that the interactions are caused by hyperforin is acknowledged in the assessment report. However, interaction studies with low-hyperforin extracts were restricted to duration of use of 2 weeks. This does not reflect the practical use (see: duration of use). At the moment there is no clear evidence that low-hyperforin extracts do not induce CYP enzymes or PGP. Additionally there is no limit established for the definition of 'low-</p>

The interaction potential of *Hypericum perforatum* was examined in a multitude of studies – many of them clinical experiments with the application of probe substances for the assessment of the effect of St. John's wort (and isolated constituents) on the activity of metabolizing enzymes. It has been determined that three of these systems are relevantly activated by St. John's wort extracts: Cytochrome P450 isoforms 3A4 and 2C19, and the para-glycoprotein transporter pPG. All three mechanisms share a common activation by the steroid-X-receptor (SXR), also called the pregnane-X-receptor (PXR). The constituent responsible for the effect has been identified: Hyperforin irreversibly binds to the SXR, and as a consequence of the binding causes an activation of cytochrome P450 3A4/2C19 and pGP (Chen et al. 2004; Moore et al. 2000; Wentworth et al. 2000). This activation in turn increases the metabolism and excretion of substrates of these metabolising systems, which has regularly been observed in clinical model experiments and case reports of interactions. The interaction requires, however, a minimum dose of hyperforin in order to cause clinically relevant interaction effects. Without exception, hyperforin-enriched preparations have been applied in all case reports and model studies with a positively identified interaction. Vice-versa, a relevant interaction potential has never been observed with St. John's wort preparations containing normal to low quantities of hyperforin (e.g., (Müller et al. 2006a; Will-Shahab et al. 2008d)).

The irreversible binding of hyperforin to SXR activates the expression of the genes for the mentioned metabolizing enzymes. Such a mechanism takes approximately eight days to become clinically relevant (Rengelshausen et al. 2005b), which also explains the lack of findings in some short-term studies. The relation between interaction potential and hyperforin is now well-known and is regularly mentioned in reviews (Madabushi et al. 2006; Whitten et al. 2006).

In section 4.3 (contraindications), the draft monograph states the concomitant use with cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease inhibitor, irinotecan and other cytostatic agents as contraindicated. This list does not appear to be helpful in this place:

hyperforin' extracts.

a) The list is not even exhaustive and will never be. Provided that preparations enriched with hyperforin (>4 %) are applied, the observation of a decrease of plasma levels of concomitantly applied drugs will be observed for every drug which is metabolized by cytochrome P450 3A4 or 2C19, and by pGP.

b) Since the interaction is clearly hyperforin-dependent, the interaction potential cannot be generalized to all St. John's wort preparations. Warning labels are a tool of consumer protection, but warning consumer about non-existing hazards is no contribution to their protection.

c) Even with drugs where there is an interaction potential with hyperforin-enriched preparations the interaction is not necessarily clinically relevant. E.g., the variations of plasma levels of digoxin can hardly be considered clinically relevant.

d) All drugs for which the interaction potential with hyperforin-enriched Hypericumpreparations may be clinically relevant are prescribed and closely monitored by physicians. This is especially true for immunosuppressants, anti-cancer and anti-HIV medications. An absolute contraindication is therefore not necessary, as the problem could be solved by a contraindication referring to hyperforin-enriched preparations only, and/or advising to closely monitor blood levels of the concomitantly taken drugs. In most cases, however, a relative contraindication and a recommendation to closely monitor blood levels of concomitantly taken drugs should be sufficient.

The following table lists studies where the effect on pGP has been examined:

Type of Report	Interaction with	No. of patients	SJW product	Main results	Reference
Case report	Phenprocoumon	1	presumably LI 160	Decreased blood thinning efficacy	(Bon et al. 1999)
Interaction trial	Digoxin	25	LI 160, 3×300 mg, 10 days	Decrease of AUC by 25 %	(Johne et al. 1999a; Johne et al. 1999b)
Interaction trial	Phenprocoumon	10	LI 160, 3×300 mg, 11 days	Significant decrease of AUC	(Maurer et al. 1999)
Interaction trial	Digoxin	8	LI 160, 3×300 mg, 14 days	Decrease of AUC by 18 %	(Dürr et al. 2000b)
Interaction trial	Digoxin	17	Ze 117, 2×250 mg, 14 days	No interaction	(Will-Shahab et al. 2008c)
Interaction trial	–	15	Good n'Natural, 3×600 mg, 15 days	4.2fold expression of PGP	(Hennessy et al. 2002)
Interaction trial	Fexofenadine	12	Sundown (33 mg hyperforin/day), 3×300 mg, 14 days	47 % increase of oral clearance	(Wang et al. 2002)
Interaction trial	Fexofenadine	21	LI 160, 3×300 mg, 12 days	94 % increase of oral clearance	(Dresser et al. 2003c)
Interaction trial	Digoxin	96	Ze 117, LI 160 and other SJW preparations, 14 days	Clear correlation of AUC reduction with hyperforin content	(Müller et al. 2004a)
Interaction trial	Digoxin	16	Esbericum (3.5 mg hyperforin/day), 240 mg/d, 10 days	No interaction	(Arold et al. 2005)
Interaction trial	Fexofenadine	30	presumably LI 160	Reduced plasma concentrations	(Xie et al. 2005)
Interaction trial	Talinolol	9	LI 160, 3×300 mg, 12 days	93 % increase in oral clearance, 31 % reduction of AUC	(Schwarz et al. 2007)

The correlation between hyperforin contents and an increased pGP activity has been especially well-examined with digoxin (Müller et al. 2004b)

Preparation	Characterization	Drug equivalents per day (mg)	Hyperforin per day (mg)	Interaction with digoxin		
				C _{max}	AUC ₀₋₂₄	C _{through}
Hyperforin rich extract (LI 160)	DER 4-7:1, 3×300 mg	4950 mg	28.9 mg	-37 %*	-25 %*	-19 %*
Drug powder	high hyperforin content	4000 mg	21.1 mg	-38 %*	-27 %*	-19 %*
		2000 mg	10.6 mg	-21 %*	-18 %*	-13 %*
		1000 mg	5.3 mg	-5 %	-2 %	+15 %
		500 mg	2.6 mg	+15 %	+1.5 %	+8 %
Drug powder	low in hyperforin	2000 mg	0.3 mg	-14 %*	-9 %	0 %
Fresh plant pressed juice	2x10 ml corresponding to 33 g fresh plant	ca. 10.000 mg	3.56 mg	-5 %	-7 %*	-1 %
Tea	normal hyperforin content	3.500 mg	0.04 mg	+4 %	0 %	+13 %
Hypericum oil	5x200 mg	90 mg	0.13 mg	-4 %	-5 %	0 %
Ze 117	DER 4-7:1, low in hyperforin	2750 mg	0.38 mg	-4 %	-6 %	-1 %
Placebo	—	—	—	-6 to +13 %	-3 to +4 %	-0.5 to +11 %

A significant decrease of still doubtful clinical relevance was only found with preparations with high hyperforin contents. A similar situation is found with drugs metabolized by cytochrome P450 3A4 and 2C19:

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
Pharmacokinetic trial	Contraceptives, CyP 3A4	9 (2f) / 7 (3f)	WS 5572 (5% hyperforin) / WS 5573 (0.5% hyperforin), 3×300 mg, 7 days	Breakthrough bleedings in 2/2 subjects with WS 5572 and 0/3 with WS 5573	(Biber et al. 1998)
Case report	Phenprocoumon, CyP 3A4	1	LI 160	Quick value ↑	(Bon et al. 1999)
Case reports	Cyclosporine, CyP 3A4	2	LI 160	Blood levels ↓	(Bon et al. 1999)
Case reports	Contraceptive, CyP 3A4	3	LI 160	Breakthrough bleedings	(Bon et al. 1999)
Model trial	Dextromethorphan, CyP 3A4/2D6	16	unknown, 3×300 mg, 8 days	No interaction	(Ereshesky et al. 1999)
Case report	Cyclosporine,	1	Unknown, 2×300	Beginning graft	(Barone et al.

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
	CyP 3A4		mg/day, 4-8 weeks	rejection	2000)
Case reports	Cyclosporine, CyP 3A4	45	SJW, 3×300 mg/day	Blood levels ↓	(Breidenbach et al. 2000a; Breidenbach et al. 2000b)
Model trial	Carbamazepine, CyP 3A4	8	HBC (3 % hyperforin), 3×300 mg, 14 days	No observable effect due to auto-induction	(Burstein et al. 2000)
Model trial	Intestinal biopsies, CyP 3A4, PGP	4	Ze 117, 750 mg/day, 7 days	1.6-fold activation of PGP (p=0.056), 2.4-fold activation of CyP 3A4 (n.s.)	(Drewe et al. 2000)
Model trial	Activation of PGP/CyP 3A4 in lymphocytes	4	Ze 117, 750 mg/day, 7 days	No activation	(Drewe et al. 2000)
Model trial	Erythromycin, CyP 3A4	8	LI 160, 3×300 mg, 14 days	CyP 3A4 ↑	(Dürr et al. 2000a)
Case report	Cyclosporine, CyP 3A4	1	SJW, 3×600 mg, 2 weeks	Graft rejection	(Karlova et al. 2000)
Case report	Cyclosporine, CyP 3A4	1	LI 160, 300 mg/day, 4 weeks	Blood levels ↓	(Mai et al. 2000)
Case report	Cyclosporine, CyP 3A4	1	Unknown, 3 days	Blood levels ↓	(Mandelbaum et al. 2000)
Model trial	Alprazolam, CyP 3A4	7	Solaray, 4% hyperforin, 3×300 mg, 3 days	No clear interaction	(Markowitz et al. 2000)
Model trial	Indinavir, CyP 3A4	8	HBC (3 % hyperforin), 3×300 mg, 14 days	Blood levels ↓	(Piscitelli et al. 2000)
Model trial	Cortisol, CyP 3A4	13	HBC (3 % hyperforin), 3×300 mg, 14 days	CyP 3A4 ↑	(Roby et al. 2000)
Case reports	Cyclosporine, CyP 3A4	2	LI 160, 3×300 mg	Beginning graft rejection	(Ruschitzka et al. 2000)
Case reports	Contraceptive, CyP 3A4	8	unknown	Breakthrough bleedings	(Yue et al. 2000b)
Case reports	Warfarin, CyP	7	unknown	INR ↓	(Yue et al.

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
	3A4/2C9				2000a)
Case reports	Cyclosporine, CyP 3A4	3	Unknown, different doses	Dose-dependent drop of blood levels	(Ahmed et al. 2001)
Case reports	Cyclosporine, CyP 3A4	2	"Your Life", 23×300 mg/day	Blood levels ↓	(Barone et al. 2001; Turton-Weeks et al. 2001)
Case report	Cyclosporine, CyP 3A4	1	Neuroplant, 3×300 mg/day	Blood levels ↓	(Beer and Ostermann 2001)
Case reports	Nevirapine, CyP 3A4	5	Unknown, several months	Blood levels ↓	(de Maat et al. 2001)
Case report	Cyclosporine, CyP 3A4	1	Unknown, 2×300 mg/day, 2 weeks	Blood levels ↓	(Moschella and Jaber 2001)
Case report	Contraceptives, CyP 3A4	1	LI 160, 3×300 mg/day, 2 weeks	Dysmenorrhoea, causality doubtful	(Rätz et al. 2001)
Case reports	Contraceptive, CyP 3A4	8	LI 160	Breakthrough bleedings	(Schulz 2001)
Model trial	Nifedipine, CyP 3A4	22	SJW extract (unspecified), 900 mg/day, 18 days	Plasma levels ↓ by 53 %	(Smith et al. 2001)
Model trial	Simvastatin, CyP 3A4	8	LI 160, 3×300 mg/day, 14 days	Intestinal CyP 3A4 or PGP ↑	(Sugimoto et al. 2001a)
Model trial	Pravastatin (no PGP/CyP 3A4 substrate)	8	LI 160, 3×300 mg/day, 14 days	No interaction	(Sugimoto et al. 2001b)
Model trial	Midazolam p.o., CyP 3A4	12	Sundown, 33 mg hyperforin/dose, single dose	No significant induction	(Wang et al. 2001a)
Model trial	Midazolam p.o. and i.v., CyP 3A4	12	Sundown, 33 mg hyperforin/dose, 3×300 mg, 14 days	Intestinal > hepatic CyP 3A4 ↑	(Wang et al. 2001b)
Model trial	Cortisol, CyP 3A4	48	LI 160, 6×300 mg, 14 days	CyP 3A4 ↑	(Bauer et al. 2002)
Case report	Tacrolimus, CyP 3A4	1	WS 5572, 600 mg/day	Blood levels ↓	(Bolley et al. 2002)

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
Model trial	Midazolam, CyP 3A4	12	SJW (42 mg hyperforin/day), 3×300 mg, 4 weeks	Intestinal CyP 3A4↑	(Gurley et al. 2002b)
Case report	Indinavir, lamivudine, CyP 3A4	1	unknown	Virus load ↑	(Henderson et al. 2002a)
Case reports	Contraceptive, CyP 3A4	9	unknown	unwanted pregnancies	(Henderson et al. 2002b)
Model trial	Amitriptyline, PGP and CyP 3A4	12	LI 160, 3×300 mg/day, 14 days	Blood levels ↓ by induction of CyP 3A4 and PGP	(Johne et al. 2002)
Model trial	Irinotecan, CyP 3A4	5	SJW extract, 3×300 mg/day, 18 days	Blood levels ↓	(Mathijssen et al. 2002)
Model trial	Cyclosporine, CyP 3A4	11	LI 160, 600 mg, 14 days	Blood levels ↓	(Bauer et al. 2003)
Model trial	Cyclosporine, CyP 3A4	21	LI 160, 3×300 mg/day, 12 days	Blood levels ↓	(Dresser et al. 2003b)
Model trial	Midazolam p.o. and i.v., CyP 3A4	21	LI 160, 3×300 mg, 12 days	Intestinal > hepatic CyP 3A4 ↑	(Dresser et al. 2003a)
Model trial	Methadone, CyP 3A4	4	LI 160, 3×300 mg/day, 30 days	Blood levels ↓	(Eich-Höchli et al. 2003)
Model trial	Midazolam p.o. and i.v., CyP 3A4	12	Rexall (27 mg hyperforin/day), 3×300 mg, 2 months	Intestinal but not hepatic CyP 3A4 ↑	(Hall et al. 2003a)
Model trial	Contraceptive, CyP 3A4	12	Rexall-Sundown (27 mg hyperforin/day), 3×300 mg, 2 months	No effect on LH, FSH, progesterone, but blood levels of norethindrone ↓. Breakthrough bleedings in 7/12 subjects	(Gorski et al. 2002; Hall et al. 2003b)
Model trial	Tacrolimus, CyP 3A4	10	LI 160, 3×300 mg/day, 14 days	Blood levels ↓	(Mai et al. 2003b)
Model trial	Mycophenolic acid (no PGP or CyP 3A4 metabolite)	8	LI 160, 3×300 mg/day, 14 days	No interaction	(Mai et al. 2003a)
Model trial	Alprazolam, CyP 3A4	12	LI 160, 3×300 mg, 14 days	Blood levels ↓	(Markowitz et al. 2003)

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
Model trial	Contraceptive, CyP 3A4	18	LI 160, 2-3×300 mg, 2 months	No effect on serum estradiol and progesterone. Blood levels of 3 ketodesogestrel ↓. Breakthrough bleedings in 15/17 subjects	(Pfrunder et al. 2003b)
Case report	Contraceptive, CyP 3A4	1	Helarium 425 (15-65 mg hyperforin/day)	Unwanted pregnancy	(Schwarz et al. 2003)
Model trial	Cortisol, CyP 3A4	12	LI 160, 3×300 mg, 14 days	CyP 3A4 ↑	(Frye et al. 2004a)
Model trial	Imatinib, CyP 3A4	12	LI 160, 3×300 mg/day, 14 days	Blood levels ↓ by induction of intestinal CyP 3A4	(Frye et al. 2004b)
Model trial	Tacrolimus, CyP 3A4	10	LI 160, 3×300 mg/day, 18 days	Blood levels ↓	(Hebert et al. 2004)
Model trial	Warfarin, PGP and CyP 3A4/2C9	12	Bioglan (12.5 mg hyperforin/tablet), 14 days	Clearance of S- und R-warfarin ↑ Interaction at CyP 2C9 not conclusive.	(Jiang et al. 2004c)
Model trial	Cortisol, CyP 3A4	13	LI 160, 3×300 mg, 14 days	CyP 3A4 ↑	(Kawaguchi et al. 2004b)
Model trial	Quazepam, CyP 3A4	13	LI 160, 3×300 mg, 14 days	Intestinal and hepatic CyP 3A4 ↑	(Kawaguchi et al. 2004a)
Model trial	Cyclosporine, CyP 3A4	10	LI 160 900 mg/day vs. hyperforin-depleted SJW, 14 days	Blood levels ↓ with LI 160, but not with hyperforin-depleted extract	(Mai et al. 2004)
Model trial	Imatinib, CyP 3A4	10	HBC (3 % hyperforin), 3×300 mg, 14 days	Blood levels ↓, probably by induction of intestinal CyP 3A4	(Smith et al. 2004a; Smith et al. 2004b)
Model trial	Verapamil, PGP and CyP 3A4	8	Movina (3-% hyperforin), 3×300 mg, 14 days	Blood levels ↓	(Tannergren et al. 2004)
Model trial	Omeprazole, CyP 3A4/2C19	12	HBC (4 % hyperforin), 3×300 mg, 14 days	CyP 3A4 ↑, 2C19 ↑ only in extensive metabolizers	(Wang et al. 2004a)

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
Model trial	Mephenytoin, CyP 2C19	12	HBC (3.7% hyperforin), 3×300 mg, 14 days	CyP 2C19 ↑ in extensive metabolizers	(Wang et al. 2004c)
Model trial	Cortisol, CyP 3A4	16	LI 160, 3×300 mg, 14 days	CyP 3A4 ↑	(Wenk et al. 2004b)
Model trial	Alprazolam, CyP 3A4	16	Esbericum (3.5 mg hyperforin per day), 240 mg/day, 10 days	No interaction	(Arold et al. 2005)
Model trial	Midazolam, CyP 3A4	12	Vitamer (5.5 mg hyperforin/day), 3×300 mg, 4 weeks	140% induction	(Gurley et al. 2005)
Model trial	Contraceptive, CyP 3A4	16	HBC (3.7% hyperforin), 3×300 mg, 2 months	No effect on contraceptive efficacy, but reduction of blood levels of actives. More breakthrough bleedings with SJW	(Fogle et al. 2006a; Murphy et al. 2005a)
Model trial	Voriconazole, PGP, CyP 3A4, 2C19, 2C9	16	LI 160, 3×300 mg/day, 14 days	Blood levels ↓, more distinct in extensive CyP 2C19 metabolizers	(Rengelshausen et al. 2005a)
Model trial	Midazolam p.o. and i.v., CyP 3A4	30	Unknown, 3×300 mg, 10 days	Intestinal > hepatic CyP 3A4 ↑	(Xie and Kim 2005)
Model trial	Midazolam, CyP 3A4	42	6 SJW preparations with hyperforin contents from 0.1-41 mg/day	Interaction correlates with hyperforin dose	(Müller et al. 2006b)
Model trial	Ivabradine, CyP 3A4	12	SJW	AUC and C _{max} ↓	(Portoles et al. 2006)
Case reports	Cylosporine, CyP 3A4	9	SJW (unspecified)	Blood levels ↓, recovery takes 2-3 weeks	(Murakami et al. 2006)
Model trial	Simvastatin	24	Movina, 2×300 mg, 4 weeks	LDL and total cholesterol ↓	(Andren et al. 2007; Eggertsen et al. 2007)
Model trial	Prednisone	8	HBC (>4% hyperforin), 3×300 mg, 4 weeks	No interaction	(Bell et al. 2007)
Model trial	Nifedipine	12	SJW extract (Schwabe, 5% hyperforin), 3×300 mg/day, 2 weeks	Plasma levels of nifedipine ↓ and of metabolite ↑	(Wang et al. 2007)
Model trial	Contraceptive, CyP 3A4	16	Ze 117, 2×250 mg, 2 weeks	No interaction	(Will-Shahab et al. 2008b)

No interaction potential was found at cytochrome P450 2D6.

<p>4.4. Special warnings and precaution for use</p> <p>Well-established use</p>	<p>Comments:</p> <p>We consider the statement “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia” as too generalised and not scientifically justified.</p> <p>Some drugs potentially used during anaesthesia like alprazolam or midazolam for sedation are listed under 4.5 (Interactions). However, there is no proof for the entirety of anaesthetics to trigger interactions with St. John’s Wort (SJW); thus, the scope of the proposed wording is too broad. Anyhow, even if an effect on pharmacokinetics or pharmacodynamics of single benzodiazepines had been found in in-vitro or in-vivo-studies, a clinical relevance wouldn’t be a logical consequence, since it appears possible that, regardless of a certain hypothetical alteration of blood plasma levels of benzodiazepines by SJW, the sedative effect of the benzodiazepines might stay uninfluenced.</p> <p>In a hospital survey published in 2000¹, a total of 1017 surveys were submitted over a period of 5 months, out of which 755 surveys were assessed as valid surveys. 30% of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates that “pseudoephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided.” The survey did not reveal any risk, within anaesthesiology practice, for the concomitant intake of SJW and benzodiazepines.</p> <p>An article published in <i>The Lancet</i> by Marilyn Larkin² apparently reports about research from various centres in the USA which warns that patients who use herbal remedies may suffer from herb/anaesthesia interactions³. However, the evidence of this article is rather weak, since there is no scientific basis for the statement that “SJW: May prolong effects of some narcotics and anaesthetics”. Neither narcotics nor anaesthetics are specified more closely; no backup evidence is given for this statement.</p>	<p>Partly endorsed.</p> <p>Proposed wording:</p> <p>Prior to elective surgery possible interactions with products used during general and regional anaesthesia should be identified. If necessary the herbal medicinal product should be discontinued.</p>
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Marilyn Larkin published another article in 2001⁴ in which she specifies the aspect of a “safe use of herbal products before surgery” for, amongst others, SJW: “Major concerns: Diminished effects of other drugs such as ciclosporin, warfarin, steroids &c. Stop before surgery: At least 5 days”. Narcotics and anaesthetics are not listed here.

References

1. Kaye AD et al. Herbal Medicines: Current Trends in Anesthesiology Practice – A Hospital Survey. J Clin Anesth 2000; 12: 468-471.
2. Larkin M. Surgery patients at risk for herb-anaesthesia interactions. The Lancet 1999; 354: 1362.
3. Qureshi B. How herb-anaesthesia interactions can be fatal during a surgical operation. The Journal of the Royal Society for the Promotion of Health 1999; 119(4): 209-10.
4. Larkin M. Safe use of herbal products before surgery proposed. The Lancet 2001; 358: 128.

Proposed change:

We propose to change

“The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.”

into

“Regarding potential interactions with medicinal products used during general and regional anaesthesia, please refer to 4.5 Interactions.”

<p>4.4</p>	<p>Comments :</p> <p>Following recent implementation of a class wording on suicidal risks for all antidepressants, we are of the opinion that a minimal information about this risk of suicidal events is also needed for <i>Hypericum perforatum</i>, in relation with the claimed indication</p> <p>Proposed change</p> <p>Well-established use</p> <p>Patients with a history of moderate to severe EDM or those exhibiting more than 5 disabling symptoms should take a medical advice before starting use of <i>Hypericum perforatum</i>.</p> <p>If symptoms are present for more than 2 weeks, a medical advice could be considered.</p> <p>Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). <i>Hypericum perforatum</i> (St. John's Wort) is not indicated in patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment. In such a case, a doctor should be consulted.</p> <p><i>Hypericum perforatum</i> (St. John's Wort) is not an antidepressant and is not indicated in well-defined major depressive episode (MDE). <i>Hypericum perforatum</i> induces serious interactions with other medicinal products.</p> <p>Patients should be advised about the need to mention that they are taking <i>Hypericum perforatum</i> to their doctor/pharmacist In general for patients treated with other drugs <i>Hypericum perforatum</i> is not recommended. Efficacy and safety of <i>Hypericum perforatum</i> is not demonstrated in the elderly. Furthermore, elderly patients are specially, exposed to the risk of interaction with other medicinal products (See 4.3 and 4.8).</p>	<p>Statement of risk of suicide: could be implemented on a national basis.</p> <p>Other proposals partly endorsed. The wording of warnings should not be more restrictive than for other drugs which induce metabolic enzymes.</p> <p>According SPC-guideline Interactions are discussed under 4.5, not under 4.4.</p> <p>See also comments in the relevant sections.</p> <p>Statement on UV-exposure already considered.</p>
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	<p>Moreover, cases of serotonergic syndrome have been reported in the elderly in case of concomitant antidepressant treatment.</p> <p>During the treatment intense UV-exposure should be avoided.</p> <p>The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.</p> <p>Since no sufficient data on the safe use in children are available the use in children and adolescents under 18 years of age is not recommended.</p>	
<p>4.4.</p>	<p><u>Well established use</u></p> <p>Comments:</p> <p>When co-administered with anti-coagulants from the coumarin-type or with digoxin the serum concentration of these substances should be controlled regularly.</p> <p>During the treatment intense UV-exposure should be avoided.</p> <p>The continuation of the product should be discontinued at least 10 days reconsidered according to “4.5 Interactions” prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.</p> <p>Since no sufficient data on the safe use in children are available the use in children and adolescents under 18 12 years of age is not recommended.</p> <p>Rationale:</p> <p>Digoxin should be moved to 4.4 from 4.3 (see 4.3 for further explanations).</p> <p>Surgery: A general discontinuation of the use 10 days prior to elective surgery seems not justified, as from current knowledge there are no drug interactions with anesthetics to be expected.</p> <p>Comments on age group see 4.2 Children and adolescents.</p>	<p>Endorsed.</p> <p>See discussion in the relevant sections.</p>

<p>4.4.</p>	<p><u>Well-established use</u></p> <p>a) When co-administered with anti-coagulants from the coumarin-type or digoxin the serum concentration of these substances should be controlled regularly.</p> <p>Comment: Digoxin has been moved here from 4.3. (for comment see section 4.5).</p> <p>b) During the treatment intense UV-exposure should be avoided.</p> <p>Comment: Comments to the underlying data are given in the assessment report (relating to pp 26-29 and 61 - 62).</p> <p>c) Instead of "The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia" we propose "Regarding potential interactions with medicinal products used during general and regional anaesthesia please refer to 4.5 Interactions."</p> <p>Comment: Drugs potentially used during anaesthesia like alprazolam or midazolam for sedation are listed under 4.5. There is no proof for the entirety of anaesthetics to trigger interactions with Hypericum perforatum, thus the range in the proposed wording is too extensive. If there should be a clinical relevant effect on pharmacokinetics or pharmacodynamics of certain benzodiazepines, this is also reflected in section 4.5, so that it needs not to be mentioned here in duplicate. Published data underline that there is no general risk related to the concomitant use of anesthetics and hypericum preparations. In a published hospital survey (Kaye 2000) a total of 1017 surveys were submitted over a period of 5 months out of which 755 surveys were assessed as valid surveys. 30 % of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates the "pseudo ephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided." The survey did not reveal any risk within anaesthesiology practice for the concomitant intake of SJW and benzodiazepines. An article published in The Lancet (Larkin 1999) reports about</p>	<p>Endorsed.</p> <p>Text shifted to 4.5.</p>
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	<p>research from various centres in the USA warning patients who use herbal remedies may suffer from herb-anaesthesia interactions. However, the evidence of this article is rather weak, since there is no scientific basis for the statement that "SJW: May prolong effects of some narcotics and anaesthetics". Neither narcotics nor anaesthetics are closer specified, there is no background given for this statement. In another article (Larkin 2001), the same author specifies the aspect of a "safe use of herbal products before surgery" for, amongst others, SJW: "Major concerns: Diminished effects of other drugs such as cyclosporine, warfarin, steroids etc. Stop before surgery: At least 5 days". Narcotics and anaesthetics are not listed here.</p> <p>d) Since no sufficient data on the safe use in children are available the use in children and adolescents under 12 18 years of age is not recommended.</p> <p>Comment: For use in children, see chapter 4.2.</p>	
<p>4.4.</p>	<p>The warning related to blood levels of warfarin again refers to a potential interaction, and should be presented in section 4.5. The same applies to the recommendation for discontinuation prior to elective surgery.</p> <p>The warning against the use of the well-established preparations in patients under the age of 18 years has already been discussed: it does neither seem appropriate nor justified by the available clinical experience. Hypericum preparations have been applied in children and adolescents without any specifically age-related problems. The corresponding trials are cited in the assessment report of the HMPC.</p> <p>We suggest to change the age limitation to 12 years.</p>	<p>Partly endorsed.</p> <p>Text shifted to 4.5.</p> <p>Use in adolescents: not endorsed, see above.</p>
<p>4.4.</p>	<p>Proposed change:</p> <p>We propose to change</p> <p>“The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.”</p>	<p>Endorsed.</p>

into

“Regarding potential interactions with medicinal products used during general and regional anaesthesia please refer to 4.5 Interactions.”

Comments:

We consider the statement “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.” as too broad and not scientifically justified.

Some drugs potentially used during anaesthesia like alprazolam or midazolam for sedation are listed under 4.5 (Interactions). However, there is no prove for the entirety of anaesthetics to trigger interactions with St. John’s Wort (SJW), thus the range in the proposed wording is too extensive. Anyhow, even if an effect on pharmacokinetics or pharmacodynamics of single benzodiazepines might have been found in in-vitro or in-vivo-studies, a clinical relevance is not a logical consequence, since it appears possible that regardless of a hypothetic certain alteration of blood plasma levels of benzodiazepines by SJW, the sedative effect of the benzodiazepines might stay uninfluenced.

In a hospital survey published in 2000 (1) a total of 1017 surveys were submitted over a period of 5 months out of which 755 surveys were assessed as valid surveys. 30% of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates the “pseudoephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided.” The survey did not reveal any risk within anaesthesiology practice for the concomitant intake of SJW and benzodiazepines.

An article published in The Lancet by Marilyn Larkin (2) apparently reports about research from various centres in the USA which warns the patients who use herbal remedies may suffer from herb-

	<p>anaesthesia interactions (3). However, the evidence of this article is rather weak, since there is no scientific basis for the statement that “SJW: May prolong effects of some narcotics and anaesthetics”. Neither narcotics nor anaesthetics are closer specified, there is no background given for this statement.</p> <p>Marilyn Larkin published another article in 2001 (4) in which she specifies the aspect of a “safe use of herbal products before surgery” for, amongst others, SJW: “Major concerns: Diminished effects of other drugs such as ciclosporin, warfarin, steroids &c. Stop before surgery: At least 5 days”. Narcotics and anaesthetics are not listed here.</p>	
<p>4.5. Interactions</p>	<p>Comments:</p> <p>The inclusion of „benzodiazepines“ as a class of drugs, beyond the already listed benzodiazepines alprazolam and midazolam, is scientifically not justified.</p> <p>Literature research concerning interactions between SJW and different benzodiazepines like lorazepam, diazepam, bromazepam, clonazepam and others (except midazolam and alprazolam) did not reveal clinically significant hits. The scarce hits mostly concerned experimental studies.</p> <p>Benzodiazepines are a large class of at least 43 drugs with diverse chemical structures and metabolic pathways. Principal steps in benzodiazepine metabolism are 3-hydroxylation, N-dealkylation and glucurination. Although CYP 3A4 is involved in phase I metabolism of certain benzodiazepines and their active metabolites, like midazolam or alprazolam, for a number of benzodiazepines with 3-hydroxyl group, like temazepam, oxazepam, lorazepam, or lormetazepam, conjugation is the major route of metabolism, and interactions with CYP3A4 inducers cannot be expected¹. In line with these pharmacological principals, interactions between SJW and midazolam or alprazolam have been consistently reported from numerous trials and an interaction with quazepam has been reported</p>	<p>Not endorsed.</p> <p>According to the review of Moody (2004) CYP 3A4 is involved in the metabolisms of many benzodiazepines. Also for substances with a 3-hydroxyl group, like temazepam, major involvement of CYP 3A4 is mentioned. It is correct that there are also different metabolic pathways for benzodiazepines. However, in medical practice the evaluation of quantitative differences in metabolism is impossible. For safety reasons all benzodiazepines should be considered in the interactions section.</p>

	<p>in a single trial, but interactions have not been established for other benzodiazepines². Therefore, the available data cannot be extrapolated to the whole class of benzodiazepines, and a general warning is not justified.</p> <p><i>References</i></p> <ol style="list-style-type: none"> 1. Moody DE: Drug Interactions with Benzodiazepines. In: Mozayani A, Raymon LP (Eds.): Handbook of Drug Interactions: A Clinical and Forensic Guide. Humana Press, Totowa, NJ, 2004, pp. 3-89. 2. Whitten DL et al.: The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. Br J Clin Pharmacol 2006; 62 (5): 512-526. <p>Proposed change:</p> <p>We propose to change</p> <p>„Special care should be taken with alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because...“</p> <p>into</p> <p>„Special care should be taken with alprazolam, amitriptyline, fexofenadine, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because...“</p>	
4.5	<p>Comments:</p> <p>The proposed wording raised some public health concerns, due to the safety profile of <i>Hypericum perforatum</i> in relation with numerous interactions with non herbal medicinal products</p>	See above.

	<p>Proposed change</p> <p>Well-established use Contraindicated is the concomitant use of oral anticlotting agents, metabolised antiepileptic agents, estroprogestative contraceptive agents, progestative contraceptive agents, immunosuppressive agents (cyclosporine, sirolimus, tacrolimus), digoxin, amprenavir, indinavir and other protease-inhibitors, tyrosine kinase inhibitors, irinotecan and other cytostatic agents, theophyllin.</p> <p>The reduction of plasma concentrations of oral contraceptives may lead to bleeding and unwanted pregnancies (See 4.3).</p> <p>Not recommended is the concomitant use of carbamazepin, cyproterone, telithromycin, due to the risk of change in plasma concentrations.</p> <p>Special care should be taken with proton pump inhibitors, antisecretory drugs, alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.</p> <p>Hypericum dry extract may cause a serotonergic syndrome when combined with linezolid, antidepressants such as selective A-IMAO or non selective IMAO, serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone.</p> <p>Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum.</p>	
<p>4.5.</p>	<p>Interactions: “Special care should be taken with alprazolam, amitriptyline, fenofenadine, fexofenadine benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.”</p> <p>The listing of theophylline in this section is based on a single case report (Nebel et al. (1999)): A 42 year old patient was taking a St.</p>	<p>Endorsed. See above.</p>

	<p>John's wort preparation together with 11 further drugs as well as 1600 mg theophylline. After discontinuation of St. John's wort, the blood level of theophylline was reported to have doubled. Due to this report, Morimoto et al. (2004) conducted a specific study in 12 healthy volunteers under the respective comedication over 14 days. Identical blood concentration curves of theophylline with or without <i>Hypericum</i> were shown. Listing theophylline under "warnings" has therefore no scientific rationale.</p> <p>Proposed Change: Same text supplemented by digoxin but without theophylline.</p>	
<p>4.5.</p>	<p>Comments:</p> <p>Hypericum dry extract must not be used concomitantly with cyclosporine, tacrolimus for internal use, digoxin, amprenavir, indinavir and other protease inhibitors, irinotecan and other cytostatic agents.</p> <p>Special care should be taken with digoxin, alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.</p> <p>The possible reduction of plasma concentrations of oral contraceptives (especially of low dose formulations) may lead to increased intermenstrual bleeding and reduced safety in birth control. unwanted pregnancies. To women using oral contraceptives it should be recommended to take additional precautions for a better reliability.</p> <p>Hypericum dry extract may contribute to cause a serotonergic syndrome effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone.</p> <p>Rationale For comments on the displacing of digoxin see "4.3</p>	<p>First paragraph: endorsed.</p> <p>Second paragraph: Benzodiazepines – see above. Theophylline: see above Methadone: in principal the comments are correct, similar views are shared by reviews of the interactions with hypericum. However, the concomitant use is not contraindicated; the doctor is advised to take special care. Since the interaction potential with methadone is not fully clear the substance should be kept in this section of the monograph.</p> <p>Triptans: it is correct to delete the triptans from this paragraph, because there is no evidence for the reduction of plasma levels of triptans caused by Hypericum. However, it is recommended that triptans are not used concomitantly with substances which have an influence on the serotonin metabolism. Therefore it is proposed to shift the triptans to the paragraph of the serotonergic reactions.</p> <p>Third paragraph: Interactions with oral contraceptives: It is a fact that in all interaction studies with hyperforin-containing preparations some changes in the pharmacokinetic properties of the oral contraceptive and an increase of intermenstrual bleeding were observed. Until now there is no evidence that ovulation takes place</p>

<p>Contraindications”.</p> <p>We suggest omitting the listing of "benzodiazepines" as whole group of drugs in this context, because there is no substantiated evidence for interactions apart from the benzodiazepines alprazolam and midazolam listed anyhow. Available literature data on concomitant use of Hypericum with other benzodiazepines (e.g. lorazepam, diazepam, bromazepam, clonazepam) did not show clinically significant hints.</p> <p>For midazolam, primarily used in premedication settings, the increase of clearance was less pronounced after intravenous than after oral application (1,5-fold or 2,7 fold, respectively; Dresser et al. 2003). Therefore, the clinical relevance of maintaining a long-term steady-state of plasma level for a sedating agent used only shortly before clinical intervention is questionable.</p> <p>Methadone: The only clinical data on interactions between Hypericum and pharmacokinetics of methadone which are cited in some reviews (Zhou et al. 2004, Izzo 2004, Di et al. 2008) seems to be the findings of Eich-Höchli et al. (2003), subtitled with “A case report”. There are many flaws in the general design of the “study” described there. First of all the number of subjects enrolled was very low (n=4). The timing for the second blood sampling varied from 14 to 47 days of treatment with St. John’s wort, the methadone doses administered varied also remarkably (7 to 80 mg/d, changing to 7 to 90 mg/d after the first blood sampling), as did the plasma levels in consequence, necessitating a normalization of the original baseline values to 100%. Furthermore three of the four patients were receiving comedication: two patients were receiving oxazepam and one doxepin. As these patients have a drug abuse history, it is also unclear, whether these substances were the only add-on pharmaceuticals consumed during the study period as there is no evidence of further control. From our point of view, these findings have to be interpreted very critical and should not be used as basis for another warning for possible interactions. Methadone therefore should not be mentioned here.</p>	<p>within the tested period of concomitant use. The duration of the study with the low-hyperforin extract (2 weeks) seems to be too short for final conclusions.</p> <p>Proposed wording: The reduction of plasma concentrations of oral contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using oral contraceptives should take additional contraceptive measures.</p> <p>Fourth paragraph: Serotonergic syndrome: The proposed changes are endorsed. The interpretation of case reports is highly controversial in scientific literature. Therefore the modified wording seems to be suitable to alert the doctor and the patient. We propose additionally to include the triptans in this paragraph, since there was recently a case published where triptans, fluoxetine and hypericum were involved (Bonetto et al 2007).</p>
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Theophylline: As Madabushi et al. stated in 2006, theophylline has been listed under the drugs of possible interactions by several papers, all citing the very same case report (Nebel et al. 1998), where the patient was a smoker and used 11 further drugs. In contrast, Morimoto et al. (2004) were unable to detect any changes in the pharmacokinetics of theophylline in their follow-up study in 12 healthy volunteers. This is not surprising, as theophylline is mainly metabolized by CYP1A2 and only in part by CYP3A4. The induction of CYP3A4 is responsible for the most of the interactions with Hypericum preparations, while the induction of CYP1A2 is implausible with regard to the available evidence (Wang et al. 2001; Morimoto et al. 2004). Therefore the listing of theophylline herein should be deleted from the listing.

Triptans: There is no scientifically convincing evidence for interactions between Hypericum and triptans. Although triptans have been listed in several reviews as possibly pharmacodynamically interacting agents, the basis of these suspicions usually is not given there (e.g. Henderson et al. 2002). The only source of original data seems to be a case report where a serotonin syndrome was diagnosed after concomitant administration of Hypericum together with fluoxetine and eletriptan (Bonetto et al. 2007). After withdrawal of the Hypericum product the symptoms did not vanish, but after withdrawal of the triptan and the fluoxetine they did. The causality of Hypericum administration for the described interactions is in no way proven by this case report. In addition, Evans (2008) questioned whether the symptoms described were indeed compatible with the Hunter serotonin toxicity criteria and whether other aetiologies were completely ruled out. Triptans therefore should not be mentioned here.

Oral contraceptives: The causality between concomitant use of oral contraceptives with Hypericum products and unintended pregnancies has never been proven to date. The proposed wording is possibly misleading and may generate uncertainty without providing a practicable solution. Although it has to be considered that in nearly

every clinical trial women of reproductive age are included, who use oral contraception. The only and always cited evidence of unintended pregnancies after concomitant use of oral contraceptives and St. John's wort extracts is derived from some case reports with more or less imprecise specifications of products or chronological correlations. Moreover: Intermenstrual bleedings are frequent adverse effects (> 10 %) of oral contraceptives (Standard SPC Germany). Bleedings do not always result in attenuation of effect: In two studies (Hall et al. 2003, Pfrunder et al. 2003) an increase of menstrual irregularities had been found, but no increase in ovulations, which leads to the conclusion that the safety of contraception was not compromised. Oral contraceptives therefore should not be mentioned here.

Antidepressants: Causality between use of St. John's wort and the development of a serotonin syndrome is not substantiated by clinical evidence. Of the single cases reported in this context (Lantz et al., 1999, Waksman et al. 2000), the case reports of Lantz et al. show partly deficiencies in diagnostics, so that the diagnosis of a true "serotonine syndrome", which is a really severe and life threatening state of the patient - in contrast to single symptoms often experienced in the geriatric patient - has been discussed by Schulz et al. (2006). In the case report of Waksman a close chronological relation to the use of Hypericum is not given, as this had been already withdrawn three days before starting the application of paroxetine. Furthermore it is known that some antidepressants of the SSRI type cause serotonergic effects without further comedication just in case of high dosages (SPCs, Fischer 1995). The mainly theoretical discussion whether there are pharmacodynamic interactions should be critically assessed. Some earlier publications substantiate suspicions for pharmacodynamic interactions on the outdated assumption that the basic principle of action of Hypericum preparations is the MAO inhibition (e.g. Gordon 1998). Concomitant use of MAOIs and SSRIs is strictly contraindicated. However, as has been shown in more recent investigations, in clinically effective concentrations MAO inhibition was not found (as e.g. reviewed by Butterweck 2003). Therefore a modification of the text is proposed.

4.5.

Well-established use

Proposal:

~~Contraindicated is the~~ Concomitant use of cyclosporine, tacrolimus for internal use, digoxin, amprenavir, indinavir and other protease inhibitors, irinotecan and other cytostatic agents **should be avoided**.

Special care should be taken with **digoxin**, alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.

~~The reduction of plasma concentrations of oral contraceptives may lead to bleeding and unwanted pregnancies.~~

Women using oral contraceptives (especially of low dose formulation) **should be** alerted to the possibility of interactions leading to bleedings and reduced protection. Patients should take additional precautions to ensure birth control.

Hypericum dry extract ~~may cause a~~ **is discussed to contribute to** serotonergic syndrome when combined to antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or buspirone.

Comments: The interaction of St. John's wort preparations with concomitantly applied drugs is a well-known phenomenon. It is entirely attributable to the activation of Cytochrome P450 3A4/2C19 and, by the same basic mechanism of binding the steroid X-receptor (which in turn activates both systems) (Chen et al. 2004; Moore et al. 2000; Wentworth et al. 2000), the activation of the p-glycoprotein transporter system. As the gene expression of PGP and CYP enzymes upon binding of hyperforin to the steroid-X-receptor takes approximately 8 days to become effective, the interaction does not immediately set in (Rengelshausen et al. 2005). The identification of hyperforin as a strong and selective activator of the PXR system, and thus of drug excretion by PGP, CYP 3A4, 2C9 and 2C19, is confirmed by all clinical evidence, without exception.

We propose to delete Theophylline according to new data published by Morimoto et al. (2004) which show that there is no interaction potential.

See above.

Johne et al. (1999) as well as Mueller et al. (2004) found a 25% net difference in digoxin AUC (0-24) after 10 or 14 days, respectively, of concomitant use with SJW's extract, while $t_{RR_{1/2}}$ of terminal digoxin elimination remained constant.

Because the oxidative hepatic metabolism plays only a minor role in elimination of digoxin, and therefore an induction of CYP3A4 can not contribute to explain these findings, the authors hypothesize an influence by induction of P-glycoprotein after multiple-dose treatment with hypericum extract. Firstly, according to valid rules for bioequivalence fluctuations of 20 % in bioavailability have to be tolerated even between two pharmaceuticals containing an identical active agent. The pharmacokinetics of digoxin show fluctuations in resorption rate between 70 and 90 % even without comedication (Mutschler et al., 2001). Moreover, the deduced interactions result in a reduction of digoxin levels, not in increasing, meaning there is no risk of an intoxication of the patients. The at least minor decreases in plasma concentrations can be regulated by responsible drug monitoring of the physician, who will always be consulted in case of an application of digoxin. Therefore we suggest to delete digoxin in "4.3 Contraindications" and to list it under "4.4 Special warnings and precautions for use" instead.

Furthermore, there is not enough evidence for inclusion of "benzodiazepines" as whole group of drugs beyond the anyhow listed benzodiazepines alprazolam and midazolam. Literature data on SJW and different benzodiazepines like lorazepam, diazepam, bromazepam, clonazepam and others (except midazolam and alprazolam) did not reveal clinically significant hits. The scarce hits mostly concerned experimental studies.

To our opinion there is no proof for hypericum preparations are the actual reason for attenuation of the effect of hormonal contraceptives. Plausibility alone, as a logical consequence of the induction of CYP 3A4 is not sufficient to claim causality. Intermenstruel bleedings are among the most frequent adverse effects (> 10 %) of oral contraceptives and not always automatically combined with attenuation of effect. Two studies (Hall et al. 2003, Pfrunder et al. 2003), reanalyzed by Schulz (2004a) showed an increase of menstrual

	<p>irregularities (breakthrough bleedings), but no increase in ovulations meaning the contraceptive protection persisted. In contrast to these findings a more recently published study (Murphy et al., 2005) revealed at least inconsistent hints of possible coherence between breakthrough ovulation and the treatment with St John's wort. The authors themselves state that the contraceptives used has been a lower dose formulation than in the above mentioned studies. Furthermore it has to be considered that of the three women showing signs of "possible ovulation" during the treatment cycle, one showed the same signs under placebo as well.</p> <p>The existence of a serotonin syndrome triggered by the intake of SJW preparations is still under debate (Evans 2008). The existing case reports do not prove causality. Still, the concomitant intake of SJW preparations and chemically defined antidepressants does not make sense from the clinical point of view, and should be avoided.</p>	
<p>4.5.</p>	<p>In section 4.5 (Interactions) theophylline appears among the specified drugs. Theophylline is, however, not metabolized by the cytochrome P450 isoforms activated by St. John's wort/hyperforin. Like caffeine it is metabolized by cytochrome P450 1A2, on which St. John's wort and hyperforin have no effect. The concern about theophylline is derived from an older case report with clinically non-relevant observation in a single patient which has not only been questioned, but for which the causal relation with Hypericum also shown wrong by systematic clinical examinations. Theophylline should no longer be mentioned in a list of drugs potentially interacting with St. John's wort extracts.</p>	<p>Statement on theophylline: endorsed.</p> <p>Other comments: not endorsed, see above.</p>

Type of Report	Interaction with/enzyme system	No. of patients	SJW product	Main results	Reference
Case report	Theophylline, CyP 1A2	1	Unknown, 0.3% hyperforin	Blood levels ↓, causality doubtful	(Nebel et al. 1999)
Model trial	Theophylline, CyP 1A2	12	LI 160, 3×300 mg/day, 15 days	No interaction	(Morimoto et al. 2004)
Model trial	Caffeine, CyP 1A2	16	Unknown, 3×300 mg/day, 2 weeks	No interaction	(Gewertz et al. 1999)
Model trial	Caffeine, CyP 1A2	12	Sundown (33 mg hyperforin/day), 3×300 mg/day, 2 weeks	No interaction	(Wang et al. 2001c)
Model trial	Caffeine, CyP 1A2	12	Unknown (42 mg hyperforin/day), 3×300 mg, 4 weeks	Significant, but not relevant increase of metabolite ratios	(Gurley et al. 2002a)
Model trial	Caffeine, CyP 1A2	12	HBC (3.7% hyperforin), 3×300 mg, 14 days	No interaction	(Wang et al. 2004b)
Model trial	Caffeine, CyP 1A2	16	LI 160, 3×300 mg/day, 14 days	No relevant interaction	(Wenk et al. 2004a)
Model trial	Caffeine, CyP 1A2	16	Esbericum (3.5 mg hyperforin/day), 240 mg/day, 10 days	No interaction	(Arold et al. 2005)
Model trial	Caffeine, CyP 1A2	12	Vitamer (5.5 mg hyperforin/day), 3×300 mg, 4 weeks	No interaction	(Gurley et al. 2005)

The bibliographic data regarding the potential for herb-drug interactions is discussed with section 4.3 (Contraindications). We suggest combining the corresponding warnings from sections 4.3 and 4.4 in this place, as information on interactions would be expected here.

Warnings related to interactions must take the hyperforin content into account. It should at least be mentioned that clinically relevant interactions are not to be expected with preparations with hyperforin levels < 3 %. This is especially important for the preparations listed in the section of traditionally used products. The typical traditional preparations do usually not contain relevant quantities of hyperforin. E.g., Hypericum oil is devoid of hyperforin, and in the comminute substance hyperforin will be destroyed by adding boiling water in the tea preparation. The warnings against herb-drug interactions are therefore of highly questionable relevance for these products.

It has already been outlined in section 4.3 that the given absolute contraindications are only relevant in cases of the combined use of

immunosuppressant, anti-cancer and anti-HIV preparations, and even than only when hyperforin-enriched preparations are applied. A warning related to the regular control of blood levels should be sufficient for most other drugs, combined with a reference to hyperforin levels. Likewise, the recommendation to discontinue herbal products 10 days prior to elective surgery should be placed here, potentially again with reference to hyperforin.

The warning related to warfarin blood levels again refers to an interaction caused by hyperforin on the level of cytochrome P450 3A4 and pGP. A corresponding induction of warfarin clearance has been observed in a model trial in 12 healthy male subjects who received a single dose of racemic warfarin before and after administration of SJW (Bioglan, 0.825 mg hypericin and 12.5 mg hyperforin per tablet) for 14 days (Jiang et al. 2004b).

However, warfarin pharmacodynamics and metabolism are enantiomer dependent. S-Warfarin, which exhibits two to five times the anti-coagulant activity of R-warfarin, is metabolized to S-7-hydroxywarfarin by CyP 2C9, on which Hypericum and hyperforin have no activating effect. R-warfarin is metabolized by CyP 1A2 or CyP 3A4. Warfarin is also eliminated via PGP (Wadelius et al. 2004). As hyperforin would only influence a partial mechanism of warfarin metabolism, which in addition only refers to the pharmacologically less active R-enantiomer, a clinically relevant effect of Hypericum extracts is not to be expected even with preparations with a high level of hyperforin. Correspondingly, Jiang et al. (2004) did not observe an effect of St. John's wort on platelet aggregation and the INR, although they did find an increased metabolism (Jiang et al. 2004a).

The warning related to warfarin has no clinical correlate in the available bibliographic data. There is therefore no reason to overemphasize a potential interaction.

Similarly, the clinical relevance of the postulated interaction between Hypericum and contraceptives has been questioned. The hormones of the contraceptives are metabolized via cytochrome P450 3A4 and are

therefore a potentially relevant target for interactions with hyperforin.

SJW extracts have been accused to reverse the efficacy of oral contraceptives through an increased metabolic excretion of the contraceptive hormones via CYP 3A4. Such allegations were based on reports of spotting or break-through bleedings (Ernst 1999). However, breakthrough bleedings are usually reported by 4-7 % of women taking oral contraceptives, and might therefore not specifically be related to the intake of SJW (Archer 2007; Audet et al. 2001; Mishell, Jr. et al. 2007). Still, a higher rate of breakthrough bleedings has in fact been observed in women concomitantly applying Hypericum preparations. However, even in women reporting breakthrough bleedings no loss of contraceptive protection was found. Unwanted pregnancies due to the intake of SJW preparations would therefore appear rather unlikely (Schulz 2004).

Hall et al. (2003) determined whether SJW administration to 12 healthy female volunteers would alter the disposition and efficacy of oral contraception. Subjects received a combination of ethinylestradiol and norethindrone for 3 months. SJW (Rexall-Sundown, 3 × 300 mg/day, 26.7 mg hyperforin in the daily dose) was administered during months 2 and

3. FSH, LH, and progesterone concentrations were not altered on cycle days 11-16. Consequently, the contraceptive protection was not influenced. However, treatment with SJW significantly increased oral clearance of norethindrone from 8.2 ± 2.65 to 9.5 ± 3.43 l/h, and decreased peak concentrations from 17.4 ± 5.1 ng/ml to 16.4 ± 5.2 ng/ml ($p = 0.45$), whereas half-life or time to maximum serum concentrations was not influenced. Half-life of ethinyl estradiol was significantly shortened (23.4 ± 19.5 hours to 12.2 ± 7.1 hours, $p = 0.023$), but oral clearance, C_{max} and t_{max} remained unchanged. 7/12 participants experienced breakthrough bleedings during month 3, as compared to 2/12 in the control cycle 1 (Gorski et al. 2002; Hall et al. 2003c).

Pfrunder et al. (2003) published a clinical trial with the aim of examining a potential interaction of a SJW product rich in hyperforin (LI 160) with oral contraceptives. 18 healthy females were treated with a low-dose oral contraceptive (0.02 mg ethinylestradiol,

0.150 mg desogestrel) alone (control cycle) or combined with 300 mg SJW extract given b.i.d. (cycle A) or t.i.d. (cycle B). Ovarian activity was assessed by measuring follicle maturation and serum estradiol and progesterone concentrations. The number of break-through bleeding episodes and the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel were assessed under steady-state conditions. No significant change in follicle maturation, serum estradiol or progesterone concentration was found under administration of SJW extract. However, significantly more subjects reported intracyclic bleeding during cycles A (13/17; 77 %, $p < 0.015$) and cycle B (15/17; 88 %, $p < 0.001$) than with oral contraceptives alone (6/17; 35 %). The AUC₀₋₂₄ and C_{max} of ethinylestradiol remained unchanged during all study cycles, whereas the AUC₀₋₂₄ and C_{max} of 3-ketodesogestrel decreased significantly, already in cycle A. There was no evidence of ovulation during low-dose oral contraceptive and SJW extract combination therapy, but intracyclic bleeding episodes increased (Pfrunder et al. 2003a).

Murphy et al. (2005) evaluated the effect of SJW (*Hypericum* Buyers Club, 0.3 % hypericin and 3.7 % hyperforin) supplementation on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and break-through bleeding. 16 healthy women were treated with a low-dose oral contraceptive and a placebo for two consecutive cycles. Treatment with 3 × 300 mg SJW was then added for two additional cycles, which corresponds to a daily dose of 33.3 mg of hyperforin. For both contraceptive steroids, norethindrone and ethinyl estradiol, there was no difference between placebo and SJW treatments in C_{max}, t_{max} and distribution volume. There was, however, a significant 13-15% difference with respect to AUC and apparent clearance, which implies a reduced relative bioavailability of the contraceptive steroids under the influence of SJW. Break-through bleeding increased already in the first treatment cycle with SJW (56 % vs. 31 % with placebo, $p < 0.05$), however, 6 subjects reported missing OC pills during cycles 2 (placebo) and 3 (SJW). Breakthrough bleedings unrelated to missed pills were still significantly more frequent in the SJW cycle 3 than in the placebo cycle 2 (50 % vs. 19 %, $p < 0.05$). Follicle size was larger after 2 cycles of SJW treatment (mean: 17 mm in cycle 2 [placebo] and

25 mm in cycle 4 [SJW]). Six subjects developed a pre-ovulatory follicle in the placebo-cycle 2, as compared with 9 subjects in SJW cycle 4. With progesterone levels used as an indicator of ovulation 1/16 subjects had ovulated in the placebo phase, and 3/16 in the SJW phase, with the subject ovulating in the placebo phase also ovulating in the SJW phase (Murphy et al. 2005b).

In a secondary analysis of the study of Murphy et al. (2005), Fogle et al. (2006) re-examined the effect of SJW (Hypericum Buyers Club, 0.3 % hypericin and 3.7 % hyperforin) supplementation on the hormonal effect of the oral contraceptive, using the data of 15 subjects. Androgen and sex hormone-binding globulin (SHBG) levels were measured in serum by immunoassay methods. There were no statistically significant differences in androgen levels before and after SJW intake. However, there were decreases in total testosterone and free testosterone levels (-10.7 % and -15.8 %, respectively) along with a small increase in SHBG levels (+7.0 %), which reflects an even more favourable androgen profile. These results do not point to an interference of SJW with the hormonal effects of oral contraceptives, and stand in contrast with the earlier conclusion of ovulations during treatment with SJW (Fogle et al. 2006b; Murphy et al. 2005c).

The hypothesis that SJW preparations not enriched in hyperforin do not have a relevant potential for interactions on the level of CyP 3A4 is supported by the results of an interaction trial, where the extract Ze 117 was administered for 14 days to 16 female volunteers stably adjusted to the intake of a low-dose contraceptive combination of ethinylestradiol and 3ketodesogestrel in a non-controlled study. Pharmacokinetic data (AUC, C_{max}, t_{1/2}) of ethinylestradiol and 3-ketodesogestrel were measured before and at the end of coadministration of SJW from day 6 to 21 of the menstruation cycle. No change in kinetic parameters was observed between groups (Will-Shahab et al. 2008a).

In conclusion, the warning that Hypericum preparations may cause unwanted pregnancies is not covered by the available clinical data, not even for preparations rich in hyperforin where at least an increased incidence of break-through bleedings must be expected. For the traditional preparations with low hyperforin contents, such effects

	<p>are clearly not to be expected. We recommend to delete the corresponding warning in the traditional section, and to add a reference to hyperforin levels for the remaining potential interactions.</p> <p>Finally, the draft monograph mentions potential serotonin syndrome on concomitant use of SJW preparations and SSRI. The existence of a serotonin syndrome triggered by the intake of SJW preparations is still under debate. However, the concomitant intake of chemically defined antidepressants and of SJW is not recommended from a clinical point of view. We suggest that a corresponding warning be placed in section 4.4 – not with reference made to the interaction potential, but to general clinical considerations.</p>	
<p>4.5.</p>	<p>Proposed change:</p> <p>We propose to change “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.”</p> <p>into</p> <p>“Regarding potential interactions with medicinal products used during general and regional anaesthesia please refer to 4.5 Interactions.”</p> <p>Comments:</p> <p>We consider the statement “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.” as too broad and not scientifically justified.</p> <p>Some drugs potentially used during anaesthesia like alprazolam or midazolam for sedation are listed under 4.5 (Interactions). However, there is no prove for the entirety of anaesthetics to trigger interactions with St. John’s Wort (SJW), thus the range in the proposed wording is too extensive. Anyhow, even if an effect on pharmacokinetics or pharmacodynamics of single benzodiazepines might have been found</p>	<p>No such wording in 4.5, well-established use. Wording under 4.4. adjusted.</p>

	<p>in in-vitro or in-vivo-studies, a clinical relevance is not a logical consequence, since it appears possible that regardless of a hypothetical certain alteration of blood plasma levels of benzodiazepines by SJW, the sedative effect of the benzodiazepines might stay uninfluenced.</p> <p>In a hospital survey published in 2000 (1) a total of 1017 surveys were submitted over a period of 5 months out of which 755 surveys were assessed as valid surveys. 30% of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates the “pseudoephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided.” The survey did not reveal any risk within anaesthesiology practice for the concomitant intake of SJW and benzodiazepines.</p> <p>An article published in The Lancet by Marilyn Larkin (2) apparently reports about research from various centres in the USA which warns the patients who use herbal remedies may suffer from herb-anaesthesia interactions (3). However, the evidence of this article is rather weak, since there is no scientific basis for the statement that “SJW: May prolong effects of some narcotics and anaesthetics”. Neither narcotics nor anaesthetics are closer specified, there is no background given for this statement.</p> <p>Marilyn Larkin published another article in 2001 (4) in which she specifies the aspect of a “safe use of herbal products before surgery” for, amongst others, SJW: “Major concerns: Diminished effects of other drugs such as ciclosporin, warfarin, steroids &c. Stop before surgery: At least 5 days”. Narcotics and anaesthetics are not listed here.</p>	
<p>4.6.</p>	<p><u>Well-established use</u></p> <p>Comments:</p> <p>No specific risk is known from preclinical studies and from ample clinical use. In the absence of sufficient clinical studies, the use during pregnancy and lactation is not recommended.</p>	<p>Not endorsed.</p> <p>The study of Chan et al (2001) demonstrates, that with hypericin concentrations which can be achieved with dry extracts of Hypericum morphological changes can be induced in rat embryos. Therefore there is a specific risk known from preclinical studies.</p>

<p>Rationale:</p> <p>Data from preclinical studies and from a restricted number of observations do not point to safety problems regarding the use of Hypericum preparations during pregnancy and lactation. A careful risk-benefit evaluation is therefore recommended.</p> <p>The use of SJW in pregnancy and lactation is obviously wide-spread, especially the approx 10 % women experiencing postnatal depression as approximately 10 % of women do (Dugoua et al. 2006). Because of existing data on reproduction toxicity, which are part of the dossiers submitted with applications for marketing authorisation of certain Hypericum preparations, and of the long standing use of St. John's wort preparations for example in Germany, which has not been excluding pregnant or breast-feeding women before, specific risks for fetuses and breast-fed children should have been identified by now, if they were clinically relevant. Moreover, in several post-marketing surveillances also pregnant women have been included, without any evidence for special risks for adverse effects in this population (Demling et al. 2004, Rudolf and Zeller 2004). Furthermore the results of several smaller studies, including the investigation of breastmilk as well as plasma levels of breastfed infants and their mothers (Klier et al. 2002, 2006), or maternal and infant adverse events, infant weight over the first year of life, and whether or not the mother experienced lactation problems (Lee et al. 2003), did not reveal new specific adverse effects after maternal consumption of Hypericum preparations.</p> <p>The reasons for the absence of sufficient data from "high quality human research" as demanded by the rapporteur (Ass Rep p23/65) for the use of medications during pregnancy and lactation are well-known. For most pharmaceuticals, studies in this patient group are lacking, leading to wide-spread off-label use, which may pose a risk to the physician, or undertreatment, bearing other risks at least in some cases. Because of these facts and of the in general low risk of - only mild - adverse effects of Hypericum preparations, we suggest, that the decision, whether in the individual situation the administration of a Hypericum product might be helpful for a woman or not, is left to the physician.</p>	<p>Although pregnant women were included in some observational trials there is insufficient evidence for a safe use during pregnancy and lactation. A recommendation cannot be given. As for synthetic antidepressants it will be the duty of the doctor to evaluate between the benefit for the mother and the risk for the foetus.</p> <p>Limited data are available for the lactation period. Hyperforin is excreted into the breast milk. Hypericin and hyperforin are below the detection limit in the infant's plasma. Lee et al (2003) could not find differences in milk production, maternal events and infant weight over first year of life between Hypericum treated women and control groups. However, the number of observed patients is too small in order to draw conclusions.</p> <p>Therefore the use during pregnancy and lactation is not recommended.</p>
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<p>4.6.</p>	<p>The statement regarding the use in pregnant and lactating women was to be expected, although it is difficult to see how such data could ever be produced under controlled conditions. In addition, the question must be asked, how much data will ever be regarded as “sufficient”. <i>Hypericum</i> has been negatively tested for teratogenicity, and the available clinical does not point to any problem with the course of pregnancy or the development of the child.</p> <p>The general disclaimer will also leave the women and their physicians in an intolerable situation, as the alternative, the application of chemically defined antidepressants, is likewise not recommended for pregnant and lactating women.</p> <p>In fact, the experience with SJW preparations in pregnant and lactating women might even be better than that of the therapeutic alternatives, especially in view of the wide-spread use of <i>Hypericum perforatum</i>. In fact, there are publications reporting the absence of negative effects in pregnant and lactating women and their children (Demling et al. 2004; Dugoua et al. 2006; Grush et al. 1998; Hammerness et al. 2003; Klier et al. 2002; Klier et al. 2006; Lee et al. 2003). The overall number of examined women and children may still be relatively low. However, the available data at least allows adding a comment to the disclaimer, e.g.: “Experience from a limited number of observations does not point to specific risks related to the intake of <i>Hypericum</i> preparations during pregnancy and lactation. However, in the absence of sufficient data, ...”</p>	<p>See above.</p>
<p>4.7. Effects on ability to drive and use machines</p> <p>Well-established use</p>	<p>Comments:</p> <p>To our opinion, the statement “No studies on the effect on the ability to drive and use machines have been performed” in the draft monograph is not correct.</p> <p>Four randomized double-blind placebo-controlled trials specifically designed to assess psychomotor functioning relevant for the ability to drive and use machines did not find untoward effects of standardised SJW preparations alone or in combination with alcohol:</p> <ul style="list-style-type: none"> • Schmidt U, Harrer G, Kuhn U, Berger-Deinert W, Luther D: 	<p>Not endorsed.</p> <p>It is correct that there are several publications on the impact of <i>Hypericum</i> on mental performance. However, Herberg (1994) and Schmidt et al (1993) studied the effects of <i>Hypericum</i> in volunteers after alcohol intake. The studies demonstrate that there is no additional effect on mental performance caused by <i>Hypericum</i> compared to ethanol alone (blood alcohol concentrations 0.45-0.8‰).</p> <p>Friede et al (1998) demonstrated for the low-hyperforin extract Ze 117 the absence of sedative effect. It is unclear whether these findings are relevant for hyperforin-</p>

	<p>Wechselwirkungen von Hypericum-Extrakt mit Alkohol. [Interactions of Hypericum Extract with Alcohol]. Nervenheilkunde 1993; 12 (6): 314-319.</p> <ul style="list-style-type: none"> • Schmidt U, Sommer H: Johanniskraut-Extrakt zur ambulanten Therapie der Depression - Aufmerksamkeit und Reaktionsvermögen bleiben erhalten. [St. John's wort extract for outpatient treatment of depression - Uncompromised attention and alertness]. Fortschr Med 1993; 111 (19): 339-342. • Herberg KW: Psychotrope Phytopharmaka im Test. Therapiewoche 1994; 44 (12): 704-713. • Friede M: Untersuchungen zur Alltagssicherheit des Johanniskrautextraktes Ze117. In: Rietbrock N (Ed.): Phytopharmaka VI Forschung und klinische Anwendung. Steinkopff, Darmstadt 2000. pp. 67-74. <p>Please refer to <u>attachment 2</u> for summaries of these studies.</p> <p>Proposed change:</p> <p>We propose to change</p> <p>“No studies on the effect on the ability to drive and use machines have been performed”</p> <p>into</p> <p>“No impairment of the ability to drive and use machines was seen in clinical studies.”</p>	<p>containing extracts too.</p> <p>Girzu et al (1997) found considerable sedative effects of a dry extract of Hypericum.</p> <p>In the absence of a clear evidence the sentence will be changed to:</p> <p>No adequate studies on the effect on the ability to drive and use machines have been performed.</p>
<p>4.7.</p>	<p>Comments:</p> <p>We suggest to substitute the following sentences:</p> <p><u>Well-established use</u></p> <p>No studies on the effect on the ability to drive and use machines have been performed.</p> <p>There is no evidence for a possible influence on the ability to drive and use machines.</p>	<p>See above.</p>

	<p>Rationale:</p> <p>There is a published study showing that there is no negative effect on the ability to drive and use machines investigating preparation B (2) (Herberg 1994). In this study there were no clinically relevant impairments of motor performance or loss of vigilance observed. We therefore suggest replacing the wording in the draft by the proposed entence.</p>	
4.7.	<p><u>Well-established use</u></p> <p>No effects on the ability to drive and use machines are to be expected. No studies on the effect on the ability to drive and use machines have been performed.</p>	See above.
4.7.	<p>It is not correct that “no studies have been performed”. In fact, SJW preparations have been tested on their effects on mental performance and reaction time in controlled experiments (Friede et al. 1998; Johnson et al. 1994). SJW preparations do not have sedative effects; hence, no negative impact on the ability to drive and use machines is anticipated (Boettcher et al. 2000).</p> <p>We suggest changing the disclaimer correspondingly.</p>	See above.
4.7.	<p>Proposed change:</p> <p>We propose to change</p> <p>“No studies on the effect on the ability to drive and use machines have been performed.”</p> <p>into</p> <p>“No impairment of the ability to drive and use machines was seen in clinical studies.”</p> <p>Comments:</p> <p>To our opinion, the statement “No studies on the effect on the ability to drive and use machines have been performed.” in the draft monograph is not correct.</p>	See above.

	<p>Four randomized double-blind placebo-controlled trials specifically designed to assess psychomotor functioning relevant for the ability to drive and use machines did not find untoward effects of standardized SJW preparations alone or in combination with alcohol (Schmidt [1993a], Schmidt [1993b], Herberg [1994], Friede [2000]).</p>	
4.8	<p>Comments:</p> <p>Due to the potential seriousness of serotonergic syndrome, an information on the risk is of major interest for the user of <i>Hypericum perforatum</i></p> <p>Proposed change</p> <p>Well-established use and Traditional use, indication1</p> <p>Cases of serotonergic syndrome have been reported in elderly patients in case of concomitant treatment with ISRS. Symptoms have decreased after discontinuation of <i>Hypericum perforatum</i>.</p> <p>Gastrointestinal disorders, allergic reactions of the skin, fatigue and restlessness may occur. The frequency is not known.</p> <p>Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight.</p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>	<p>Not endorsed.</p> <p>Adverse affects resulting from concomitant treatment with other drugs should be reported in the interactions section of the monograph.</p>
4.8.	<p><u>Well-established use</u></p> <p>Gastrointestinal disorders, allergic reactions of the skin, fatigue and restlessness may occur. The frequency is not known.</p> <p>Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight.</p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>	<p>Not endorsed.</p> <p>Data on the frequency of certain adverse events differ between clinical studies and are not consistent. In the case that no information on the frequency can be given, the sentence “The frequency is not known” has to be included.</p>

	<p>Comments: We propose to delete the second sentence, because "may occur" is sufficient.</p>	
<p>4.9. Overdose</p>	<p>Comments:</p> <p>The information that symptoms from intoxication with SJW extract preparations have not been reported up to now, is a relevant information for the patient as well as physicians. However it is important that, based on the safety profile of SJW concerning the exposure to sunlight and other UV-sources, after ingestion of <u>massive</u> overdose, the patient should be protected from sunlight and other UV-sources for 1-2 weeks.</p> <p>Proposed change:</p> <p>We propose to change</p> <p>“After ingestion of overdose the patient should be protected from sunlight and other UV-sources for 1 – 2 weeks.”</p> <p>into</p> <p>„Symptoms from intoxication with products containing St. John's Wort extract have not been reported up to now. However, after ingestion of massive overdose, the patient should be protected from sunlight and other UV-sources for 1-2 weeks”.</p>	<p>Not endorsed.</p> <p>Karalapillai & Bellomo (2007) report symptoms after a case of overdose. According SPC-Guidelines data on symptoms and on the management of the overdose should be provided.</p>
<p>4.9.</p>	<p><u>Well-established use</u></p> <p>We suggest to delete the sentence "After ingestion of overdose the patient should be protected from sunlight and other UV-sources for 1 – 2 weeks." And to replace by either "After ingestion of overdoses no other measures than those given in the section "special measures and precautions for use" are necessary." or "Symptoms from intoxication with Hypericum dry extract have not been reported up to now. However, after ingestion of massive overdose, intense UV-exposure should be</p>	<p>Not endorsed.</p> <p>The reference Grzylak et al (2007) provides data from poison control centres in the United States. No details on the ingested amounts of Hypericum are given. Moreover, all products marketed in the US are dietary supplements. It is known that dietary supplements may contain considerably less extract compared to the labelling of the product. The fact that no life-threatening toxic symptoms have been reported may be influenced by that fact.</p>

	<p>avoided"</p> <p>Comments: After ingestions of overdoses of St. John's wort extract no life-threatening toxic symptoms have been observed (Grzylak 2007). An enhanced photosensitivity is also not to be expected after overdose due to incidental or suicidal ingestion. The information that symptoms from intoxication with preparations containing the extract of St. John's Wort have not been reported up to now is a relevant information for the patient as well as physicians. It is also important that such phenomena seem to be possible after massive overdose over a prolonged time only.</p>	
4.9.	<p>Proposed change:</p> <p>We propose to change</p> <p>“After ingestion of overdose the patient should be protected from sunlight and other UV-sources for 1 – 2 weeks.”</p> <p>into</p> <p>„Symptoms from intoxication with products containing St. John's Wort extract have not been reported up to now. However, after ingestion of massive overdose the patient should be protected from sunlight and other UV-sources for 1 – 2 weeks</p> <p>Comments: The information that symptoms from intoxication with SJW extract preparations have not been reported up to now is a relevant information for the patient as well as physicians.</p>	<p>Not endorsed. See above.</p>
5.1.	<p>Hypericum dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, and serotonin and dopamine. Subchronic treatment causes a downregulation of beta-adrenoreceptors; it changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) comparable to other antidepressants. Naphodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and</p>	<p>Endorsed.</p>

	<p>flavonoids contribute to the activity.</p> <p>Rationale:</p> <p>We suggest adding “dopamine” to the list of neurotransmitters because its reuptake inhibition has been shown in several investigations (see e.g. Butterweck et al. 2003 for review).</p>	
5.1.	<p><u>Well-established use</u></p> <p>Pharmacotherapeutic group: Other antidepressants ATC code: N06AX</p> <p>Hypericum dry extract inhibits the synaptosomal uptake of the neurotransmitters noradrenaline, serotonin and dopamine. Subchronic treatment causes a downregulation of beta-adrenoreceptors; it changes the behaviour of animals in several antidepressant models (e.g., forced swimming test) similar to other antidepressants. Naphodianthrones (e.g. hypericin, pseudohypericin), phloroglucin derivatives (e.g. hyperforin) and flavonoids contribute to the activity.</p> <p>Comments: There is sufficient evidence for a reuptake inhibition of dopamine, see e.g. Butterweck et al. (2003). Hence, this should be added.</p>	Endorsed.
5.2.	<p>The absorption of hypericin is delayed and starts about 2 hours after administration. The elimination half-life of hypericin is about 24 hours, the mean residence time about 375 hours.</p> <p>Maximum hyperforin levels are reached about 3 hours after administration; no accumulation could be detected. Hyperforin and the flavonoid miquelianin can cross the blood-brain-barrier.</p> <p>Hyperforin induces the activity of the isoenzyme CYP3A4. The elimination of other drug substances may be therefore accelerated, resulting in decreased plasma concentrations.</p>	<p>Endorsed.</p> <p>The pharmacokinetic data are different depending on the concentration of substances given per single dose. The values given in this section of the monograph should represent a mean value.</p>

	<p>Rationale:</p> <p>A number of investigations on bioavailability and pharmacokinetics of active components of Hypericum extract are available, all of them including hypericin, most of them also hyperforin and two most recent of them (Schulz et al. 2005a, b) in addition flavonoids.</p> <p>There is a remarkable difference between the elimination half-life and the mean residence time of a substance that we ask to take into account here. We propose to relate to the study of Schulz et al. 2005a and give values of 24 h for the elimination half life and 35 h for the mean residence time.</p>	
5.2.	<p><u>Well-established use</u></p> <p>The absorption of hypericin is delayed and starts about 2 hours after administration. The elimination half-life of hypericin is about 18 hours, the mean residence time about 357 hours.</p> <p>Maximum hyperforin levels are reached about 3 hours after administration; no accumulation could be detected. Hyperforin and the flavonoid miquelianin can cross the blood-brain-barrier.</p> <p>Hyperforin induces the activity of the isoenzyme metabolic enzymes CYP3A4, CYP2C19 and PGP via activation of the PXR system. The elimination of other drug substances may be therefore accelerated, resulting in decreased plasma concentrations.</p> <p>Comments: For pharmacokinetic parameters see the publication of Schulz et al. 2005, presenting studies with STW 3-VI and cited in the assessment report. It is necessary to differentiate between elimination half-life (18 h) and mean residence time (35 h). For comments on the interaction potential see section 4.5.</p>	<p>Endorsed.</p> <p>See also above.</p>
5.2.	<p>The activation of the metabolic enzymes cytochrome P450 2C19 and pGP might be added. We otherwise suggest mentioning the dose-dependency.</p>	<p>Endorsed.</p>

<p>5.3</p>	<p>Preclinical safety data:</p> <p>No adequate tests on reproduction toxicity have been performed.</p> <p>Tests on the carcinogenic potential have not been performed.</p> <p>Preclinical safety data, as presented in the monograph and the respective assessment report, do not take into account the most important toxicity study, which has been conducted with a typical dry extract (LI 160/WS 5570, DER 4-7:1, extraction solvent methanol [80% v/v]) between 1996 and 1999 in the <i>LPT Laboratory of Pharmacology and Toxicology</i>, Hamburg/Germany with J. Leuschner as head of the study. All <i>in vitro</i> and <i>in vivo</i> toxicological tests, which have to be performed for an application for marketing authorisation in this indication were done: Acute oral and intraperitoneal toxicity in mice and rats; 26-week oral toxicity in rats and dogs (partly included in section II.2.3.1.2 of the respective assessment report); oral reproductive toxicity in rats, 6th – 17th day pc as well as 14th day ac to 21st day of lactation; oral reproductive toxicity in rabbits, 6th – 20th day pc; mutagenic potential (AMES, Salmonella, V79, lymphocytes with and without metabolic activation; carcinogenic potential in about 400 mice and rats for a duration of about 100 resp. about 120 weeks until spontaneous mortality of about 75% of the animals. These studies did not give any hints to serious toxic risks due to the administration of <i>Hypericum</i> extract.</p> <p>The results of these studies have not been not published. However, they are available as single files as well as part of scientific assessment reports in the archives of the German regulatory authority (BfArM).</p> <p>Proposed Change:</p> <p>Studies on reproduction toxicity in rats and rabbits have been conducted; the NOEL in rats was 100 mg/kg/d orally.</p> <p>Studies on carcinogenic potential in mice and rats over a duration of approx. 100 resp. approx. 120 days did not give hints to a carcinogenic risk.</p>	<p>The information is included in the text.</p>
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<p>5.3.</p>	<p><u>Well-established use</u></p> <p>Studies on acute toxicity and repeated dose toxicity did not show signs of toxic effects.</p> <p>The weak positive results of an ethanolic extract in the AMES-test (Salmonella typhimurium TA 98 and TA 100 with and without metabolic activation) could be assigned to quercetin and are irrelevant for human safety. No signs of mutagenicity could be detected in further in vitro and in vivo test systems.</p> <p>No adverse effects have been observed in reproduction toxicity testing.</p> <p>No adequate testes on reproduction toxicity have been performed.</p> <p>No genotoxicity was observed in corresponding test models.</p> <p>Tests on the carcinogenic potential have not been published performed.</p> <p>Phototoxicity:</p> <p>After oral application of dosages of 1800 mg of an extract per day for 15 days the skin sensitivity against UVA was increased, and the minimum dose for pigmentation was significantly reduced. In the recommended dosage no signs of phototoxicity are reported.</p> <p>Comments : It should be explicitly clarified, that the fact, that weak positive results in some older mutagenicity tests could be assigned to quercetin, means, that they are irrelevant for human therapeutic safety.</p> <p>Reproduction and developmental toxicity has been examined in state of the art models, to our knowledge for at least three different preparations. No toxic effect was detected.</p> <p>Pivotal studies have e.g. been conducted, according to GLP, with the extract STW 3.</p> <p><i>Fertility in rats, embryo-fetal development in rats and rabbits, and prenatal and postnatal development including maternal functions, in rats were conducted. No signs of reproduction or developmental toxicity were found with the applied doses of up to 1000 mg STW 3 per kg b.w., so showing, that there is no reproduction toxicological effect. The studies are part of the pharmacological-toxicological documentations of the corresponding products registered in several European countries, e.g. Austria and Germany, and accessible through</i></p>	<p>Statement on quercetin: endorsed.</p> <p>Statement on reproduction toxicity: not endorsed (see section pregnancy and lactation).</p> <p>Statement on carcinogenicity: endorsed.</p>
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the respective documentations.

For the assessment of the general tolerability of treated dams during gestation and for the evaluation of the intrauterine development during the different stages of embryonic/foetal development, the extract Ze 117 was investigated in a Segment II study in rats. The study of Klaus (1998) was performed in compliance with the ICH-recommendations for "Detection of Toxicity to Reproduction for Medicinal Products". 24 inseminated female Wistar rats per group were treated daily from day 6 to 17 p.c. with the test article applied orally by gavage with doses of 0, 100, 300 and 1000 mg/kg body weight and day, respectively. There were no treatment-related effects on appearance and behaviour as well as on other clinical observations in the dams at all dose-levels tested up to and including the dose level of 1000 mg/kg b.w./day. Body weight and feed consumption were unaffected. No treatment-related gross pathological findings or mortality occurred. The pregnancy and resorption rates as well as the number of fetuses were unaffected by the treatment. Placental and fetal weights did not reveal any indication of treatment-related effects at all dose levels tested. External and visceral examinations of the fetuses revealed no treatment-related findings. The skeletal evaluation of the fetuses neither revealed any indications for treatment-related malformations nor on effects on the stage of ossification. Chan et al. (2001) examined the potential teratogenic effects of isolated hypericin, using the explanted rat's embryo model. Embryos were explanted at gestational day 9.5 and cultured in vitro for 48 hours in a culture medium containing hypericin in a final concentration of 0 to 142 ng/ml. At gestational day 11.5, embryos were examined by a blinded rater. Morphological changes were found with the highest hypericin concentrations (71.0 and 142.0 ng/ml).

The authors point to serum levels of up to 78 ng/ml after application of 1800 mg/day of Hypericum extract by Schempp et al. (1999) and thus to potentially teratogenic effects (Chan et al. 2001).

With the recommended dose schemes of SJW products this level of hypericin is not reached. In addition, the test system applied by Chan et al. (2001) allows direct contact between embryo and hypericin-containing medium, a situation not known in humans due to the blood-placental barrier.

Rayburn et al. (2000) tested the development of mice offspring in a randomized, placebo-controlled manner after antenatal exposition to SJW. A daily dose of SJW (0.75 mg/g of food consumed), equivalent to that in human beings according to body surface, was chosen. CD-1 mice were randomly assigned to consume either SJW (n = 45) or placebo (n = 45) for 2 weeks before conception and throughout gestation. Behavioural testing consisted of early developmental tasks of geotaxis, separation vocalization, and homing, followed by motor, anxiety, and depression assessments into adulthood. Birth weights of male offspring were less in the SJW group than in the placebo group (1.68 vs. 1.75 g; $p < 0.01$). Offspring in both treatment groups showed no long-term statistical differences in early developmental tasks, locomotor activity, and exploratory behaviour throughout development. Performances on a depression task (forced swim) and on anxiety tasks (elevated plus maze as juveniles and adults) revealed no differences between treatment groups. Antenatal exposure to a therapeutic dose of SJW showed no long-term deficits on selected behavioural tasks by developing mice offspring (Rayburn et al. 2000).

Rayburn et al. (2001a) investigated the cognitive impact of prenatal exposure to SJW in CD-1 mice. SJW extract (Basic organics, 0.3 % hypericin, 182 mg/kg/day) or a placebo was consumed in food bars for 2 weeks before mating and throughout gestation. One offspring per gender from each litter (SJW 13, placebo 12) was tested on each of the following tasks: juvenile runway with adult memory, adult Morris maze, adult passive avoidance, or adult straight water runway followed by a dry Cincinnati maze. Learning occurred in both genders in all tasks ($p < 0.003$) with no significant differences between treatments at the final trial. Female offspring exposed to hypericum, rather than to a placebo, required more time to learn the Morris maze task ($p < 0.05$). Postlearning sessions did not show any significant differences. In conclusion, prenatal exposure to a therapeutic dose of SJW did not have a major impact on certain cognitive tasks in mice offspring (Rayburn et al. 2001a).

Rayburn et al. (2001b) determined whether prenatal exposure to SJW affects long-term growth and physical maturation of mouse offspring. Forty CD-1 mice were randomly assigned to receive daily doses of either 180 mg/kg per day of SJW (n = 20) or placebo (n = 20) for 2 weeks before conception and throughout gestation. Perinatal

outcomes, growth, and physical milestones of the offspring were compared in a blinded manner. The gestational ages at delivery and litter sizes did not differ between the SJW-exposed and the placebo-exposed offspring. The body weight, body length, and head circumference measurements from postnatal day 3 through adulthood increased in a manner that was indistinguishable between the two groups of offspring, regardless of gender. No differences in reaching physical milestones (teeth eruptions, eye opening, and external genitalia) were noted between the 2 groups. The reproductive capability, perinatal outcomes, and growth and development of the second-generation offspring were unaffected by SJW exposure. Maternal administration of Hypericum before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring (Rayburn et al. 2001b).

In a review on safety of SJW during pregnancy and lactation, Dugoua et al. (2006) report no impact on maternal weight gain or duration of gestation on Sprague-Dawley rats exposed to dietary doses of SJW 1 to 25 times the recommended human dose. SJW had no impact on maternal weight gain or duration of gestation. Offspring body weights were similar to controls, although there was a tendency towards lower weight on treatment with SJW. There were no SJW related behavioural alterations on any measure (Dugoua et al. 2006).

Carcinogenicity has not been reported or suspected with preparations of SJW. According to the HMPC Guideline on the assessment of genotoxicity of herbal substances/preparations (EMA/HMPC107079/2007), no further genotoxic or mutagenicity testing is needed, if in vitro respective in vivo genotoxicity testing results are negative. Therefore, no carcinogenicity testing is mandatory, and therefore should not merely be mentioned as lacking by giving the statement that they “have not been performed”. It would be more appropriate to mention, that carcinogenicity is not to be expected according to the results of the existing mutagenicity and genotoxicity data.

As it is not known, whether unpublished studies exist, it would seem also to be appropriate to replace the term “have not been performed” by “have not been published”.

The lack of potential genotoxic effects is also not questioned by the

	<p>discussion of such effects of quercetin. On closer examination of the available data from <i>in vivo</i> studies, a carcinogenic effect of quercetin could not be confirmed, whereas in contrast a cancer-protective effect was proposed (Ito 1992; Stavric 1994; Zhu et al. 1994). The potential of quercetin as a carcinogenic agent has also been assessed by the International Agency for the Research on Cancer, and it was concluded that "no valid evidence exists for the carcinogenicity of quercetin in humans, since the amount of quercetin derived from the normal diet is many times higher than the amount of quercetin ingested from the therapeutic use of plants" (WHO).</p> <p>The hypericum extract STW 3 was tested on mutagenicity in mammalian test models <i>in vitro</i> (HGPRT, unscheduled DNA synthesis (UDS) assay, cell transformation assay) and <i>in vivo</i> (fur spot test and chromosome aberration test) giving negative results (Okpanyi et al. 1990). The extract Ze 117 was specifically tested on mutagenicity in the micronucleus test of the mouse. In this GLP-conform pivotal study no relevant indication of clastogenic effects after single oral treatment with doses of 1250, 2500 and 5000 mg/kg was found. The number of micronucleated nonchromatic erythrocytes did not increase relevantly in any group. The ratio of polychromatic to normochromatic cells did not vary to a biologically relevant degree in the groups treated with Ze 117 as compared with negative control (Herbold 1997).</p> <p>In a recent study quercetin was shown to be not genotoxic <i>in vivo</i> using the bone marrow micronucleus assay and the unscheduled DNA synthesis assay, supporting the absence of quercetin-related adverse effects following oral exposure (Utesch et al. 2008). In a very recent review the safety of quercetin and the lack of evidence of its <i>in vivo</i> genotoxicity and carcinogenicity were extensively discussed. The authors concluded that – despite of the genotoxic effects of quercetin observed <i>in vitro</i> – quercetin produces no adverse health effects at estimated human intake levels (Harwood et al. 2007).</p>	
	<p>It is not correct that no adequate tests on reproduction toxicity have been performed. In fact, SJW preparations have been examined in state of the art toxicological studies (Chan et al. 2001; Dugoua et al. 2006; Rayburn et al. 2000; Rayburn et al. 2001b; Rayburn et al. 2001a). However, many results from toxicity testing have not been</p>	<p>Not endorsed, since such data were not submitted.</p>

	<p>published. We assume that the corresponding data will be submitted to the HMPC in the consultation process.</p> <p>We suggest that the phrase related to reproduction toxicity be changed to “Tests on reproduction toxicity did not point to a specific risk during pregnancy”.</p> <p>It is also not correct that no carcinogenicity testing was made with SJW preparations. Again, we expect the corresponding unpublished data to be submitted in the consultation process.</p>	
6	<p><u>Well-established use</u></p> <p>Extracts should be quantified with respect to hypericin, hyperforin and flavonoids, specified according to Ph.Eur².</p>	<p>In the meaning of the European Pharmacopoeia the extracts have to be quantified with respect to hypericin only. However, the amounts of hyperforin and of the flavonoids should be additionally provided.</p> <p>Proposed wording:</p> <p>Extracts should be quantified with respect to hypericin (reference to the monograph extracts of Pharm. Eur.). The amounts of hyperforin and of flavonoids should be declared.</p>

² Ph. Eur. monograph (ref. 01/2008:0765) Extracts and St John’s wort dry extract (027/2008:1874)

SPECIFIC COMMENTS ON TEXT – Traditional use		
Section number and heading	Comment and Rationale	Outcome
<p>2. Qualitative and quantitative composition</p> <p>Well-established use</p>	<p><u>Traditional use</u></p> <p>The proposed classification of the existing preparations has been done with due care, so that only minor modifications seem to be inevitable:</p> <p>A) Dry extract (DER native 4-7:1), extraction solvent ethanol 38% v/v (m/m)</p> <p>B (1) Dry extract (DER native 3.5-6:1), extraction solvent ethanol 60% (m/m)</p> <p>B (2) Dry extract (DER native 5-7:1), extraction solvent ethanol (60% m/m)</p> <p>C) Dry extract (DER native 5-7:1), extraction solvent ethanol 70% (m/m/v)</p> <p>D) Liquid extract oily mazerate (DER native 1:4-20), extraction solvent vegetable oil⁴</p> <p>E) Liquid extract oily mazerate (DER native 1: 13), extraction solvent maize oil or other suitable vegetable oil</p> <p>F) Tincture (DER Ratio of herbal drug to extraction solvent 1:10), extraction solvent ethanol 45-50% (v/v)</p> <p>G) Tincture (DER Ratio of herbal drug to extraction solvent 1:5), extraction solvent ethanol 50% (v/v)</p> <p>H) Liquid extract (DER native 1:2), extraction solvent ethanol 50%</p> <p>I) Liquid extract Tincture (DER Ratio of herbal drug to extraction solvent 1: 5-7), extraction solvent ethanol 50%.</p> <p>J) Expressed juice from the fresh herb (DER native 1.25-2.5:1 1:0.5-2.5)⁵</p> <p>K) Comminuted or powdered herbal substance drug</p> <p>We suggest to include preparation B (2), which is marketed by Steiner, Berlin, Germany. A check of the declarations of the respective products revealed, that the extraction solvent of A should be declared m/m, while that of C should be declared v/v. For the</p>	<p>DER native: the DER mentioned in monographs refers always to the native extract. Therefore no special declaration is necessary.</p> <p>Extract A: ethanol 38% m/m endorsed</p> <p>Extract B1: matches the specification of preparation C under well-established use.</p> <p>Proposed extract B2: matches the specification of preparation C under well-established use.</p> <p>Extract C: now covered by preparation C under well-established use.</p> <p>Oily macerate: this terminology is not used in the European Pharmacopoeia. Therefore the term 'liquid extract' has to remain.</p> <p>Other suitable vegetable oil: endorsed</p> <p>Tinctures: endorsed</p> <p>Powdered herbal substance: endorsed</p> <p>DER expressed juice: data reflect the range submitted by national competent authorities. Widened to 1.1-2.5:1</p>

	<p>extraction of preparations subsumed under E also other vegetable oils are in use, and the appropriate term according to Pharm Eur would be not extract, but mazerate. Juices, as listed under J, are prepared to different DERs, so that a wider range is proposed. Besides comminuted, also powdered herbal substance (K) is in traditional use (e.g. in a product of Merz, Frankfurt, Germany).</p> <p>Correspondingly in the case of the preparations in traditional use we propose to merge similar preparations to larger groups: Preparations A to C should be merged to one group described “Dry extract (DER native 3.5-7:1), extraction solvent ethanol 38-70 % (m/m or v/v)”. Preparations D and E should be grouped as “Liquid extract (DER native 1:4-20), extraction solvent vegetable oils”. The tinctures F, G and I could be grouped as “Tinctures (ratio of herbal drug to extraction solvent 1:5-10), extraction solvent 45-50 (v/v)”.</p>	
2	<p><u>Traditional use</u></p> <p>i) Herbal substance Whole or cut, dried flowering tops, harvested during flowering time.</p> <p>ii) Herbal preparations (Footnote 3: If relevant For safety reasons, the amount of hyperforin and hypericin should be specified.)</p> <p>a) General comment on hyperforin and hypericin specification</p> <p>We do not agree upon the general statement in footnote no. 3 which recommends specifying the amount of hyperforin and hypericin in traditionally used herbal preparations. Although we fully agree to determine the content of each preparation and evaluate the risk of interactions, a specification on the label is only justified for certain preparations. It is known that some herbal preparation, e.g. preparation E (liquid extract, DER 1:13, extraction solvent maize oil) contains neither hyperforin nor hypericin. Furthermore in tea infusions hyperforin is reduced to an extremely low content by boiling water. Thus in these cases risk labeling does not make sense. We therefore propose to establish a threshold of hyperforin (1 mg, justification see chapter 4.5) above which labeling is considered</p>	<p>Footnote: endorsed.</p> <p>Other comments: see above.</p> <p>Tincture from Boiron: The mentioned preparation is a homoeopathic mother tincture prepared from the fresh whole plant (aerial and underground parts). Therefore this preparation is not included in the monograph.</p>

appropriate. Defining a specification may be of interest when it comes to assessing the risk of herb-drug interactions, but not as a parameter of efficacy (Butterweck and Schmidt 2007). It is therefore recommended not to overstress the hyperforin content for the evaluation of efficacy. In addition, hyperforin contents were rarely mentioned in the bibliographic studies. Since the most recent meta-analysis of clinical trials with St. John's wort preparations did not demonstrate a difference in outcome for the types of preparations referenced in the "well-established" column (including the extract Ze 117) (Linde et al. 2008), it does not seem necessary to define exact limits for hypericin, hyperforin and flavonoids.

b) Proposal to summarise the preparations

- A) Dry extracts (DER 3-7:1), extraction solvent ethanol 38 % (m/m) or 45 % (v/v) - 70 % (v/v) (comprises old A/B/C)*)**
- B) Oily macerates (liquid extracts, 1-4:13-20), extraction solvent vegetable oils (comprises old D/E)**
- C) Tinctures (1:5 or 1:10), extraction solvent ethanol 45-65 % (comprises old F/G and F*)**
- D) Liquid extracts (1:2-7), solvent ethanol 50 % (comprises old H/I)**
- E) Expressed juice from the fresh herb (1:0.5-0.9) (corresponds to old J)**
- F) Comminuted herbal substance or plant powder (corresponds to old K) and delete the rest.**

*) Comment on preparation A: $38 \% (m/m) = 45 \% (v/v)$

c) **Alternative proposal**

In case the HMPC prefers a detailed list of existing preparations, the following approach seems to be acceptable as an alternative:

- A) Dry extract (DER 4-7:1), extraction solvent ethanol 38% (m/m)
- B) Dry extract (DER 3.5-6:1), extraction solvent ethanol 60% (m/m)
- C) Dry extract (DER 5-7:1), extraction solvent ethanol 70% (m/m/v)
- C*) Dry extract (DER 5-7:1), extraction solvent ethanol (60% m/m)**

	<p>D) Oily macerate (liquid extract, 1:4-20), extraction solvent vegetable oil (Footnote: Preparation: maceration of the fresh or dried herbal substance with vegetable oil over a period of 2 days to several weeks under light exposure.)</p> <p>E) Oily macerate (liquid extract, 1: 13), extraction solvent maize oil or other suitable extraction solvents</p> <p>F) Tincture (1:10), extraction solvent ethanol 45-50% (v/v)</p> <p>F*) Tincture (1:10), extraction solvent ethanol 65% (v/v)</p> <p>G) Tincture (1:5), extraction solvent ethanol 50% (v/v)</p> <p>H) Liquid extract (1:2), extraction solvent ethanol 50%</p> <p>I) Liquid extract (1: 5-7), extraction solvent ethanol 50%.</p> <p>J) Expressed juice from the fresh herb (1:0.5-0.9)</p> <p>K) Comminuted or powdered herbal substance</p> <p><u>Comments:</u> Preparation A (Dry extract (DER 4-7:1), extraction solvent ethanol 38% (v/v)) should not read % (v/v), but % (m/m). Preparation C (DER 5-7:1, extraction solvent ethanol 70 %) should not read % (m/m), but % (v/v). Preparation C*: This herbal preparation is missing and has been included as C*: Dry extract (5-7:1), extraction solvent ethanol (60% m/m). The preparation is marketed by Steiner, Germany. Preparation E: There are several products in the market which are prepared which extraction solvents other than maize oil. Preparation F*: this herbal preparation is missing and has been included as F*: Tincture (1:10), extraction solvent ethanol 65% (v/v) (marketed in France by Boiron since 1965)</p> <p>Preparation J (pressed juice, 1.25 to 2.5:1) is too limited in the range, as there are also expressed juice from the fresh herb with a range of 1: 0.5 to 0.9 (as in Florabio). Preparation K: Powdered herbal substances should be included (marketed by Merz, Germany).</p>	
	<p>Among the traditionally used preparations, preparation B must be shifted to the section of well-established preparations (extraction solvent ethanol 60 %, DER 3.5-6:1) – see above. In addition, the drug-extract ratio defined for preparation J (expressed juice) seems too narrow, as there are also other preparations with different DER</p>	<p>Dry extract: endorsed. Expressed juice: see above.</p>

	<p>on the market. From a technical point of view the question must be asked whether it makes sense at all to define a DER for a pure pressed juice.</p>	
3	<p><u>Traditional use:</u> Comment: As the comminuted herbal drug is traditionally used also as herbal infusion, the following term should be added: Comminuted herbal drug K for tea preparation. In case the proposal from section 2 is followed, to merge similar preparations to one category, respective changes need to be made in this section, too.</p>	Endorsed.
3	<p><u>Traditional use</u> No change in the following wording: Comminuted herbal substance for tea preparation. ... The pharmaceutical form should be described by the European Pharmacopoeia full standard term. <u>Comments:</u> However, in case the preparations are summarised, we propose: Preparations A-F A, B, C, E, F, G, H, I, J, K in liquid or solid dosage forms for oral use. Herbal preparations B, C and F D, F, G, K in liquid or semi-solid dosage forms for cutaneous use.</p>	Endorsed.
4.1	<p>Comments: We do not support the proposed wording of indication for well-established use (“for treatment of mild depressive episodes”). The efficacy in major depressive episodes (MDE, as defined in DSM IV) is not sufficiently demonstrated for SJW. Moreover, diagnosis of MDE is based on careful medical evaluation after exclusion of moderate and severe episodes.</p>	Not endorsed. See part well-established use.

	<p>Proposed change</p> <p>Traditional use, indication 1</p> <p>Traditional herbal medicinal product for the relief of mild and transient depressive-like symptoms.</p>	
4.1	<p><u>For the traditional use</u>, the proposed therapeutic indication is as follows: “<i>Traditional herbal medicinal product for the relief of temporary mental exhaustion (neurasthenia)</i>”.</p> <p>As stated, the therapeutic indication cannot be considered as appropriate based on following considerations:</p> <ol style="list-style-type: none"> 1. As mentioned in the pre-published assessment report (EMEA/HMPC/101303/2008), ICD-10 F48.0 mentions under “neurasthenia” that “<u>considerable cultural variations occur in the presentation of this disorder and two main types occur with substantial overlap</u>”, i.e. “<i>complaint of increased fatigue after mental effort</i>” and “<i>feelings of bodily or physical weakness and exhaustion after only minimal effort</i>”. As the presentation of the disorder “neurasthenia” is subject to “considerable cultural variations”, the understanding of such wording would be not identical across EU countries which looks not appropriate. Additionally, this term is described as obsolete in some French medical dictionaries. 2. The proposed traditional use wording for St John’s wort preparations (“<i>for the relief of temporary mental exhaustion</i>”) focuses only on <u>exhaustion of mental origin</u>. This is too much restrictive as mental exhaustion represents a symptom amongst others accompanying low mood. 3. As mentioned in the draft assessment report (EMEA/HMPC/101303/2008), “<i>the indication should be clearly different from the proposed <u>health claims for food supplements</u></i>”. Considering examples which are given (e.g. 	<p>Not endorsed.</p> <p>The indication should be clearly indicate, that the traditional herbal medicinal products are not intended and not suitable for the treatment of depression or symptoms of depression.</p>

“contributes to optimal relaxation” or “helps to maintain a positive mood”), the proposed traditional indication looks much less supportive than the reported claims. Such weak and vague indication would compromise the future of already existing St John’s wort medicinal products with a traditional status (e.g. in France).

4. Therapeutic indication of licensed St John’s wort THMP in France is “*traditionally used in mild and temporary depressive manifestations (traditionnellement utilisé dans les manifestations dépressives légères et transitoires)*” [French Official Journal, 2 March 2002;4049-51].

5. The MHRA registered last year three products containing St John’s wort as active ingredient:
Hypericalm: THR 23056/0007 (Feb. 2008)
Hyperiforce: THR 13668/0014 (May 2008)
Duchy Herbals Hyperi-lift tincture: THR 01175/0123 (Oct. 2008).

The therapeutic indication granted was “*a traditional herbal medicinal product used to relieve the symptoms of slightly low mood and mild anxiety*”. Such indication could contribute effectively to define a proper indication corresponding to a grade of traditional use.

Based on former considerations, two alternative therapeutic indications are proposed.

First proposal is in line with approved therapeutic indication of registered THMP in France and with recognized use of St John’s wort throughout Western populations:

“Traditional herbal medicinal product used to relieve the symptoms of mild temporary depressed mood”.

The draft assessment report (EMEA/HMPC/101303/2008) specifies that terms like “depression” or “depressed mood” are not approved for the indication of a THMP without further comments. Meanwhile, according to the same report, a long-standing use of St John’s wort in

	<p>“<u>mood depression</u>” has been cited in different textbooks published more than 30 years ago [Irion, 1955; Auster <i>et al.</i>, 1958; Flamm <i>et al.</i>, 1940]. The wording “depressed mood” looks to be a coherent graduation between cited claims of food supplements and proposed therapeutic indication of HMP (draft EMEA/HMPC/101304/2008). Additionally, such wording is also presented in the draft assessment report as being plausible because of pharmacological and clinical data which are available for isolated compounds and alcoholic extracts of St John’s wort. The draft assessment report emphasises that “<i>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 to <u>patients with mild temporary depressed mood</u></i>”.</p> <p>Second proposal is based on the approved therapeutic indication of St John’s wort THMP registered in UK, with the addition of the term “mental exhaustion” which represents a frequent type of symptom experienced by people taking St John’s wort as traditional remedies:</p> <p><i>"Traditional herbal medicinal product used to relieve the symptoms of slightly low mood with mental exhaustion and feeling of anxiety"</i>.</p> <p>Such therapeutic indication is easily understandable by patients.</p>	
4.1	<p>The NAM appreciates the Rapporteur’s outstanding work on the Hypericum perforatum herba monograph and agrees with the Rapporteur by finding the WEU use of this medicinal plant feasible. However the traditional oral use of the plant can not be seen justified for the following clinical reasons:</p> <p><u>Firstly</u>: The traditional indication proposed is based on the ICD-10 criteria, which is seen professional medical diagnosis criteria, and not constructed to be used by a layman for self diagnosis. Furthermore, the indication criteria for the proposed ‘neurasthenia (ICD-10 F48.0)’ are found difficult already among the professional health care people and even some controversial opinions exists, yet it is frequently and always used as a differential diagnosis when the</p>	<p>Not endorsed.</p> <p>ad 1)</p> <p>The monograph is not the package leaflet. The translation into a wording which is understandable by the layman can be done on a national basis. The 30 years of tradition in the proposed indication are evident.</p> <p>ad 2)</p> <p>The remaining herbal preparations on the traditional side for oral use are known for a very low content of hyperforin, which is considered to be primarily responsible for pharmacokinetic interactions. Since the</p>

	<p>depression diagnosis is firstly excluded. Thus, when the Rapporteur is suggesting the mild and moderate depression (the wording which might also need revision) for the WEU indications, the traditional oral use indication is not in line with the WEU use. It should also be reminded that the traditional indication suggested is not supported by 30 years of medical evidence needed in traditional use.</p> <p><u>Secondly</u> the clinically significant interactions of hyperici herba are well known and recognised as indicated in the AR of the Rapporteur. For the safety reasons the products of hyperici herba are not suitable for traditional use. The safety argumentation was used also in the case of Echinacea purpurea monograph when traditional indication was excluded. The Committee should be consistent with the evaluation work.</p> <p><u>Thirdly</u>: The recently presented draft on the concept paper on the benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of herbal medicinal products indicates some basic aspects on the evaluation work. The proposed traditional use for hyperici herba is not seen to be in line with these argumentations presented in the draft benefit risk paper because of the reasons mentioned above.</p> <p><u>Forthly</u>: In general, the state of scientific knowledge relating to safety issues of hypericum products linked to the technical progress relating to the manufacturing methods of hypericum products should have direct effect to the list of herbal preparations. It is not possible to justify so-called old fashion herbal preparations of hypericum as active substances if scientific progress has proceeded notably forward. Non-quantified herbal preparations should be removed from the monograph of traditional use if corresponding quantified herbal preparations under the WEU monograph with the same route of administration exist.</p>	<p>daily intake of hyperforin with THMPs has to be lower than 1 mg and the duration of use is restricted to 1-2 weeks, interactions are not likely to occur.</p> <p>ad 3)</p> <p>The benefit-risk assessment at the end of the assessment report documents that all herbal preparations listed under traditional use have a positive benefit-risk ratio.</p> <p>ad 4)</p> <p>Quantified herbal preparations are considered in the well-established use part of the monograph. According to directive 2004/24 EC there is no need to reject herbal preparations when they fulfil the criteria for traditional use.</p>
4.1.	<p>Additional indication for traditional use: digestion disorders</p> <p>Rationale: Authorized products in Poland on the market since more than 30 years.</p>	Endorsed.

4.1.	<p><u>Traditional use:</u></p> <p>Indication 1: Herbal substance, herbal preparations A, B, C, D, E, F, G, H, I, J, K: Traditional herbal medicinal product for the relief of temporary mental exhaustion (neurasthenia), and for relieving the symptoms of slightly low mood and anxiety.</p> <p>Rationale (Indication 1): The indications for which traditional herbal medicinal products are used, are e.g. substantiated by the indication according to the German AMG § 109 a, which is “for improving the well-being in case of nerval stress”. This indication is not restricted to “mental exhaustion”, but also includes states of low mood resulting from other causes, so that the indication granted recently by MHRA seems also to be adequately describing the traditional use: "Used to relieve the symptoms of slightly low mood and anxiety, based on traditional use" (see assessment report of MHRA). Thereby this wording of MHRA should also be included into indication 1.</p> <p>In case the HMPC follows our comment regarding the classification of the preparations, version 2, respective changes are necessary.</p> <p>Indication 2: In case the HMPC follows our proposal to merge similar preparations, respective changes have to be made. Otherwise no comments.</p>	Not endorsed (see above).
4.1.	<p><u>Traditional use</u></p> <p><u>Indication 1:</u> Herbal substance, herbal preparations A-F A, B, C, E, F, G, H, I, J, K: Traditional herbal medicinal product for the relief of temporary mental exhaustion (neurasthenia).</p> <p><u>Comment:</u> In case of summarising the preparations as proposed, it should read: Herbal substance, herbal preparations A-F.</p>	Not endorsed (see above).

	<p>"Temporary" should be deleted, because there are no grounds for any restriction existing. Existing preparations have been used without any limitation for a long time.</p> <p>In accordance with the MHRA approval, the following wording should also be considered: "Used to relieve the symptoms of slightly low mood and anxiety, based on traditional use only" (MHRA Assessment Report).</p> <p>Indication 2: Herbal preparations D, F, G, K: 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 specified indications exclusively based upon long-standing use.</p> <p>Comment: No comment on the wording of indications. In case of summarising the preparations as proposed, it should read: Herbal substance, herbal preparations B, C, F.</p>	
4.2.	<p>For the traditional use, regarding Herbal preparation B [dry extract (DER 4-7:1), extraction solvent 60% (m/m)], recommended posology is:</p> <p>Single dose: 85-300 mg Daily dose: 510-600 mg.</p> <p>The range given for the single dose is in line with two Hypericum products containing herbal preparation B already registered in France as traditional herbal remedies (PROCALMIL and ARKOGELULES Millepertuis, respectively 175 mg and 250 mg). Corresponding daily doses are 350-525 mg (2 to 3 single doses of ARKOGELULES Millepertuis per day) and 500 mg (2 single doses of PROCALMIL per day). Accordingly, it is proposed to replace the drafted posology by the following one:</p> <p>Single dose: 85-300 mg Daily dose: <u>350</u>-600 mg.</p>	This herbal preparation is now under well-established use.

4.2.	<p>Additional indication for traditional use: digestion disorders</p> <p>Posology for herbal teas for digestion disorders: 1 spoon (2g) of comminuted herbal substance in 1 glass of boiling water (200 ml). Cover and keep for 30 minutes. Take 30 minutes before meal to help digestion.</p>	Endorsed.
4.2.	<p>1.1.)<u>Secondary Eneuresis nocturna</u> in children may be in part owed to psychogenic problems and is often referred to disease of psychological origin. (http://gin.uibk.ac.at/thema/kinderheilkunde/enuresis.html, 8.1.2009)</p> <p>Hyperici herba is traditionally used in pediatrics to cure Eneuresis nocturna. The posology is given with: one cup of tea in the evening (Gerlach 2008, Ulsamer 1899);</p> <p>1.2.)Hyperforat (a liquid extract DER 1:2, extraction solvent ethanol 50%) available before 1968, is/was recommended and used in pediatrics : <u>Eneuresis nocturna, irritable exhaustion, Pavor nocturnus and lingual tetubation</u>. The posology is given with: 3xdaily 5-30 drops in water; schoolchildren 2x10 e.g. reduction to equivalent doses in children. (Rote Liste 1979,Braun 1968)</p> <p>„Hyperforat“ was not only sold as a liquid but also as dragees, suppositories and ampullae. (Rote Liste 1979, Braun 1968) Considering the time it is very likely that for this preparations dry extracts were in use and not mentioned extra. By the side: clinical studies are not applicable for traditional use.</p>	<p>Not endorsed.</p> <p>Insufficient data for the safe use in the paediatric population are available. Therefore the traditional oral use is restricted to adults. No indication for children and adolescents can be granted.</p>
4.2.	<p><u>Traditional use</u></p> <p>Posology</p> <p>Indication 1:</p> <p>Some information regarding the preparations listed have to be</p>	<p>Not endorsed</p> <p>The oral use in children and adolescents cannot be supported because of the lack of data.</p> <p>Preparations B(1) and B(2): see above.</p>

	<p>changed and other information added:</p> <p>Children, adolescents, aAdults and elderly:</p> <p>Herbal preparation A: Single dose: 60-180 mg Daily dose: 120-360 mg</p> <p>Herbal preparation B (1): Single dose: 85 – 300 mg 425 mg Daily dose: 540 85-600 mg</p> <p>Herbal preparation B (2): Single dose: 60 – 180 mg Daily dose: 180 – 360 mg</p> <p>Herbal preparation C (1): Single dose: 270 mg Daily dose: 540 mg</p> <p>Herbal preparation C (2): Single dose: 180 mg Daily dose: 360 mg</p> <p>Herbal preparation E: Single dose: 200 - 270 mg Daily dose: 600 mg - 1620 mg</p> <p>Herbal preparation F: Single dose: 2-4 ml Daily dose: 6-12 ml</p> <p>Herbal preparation G: Single dose: 1-1.5 ml Daily dose: 3-4.5 ml</p> <p>Herbal preparation H: Single dose: 0.8-1.2 ml</p>	<p>Preparation E (= extract prepared with vegetable oil) is not comparable to the herbal tea.</p> <p>The proposed posology for the tea is in line with modern references on Phytotherapy.</p> <p>Duration of use indication 1: the duration is not restricted to 2 weeks. The patient should contact a doctor for proper diagnosis at least after 2 weeks.</p> <p>Wording duration of use indication 2: endorsed</p>
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	<p>Daily dose: 2.4-3.6 ml</p> <p>Herbal preparation I: Single dose: 1.3 ml Daily dose: 4.0 ml</p> <p>Herbal preparation J: Single dose: 10-20 ml Daily dose: 10-20-30 ml</p> <p>Herbal preparation K: For tea preparation: Single dose: 2-g 1.5 to 2.0 g Daily dose: 4-g 3.0 to 8.0 g</p> <p>In solid dosage forms: Single dose: 300-500 mg Daily dose: 900-1000 mg</p> <p>Rationale</p> <p>Information regarding preparation B (1) is adapted to the preparation HyperCalm registered at MHRA. B (2) is adapted to the actual declaration of the product Esbericum Kapseln, Schaper & Brümmer, Salzgitter, Germany. The preparation C (2) has been used in different doses compared to C (1). Preparation E corresponds to herbal infusions which are prepared from 1.5 to 1.75 g / tea bag. For preparation J, doses are harmonized with existing products (pressed juices). The changes in K correspond to infusions marketed in the EU.</p> <p>Children and adolescents:</p> <p>Comments: The use in children and adolescents under 1812 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').</p>	
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Rationale:

As in the case of the well established use products, traditional Hypericum preparations have been and are traditionally used also in patients of an age < 18 years. The use in children and adolescents from the age of 12 years on is, as described above, well founded also in well established use preparations, without any safety concerns known to date or to be expected.

Indication 2:

No comments.

Both indications:

In case that HMPC follows to merge preparations according to our proposal from section 2, respective adaptations have to be made.

Duration of use

Indication 1:

≥ 4 weeks

If the symptoms persist longer than **≥ 4 weeks** during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Rationale:

There are no restrictions for the duration of use of Hypericum preparations in traditional use, as well as the duration of administration of well established use preparations is not restricted. For indication 1, a duration of 2 weeks would not even allow to achieve an onset of an therapeutic effect if the time until onset of a clinically relevant effect known for well established use preparations is taken into account. The MHRA in its safety report recommends to

	<p>consult a qualified health practitioner if symptoms worsen or do not improve after 6 weeks. Nevertheless, there are no safety issues known supporting such a restriction.</p> <p>It seems to be sufficient, that a physician or health care professional is consulted in case the treatment is not efficient. As traditional preparations often are used in self medication, the patient decides by himself starting the treatment. Therefore it does not make sense to give a duration of time after which a doctor or health care practitioner should be consulted. It seems more reasonable to leave this decision onto the patient, who may earlier or possibly later than 4 weeks after onset of therapy may have the impression that symptoms persist or reappear.</p> <p>Indication 2: 1-week If the symptoms persist longer for more than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p>Rationale: There are no known safety issues limiting a safe use to only 1 week, if a correct diagnosis is given. This is assured by the information that after this time medical help should be sought.</p>	
4.2.	<p><u>Traditional use</u></p> <p>Posology</p> <p>Indication 1:</p> <p>1. Proposal to summarise the preparations</p> <p>Herbal preparation A (old A/B/C): Single dose: 60-270 mg Daily dose: 120-540 mg</p> <p>Herbal preparation B (old D/E):</p>	<p>See above.</p> <p>Posology of the expressed juice and the herbal tea widened.</p>

Single dose: 85-425 mg
Daily dose: 85-600 mg
Herbal preparation C (old F/G):
Single dose: 2-4 ml for 1:10 tinctures and 1-1.5 ml for 1:5 tinctures
Daily dose: 6-12 ml for 1:10 tinctures and 3-4.5 ml for 1:5 tinctures
Herbal preparation D (old H/I):
Single dose: 0.8-1.3 ml
Daily dose: 2.4-4 ml
Herbal preparation E (old J):
Single dose: 10-20 ml
Daily dose: 20-30 ml
Herbal preparation F (old K):
For tea preparation:
Single dose: 2 g
Daily dose: 4 g
In solid dosage forms:
Single dose: 300-500 mg
Daily dose: 900-1000 mg
Herbal preparation F*
Single dose: 100 drops of tincture
Daily dose: 300-400 drops

and delete the rest in accordance with chapter 2.

2. Alternative proposal

Adults and elderly:

Herbal preparation A:
Single dose: 60-180 mg
Daily dose: 120-360 mg

Herbal preparation B:
Single dose: **85 – 425 mg** ~~85-300 mg~~
Daily dose: 510-600 ?? mg *1)

Herbal preparation B*

<p>Single dose: 60 – 180 mg Daily dose: 180 – 360 mg *2)</p> <p>Herbal preparation C: Single dose: 270 mg Daily dose: 540 mg</p> <p>Herbal preparation C*: Single dose: 180 mg Daily dose: 360 mg *3)</p> <p>Herbal preparation E: Single dose: 200 mg up to 270 mg Daily dose: 600 mg up to 1620 mg *4)</p> <p>Herbal preparation F: Single dose: 2-4 ml Daily dose: 6-12 ml</p> <p>Herbal preparation F*: Single dose: 100 drops of tincture Daily dose: 300-400 drops</p> <p>Herbal preparation G: Single dose: 1-1.5 ml Daily dose: 3-4.5 ml</p> <p>Herbal preparation H: Single dose: 0.8-1.2 ml Daily dose: 2.4-3.6 ml</p> <p>Herbal preparation I: Single dose: 1.3 ml Daily dose: 4.0 ml</p> <p>Herbal preparation J: Single dose: 10-20 ml Daily dose: 20-30 ml *5)</p>	
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Herbal preparation K:
For tea preparation:
Single dose: ~~2-g~~ **1.5 to 2.0 g**
Daily dose: 4-g **3.0 to 8.0 g *6)**
In solid dosage forms:
Single dose: 300-500 mg
Daily dose: 900-1000 mg

Comments

*1) We agree with the Herbal Preparation B) but would suggest to correct the posology as follows: "Single dose: 85 – 425 mg". Justification: This Herbal Preparation B) is contained in a THMP "Hypericalm" (brand name: Karma) granted by MHRA in 2008, see Public Assessment Report from MHRA, page 15.

*2) The clinical study Bergmann et al. cited in the assessment report on page 44 was performed with Esbericum Kapseln with a dosage 3 x 1 capsule / day (DER 3.5-6:1, extraction solvent ethanol 60% v/v). The dosage and declaration given in the assessment report on page 43 (daily dosage 213 – 252 mg, DER 2 – 5:1, 60 % v/v ethanol) refers to the extract preparation and not to the native extract as it was common in the 1990ies. Thus, the single dosage of the "old" declaration corresponds to 60 mg native dry extracts (daily dosage 3 x 60 mg) according to current HMPC-guidelines (within the scope of the re-registration procedure in Germany the dosage of was adjusted to 2 x 3 capsules/day, corresponding to 360 mg native extract/day). Please see also our comments to the assessment report regarding Esbericum Kapseln and preparations of "low dose" regarding extract content.

3) Under section 2.ii) the following herbal preparation has been included: C Dry extract (5-7:1), extraction solvent ethanol (60% m/m). This preparation has been used in the strength 180 mg as single dose 2 times daily. It is very similar to the definition of preparation C. The added preparation (provisionally named C*) has therefore also been included into section 4.2 of the draft monograph for indication 1.

*4) There are herbal preparations in the market which correspond to preparation E used in single doses up to 270 mg and daily doses up to 1620 mg. Examples: Bad Heilbrunner Johanniskraut Tee (1.5

g/teabag), Sidroga Johanniskraut (1.75 g/teabag), Altapharma Johanniskraut (1.5 g/teabag), Salus Johannesört (Sweden) (1.75 g/teabag)

*5) The daily dose for preparation J corresponds to expressed juices in the German market.

*6) There are tea preparations in the market which correspond to preparation K used in single doses between 1.5 and 2.0 g and daily doses between 3.0 and 8.0 g.

Children, adolescents:

We suggest to replace "18 years" by "12 years". Thus the sentence should read:

The use in children and adolescents under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

Comments: The age restriction to a minimum of 12 years is reflected in the SPCs of well-established preparations with marketing authorizations, meaning that higher dosed preparations have successfully been tested to be efficient and safe. There is no specific data on differences in pharmacokinetic or pharmacodynamic parameters between children and adults after application of SJW extracts. The traditional use of St. John's wort preparations had up to now not been restricted to adults only. Furthermore, since SJW products have a very high safe dose range, and since the specific problem of herb-drug interactions is expected to be potentially relevant only for multimorbid patients, but not in children without regular intake of other drugs, no specific problem is expected from the intake of SJW preparations by children and adolescents. In contrary, data from controlled trials allow the expectation of a significantly better safety of application as compared with alternative medications such as SSRI or TCA.

Even the assessor's conclusion on the use in the paediatric population supports the use of St. John's wort in children (compare page 56 AR: "**The data support the safety of a potential use in children but not the efficacy which is necessary for well-established use.**"). Regarding traditional use this efficacy requirement is not relevant. Therefore the

	<p>traditional use in children is justified.</p> <p>Indication 2: <i>Adolescents, adults, elderly:</i> Herbal preparations B, D, K: Cutaneous administration of the undiluted herbal preparation Herbal preparations C, F, G: Cutaneous administration of the undiluted or diluted herbal preparation <i>Children:</i> The use in children under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').</p> <p>Duration of use Indication 1: If the symptoms persist longer than 42 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p>Comments For indication 1, four weeks are recommended, because as stated for the well-established use the onset of reaction can be expected within 4 weeks treatment. The reason for a restricted duration of use (two weeks) is not sufficiently justified in the assessment report (compare page 65 AR: "provided, that the duration of use is restricted to several days..."). The statement "duration of use is restricted to several days" is not automatically equal to the claim "2 weeks duration of use". The MHRA in its Assessment report states that patients should consult a doctor if symptoms worsen or do not improve after 6 weeks.</p>	
4.2.	<p>It appears confusing that the same entry is found for the cutaneous preparations D/K and F/G in the traditional section, with the only difference being the word "diluted". Both statements should be combined for more clarity, e.g. by formulating "diluted or undiluted".</p> <p>Finally, the restriction of the duration of intake to two weeks only with traditional use is incompatible with the mechanism of action. A distinct onset of an antidepressant effect can only be expected after</p>	<p>Not endorsed.</p> <p>The hypericum oil as well as the hypericum tea are usually applied undiluted. For clarity the statements remain separated.</p>

	<p>at least three weeks. The limitation to two weeks would clearly render the intake of St. John's wort preparations useless. We suggest to increase the duration of intake before medical advice should be sought to at least 3-4 weeks.</p>	
4.3.	<p><u>Traditional use</u></p> <p>Indication 1: Hypersensitivity to the active substance.</p> <p>The remaining text should be deleted.</p> <p>Indication 2: Hypersensitivity to the active substance.</p> <p>Rationale:</p> <p>Interactions, which are to a large part triggered by hyperforin, have only been observed in doses higher than those applied with recommended doses of many traditional products. The potential of interactions has led to a "Stufenplanverfahren" in Germany, which gives a lower limit of 200 mg herbal drug equivalent daily, below which labelling of interactions is not needed onwards. On the base of actual scientific data (e.g. Müller et al. 2009), this limit should be much higher, that is to say at a dose of > 1000 mg herbal drug equivalent daily.</p>	<p>Not endorsed.</p> <p>At the moment there is no limit of the hyperforin uptake established below which no interactions occur.</p> <p>For safety reasons the patients should get a clear message that some precautionary measures should be considered when taking hypericum preparations independent of the actual hyperforin content.</p>
4.3.	<p><u>Traditional use</u></p> <p>Indication 1: Hypersensitivity to the active substance. The rest should to deleted.</p> <p>Indication 2: Hypersensitivity to the active substance.</p>	<p>See above.</p>

	<p>Comments: The risk of interactions (indication 1) is dose-dependent. This has also been discussed in the German Stufenplanverfahren which came to the conclusion that a specific labeling on potential interactions is required from a daily dose of 200 mg herbal drug equivalent daily onwards. However, there are good reasons that specific labeling is only required from a daily dose of more than 1000 mg herbal drug equivalent daily. Further details are explained in the comments on section 4.5.</p>	
4.3.	<p>Proposed change:</p> <p><u>Traditional</u> Indication 1: For preparations containing 4 mg (or more) of hyperforin, we suggest to include the modified wording as we propose for well-established use preparations. For preparations containing less than 4 mg hyperforin as well as for teas, pressed juices and oily preparations, we propose "Not confirmed by recent studies" or "None reported". Indication 2: "None reported" is correct from our point of view. Comment: For SJW products a differentiation has to be made between products having different content of hyperforin. Based on literature data Arold [2005], [Whitten 2006], [Mai 2004], [Mueller 2006] and risk assessments by the health authorities FDA [1997, 2006], EMEA and BfArM, it is justified to set a limit and to establish safety measures in the community monograph which will allow to remove the contraindications and special warnings related to the interaction potential of SJW for those products which comply with these requirements. The interaction of St. John's wort preparations with concomitantly applied drugs is a well-known phenomenon. It is entirely attributable to the activation of Cytochrome P450 3A4/2C19 and, by the same basic mechanism of binding the steroid X-receptor (which in turn activates both systems), the activation of the p-glycoprotein transporter system (Chen [2004], Moore [2000], Wentworth [2000]). The identification of hyperforin as a strong and selective activator of the PXR system, and thus of drug excretion by PGP, CYP 3A4, 2C9</p>	See above.

	and 2C19, is confirmed by all clinical evidence, without exception.	
4.4	<p>Comments :</p> <p>Following recent implementation of a class wording on suicidal risks for all antidepressants, we are of the opinion that a minimal information about this risk of suicidal events is also needed for <i>Hypericum perforatum</i>, in relation with the claimed indication</p> <p>Proposed change</p> <p>Traditional use, indication 1</p> <p>Patients with a history of moderate to severe EDM or those exhibiting more than 5 disabling symptoms should take a medical advice before starting use of <i>Hypericum perforatum</i>. If symptoms are present for more than 2 weeks, a medical advice could be considered.</p> <p>Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). <i>Hypericum perforatum</i> (St. John's Wort) is not indicated in patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment. In such a case, a doctor should be consulted.</p> <p><i>Hypericum perforatum</i> (St. John's Wort) is not an antidepressant and is not indicated in well-defined major depressive episode (MDE). <i>Hypericum perforatum</i> induces serious interactions with other medicinal products.</p> <p>Patients should be advised about the need to mention that they are taking <i>Hypericum perforatum</i> to their doctor/pharmacist In general for patients treated with other drugs <i>Hypericum perforatum</i> is not recommended. When coadministered with anticoagulants from the coumarin-type the serum concentration of these substances should be controlled regularly. During the treatment intense UV-exposure should be avoided.</p>	<p>Not endorsed.</p> <p>Traditional use not for the treatment of depression.</p>

	<p>The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.</p> <p>Since no data on the safe use in children and adolescents are available, the use in children and adolescents under 18 years of age is not recommended.</p> <p>Efficacy and safety of Hypericum perforatum is not demonstrated in the elderly.</p> <p>Furthermore, elderly patients are specially, exposed to the risk of interaction with other medicinal products (See 4.3 and 4.8).</p> <p>Moreover, cases of serotonergic syndrome have been reported in the elderly in case of concomitant antidepressant treatment.</p> <p>For tinctures containing ethanol the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.</p>	
4.4.	<p><u>Traditional use</u></p> <p>Indication 1:</p> <p>a) The sentence "When co-administered with anti-coagulants from the coumarin-type the serum concentration of these substances should be controlled regularly." should be deleted, at least for preparations containing 1000 mg or less hypericum herbal drug equivalent daily.</p> <p>Comment: As explained in detail under 4.5, the risk of interaction is dose-dependent. For low-dose traditionally used preparations, no special warnings are required.</p> <p>b) Instead of "The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia" we propose "<i>Regarding potential interactions with medicinal products</i></p>	See above.

	<p><i>used during general and regional anaesthesia please refer to 4.5 Interactions."</i></p> <p>Comment: See well-established use.</p> <p>c) Since no sufficient data on the safe use in children are available the use in children and adolescents under 12 18 years of age is not recommended.</p> <p>Comment: For use in children, see chapter 4.2.</p> <p>Indication 2: Since no sufficient data on the safe use in children are available the use in children and adolescents under 12 18 years of age is not recommended.</p> <p>For use in children, see chapter 4.2.</p>	
<p>4.4.</p>	<p>Proposed change:</p> <p>We propose to change "The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia."</p> <p>into</p> <p>"Regarding potential interactions with medicinal products used during general and regional anaesthesia please refer to 4.5 Interactions."</p> <p>Comments:</p> <p>We consider the statement "The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia." as too broad and not scientifically justified.</p> <p>Some drugs potentially used during anaesthesia like alprazolam or</p>	<p>See above.</p>

midazolam for sedation are listed under 4.5 (Interactions). However, there is no prove for the entirety of anaesthetics to trigger interactions with St. John's Wort (SJW), thus the range in the proposed wording is too extensive. Anyhow, even if an effect on pharmacokinetics or pharmacodynamics of single benzodiazepines might have been found in in-vitro or in-vivo-studies, a clinical relevance is not a logical consequence, since it appears possible that regardless of a hypothetic certain alteration of blood plasma levels of benzodiazepines by SJW, the sedative effect of the benzodiazepines might stay uninfluenced.

In a hospital survey published in 2000 (1) a total of 1017 surveys were submitted over a period of 5 months out of which 755 surveys were assessed as valid surveys. 30% of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates the "pseudoephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided." The survey did not reveal any risk within anaesthesiology practice for the concomitant intake of SJW and benzodiazepines.

An article published in The Lancet by Marilyn Larkin (2) apparently reports about research from various centres in the USA which warns the patients who use herbal remedies may suffer from herb-anaesthesia interactions (3). However, the evidence of this article is rather weak, since there is no scientific basis for the statement that "SJW: May prolong effects of some narcotics and anaesthetics". Neither narcotics nor anaesthetics are closer specified, there is no background given for this statement.

Marilyn Larkin published another article in 2001 (4) in which she specifies the aspect of a "safe use of herbal products before surgery" for, amongst others, SJW: "Major concerns: Diminished effects of other drugs such as ciclosporin, warfarin, steroids &c. Stop before surgery: At least 5 days". Narcotics and anaesthetics are not listed here.

<p>4.5</p>	<p>Comments:</p> <p>The proposed wording raised some public health concerns, due to the safety profile of <i>Hypericum perforatum</i> in relation with numerous interactions with non herbal medicinal products</p> <p>Proposed change</p> <p>Traditional use, indication 1</p> <p>Contraindicated is the concomitant use of oral anticlotting agents, metabolised antiepileptic agents, estroprogestative contraceptive agents, progestative contraceptive agents, immunosuppressive agents (cyclosporine, sirolimus, tacrolimus), digoxin, amprenavir, indinavir and other protease-inhibitors, tyrosine kinase inhibitors, irinotecan and other cytostatic agents, theophyllin. cyclosporine, tacrolimus, digoxin, amprenavir, indinavir and other protease-inhibitors, irinotecan and other cytostatic agents.</p> <p>Not recommended is the concomitant use of carbamazepin, cyproterone, telithromycin, due to the risk of change in plasma concentrations.</p> <p>Special care should be taken with proton pump inhibitors antisecretory drugs, alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.</p> <p>The reduction of plasma concentrations of oral contraceptives may lead to bleeding and unwanted pregnancies.</p> <p>Hypericum dry extract may cause a serotonergic syndrome when combined with linezolid, antidepressants such as selective A-IMAO or non selective IMAO, serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone.</p> <p>Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum.</p>	<p>The interactions section is completely reworded and in line with the information given for well-established use preparations.</p>
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<p>4.5.</p>	<p>Comments:</p> <p>Hypericum dry extract must not be used concomitantly with cyclosporine, tacrolimus for internal use, digoxin, amprenavir, indinavir and other protease inhibitors, irinotecan and other cytostatic agents.</p> <p>Special care should be taken with digoxin, alprazolam, amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, theophylline, midazolam, triptans and warfarin, because a reduction of plasma concentrations is possible.</p> <p>The possible reduction of plasma concentrations of oral contraceptives (especially of low dose formulations) may lead to increased intermenstrual bleeding and reduced safety in birth control. unwanted pregnancies. To women using oral contraceptives it should be recommended to take additional precautions for a better reliability.</p> <p>Hypericum dry extract may contribute to cause a serotonergic syndrome effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine, nefazodone) or with buspirone.</p> <p>Rationale</p> <p>For comments on the displacing of digoxin see “4.3 Contraindications”.</p> <p>We suggest omitting the listing of "benzodiazepines" as whole group of drugs in this context, because there is no substantiated evidence for interactions apart from the benzodiazepines alprazolam and midazolam listed anyhow. Available literature data on concomitant use of Hypericum with other benzodiazepines (e.g. lorazepam, diazepam, bromazepam, clonazepam) did not show clinically significant hints.</p> <p>For midazolam, primarily used in premedication settings, the increase of clearance was less pronounced after intravenous than after oral application (1,5-fold or 2,7 fold, respectively; Dresser et al. 2003).</p>	<p>See above.</p>
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Therefore, the clinical relevance of maintaining a long-term steady-state of plasma level for a sedating agent used only shortly before clinical intervention is questionable.

Methadone: The only clinical data on interactions between Hypericum and pharmacokinetics of methadone which are cited in some reviews (Zhou et al. 2004, Izzo 2004, Di et al. 2008) seems to be the findings of Eich-Höchli et al. (2003), subtitled with “A case report”. There are many flaws in the general design of the “study” described there. First of all the number of subjects enrolled was very low (n=4). The timing for the second blood sampling varied from 14 to 47 days of treatment with St. John’s wort, the methadone doses administered varied also remarkably (7 to 80 mg/d, changing to 7 to 90 mg/d after the first blood sampling), as did the plasma levels in consequence, necessitating a normalization of the original baseline values to 100%. Furthermore three of the four patients were receiving comedication: two patients were receiving oxazepam and one doxepin. As these patients have a drug abuse history, it is also unclear, whether these substances were the only add-on pharmaceuticals consumed during the study period as there is no evidence of further control. From our point of view, these findings have to be interpreted very critical and should not be used as basis for another warning for possible interactions. Methadone therefore should not be mentioned here.

Theophylline: As Madabushi et al. stated in 2006, theophylline has been listed under the drugs of possible interactions by several papers, all citing the very same case report (Nebel et al. 1998), where the patient was a smoker and used 11 further drugs. In contrast, Morimoto et al. (2004) were unable to detect any changes in the pharmacokinetics of theophylline in their follow-up study in 12 healthy volunteers. This is not surprising, as theophylline is mainly metabolized by CYP1A2 and only in part by CYP3A4. The induction of CYP3A4 is responsible for the most of the interactions with Hypericum preparations, while the induction of CYP1A2 is implausible with regard to the available evidence (Wang et al. 2001; Morimoto et al. 2004). Therefore the listing of theophylline herein should be deleted from the listing.

Triptans: There is no scientifically convincing evidence for interactions between Hypericum and triptans. Although triptans have been listed in several reviews as possibly pharmacodynamically interacting agents, the basis of these suspicions usually is not given there (e.g. Henderson et al.2002). The only source of original data seems to be a case report where a serotonin syndrome was diagnosed after concomitant administration of Hypericum together with fluoxetine and eletriptan (Bonetto et al. 2007). After withdrawal of the Hypericum product the symptoms did not vanish, but after withdrawal of the triptan and the fluoxetine they did. The causality of Hypericum administration for the described interactions is in no way proven by this case report. In addition, Evans (2008) questioned whether the symptoms described were indeed compatible with the Hunter serotonin toxicity criteria and whether other aetiologies were completely ruled out. Triptans therefore should not be mentioned here.

Oral contraceptives: The causality between concomitant use of oral contraceptives with Hypericum products and unintended pregnancies has never been proven to date. The proposed wording is possibly misleading and may generate uncertainty without providing a practicable solution. Although it has to be considered that in nearly every clinical trial women of reproductive age are included, who use oral contraception. The only and always cited evidence of unintended pregnancies after concomitant use of oral contraceptives and St. John's wort extracts is derived from some case reports with more or less imprecise specifications of products or chronological correlations. Moreover: Intermenstrual bleedings are frequent adverse effects (> 10 %) of oral contraceptives (Standard SPC Germany). Bleedings do not always result in attenuation of effect: In two studies (Hall et al. 2003, Pfrunder et al. 2003) an increase of menstrual irregularities had been found, but no increase in ovulations, which leads to the conclusion that the safety of contraception was not compromised. Oral contraceptives therefore should not be mentioned here.

Antidepressants: Causality between use of St. John's wort and the development of a serotonin syndrome is not substantiated by clinical

	<p>evidence. Of the single cases reported in this context (Lantz et al., 1999, Waksman et al. 2000), the case reports of Lantz et al. show partly deficiencies in diagnostics, so that the diagnosis of a true “serotonin syndrome”, which is a really severe and life threatening state of the patient - in contrast to single symptoms often experienced in the geriatric patient - has been discussed by Schulz et al. (2006). In the case report of Waksman a close chronological relation to the use of Hypericum is not given, as this had been already withdrawn three days before starting the application of paroxetine. Furthermore it is known that some antidepressants of the SSRI type cause serotonergic effects without further comedication just in case of high dosages (SPCs, Fischer 1995). The mainly theoretical discussion whether there are pharmacodynamic interactions should be critically assessed. Some earlier publications substantiate suspicions for pharmacodynamic interactions on the outdated assumption that the basic principle of action of Hypericum preparations is the MAO inhibition (e.g. Gordon 1998). Concomitant use of MAOIs and SSRIs is strictly contraindicated. However, as has been shown in more recent investigations, in clinically effective concentrations MAO inhibition was not found (as e.g. reviewed by Butterweck 2003). Therefore a modification of the text is proposed.</p>	
<p>4.5.</p>	<p><u>Traditional use</u></p> <p>Indication 1: For preparations containing more than 1000 mg hypericum herbal drug equivalent daily, we suggest to include the modified wording as we propose for well-established use preparations. For preparations containing 1000 mg or less hypericum herbal drug equivalent daily as well as for teas, pressed juices and oily preparations, we propose "Not confirmed by recent studies" or "None reported".</p> <p>Indication 2: "None reported" is correct from our point of view.</p> <p>Comments: As can be shown in recent studies and expert opinions, the risk of interaction is dose-dependent. This has been explained in detail in a statement of BAH on behalf of German companies</p>	<p>Not endorsed. See above.</p>

submitted 23 January 2006 as justification of the formal objections of these companies to the BfArM decision in the risk assessment ("Stufenplanverfahren") on Hypericum (see reference list). Furthermore, regulatory decisions e.g. in Germany the pharmacy-only status for Hypericum preparations containing more than 1000 mg herbal drug as a daily dose take account of this dose-dependency. In detail, we would like to comment on the clinical data as follows:

1. Study with digoxin in healthy volunteers

The results of a study in healthy volunteers [Mueller, Uehleke et al. 2004b] show that the extent of interactions between Hypericum and digoxin is dose-dependent and negligible in case of up to 1.0 g powdered herbal drug with higher hyperforin content and up to 2.0 g powdered herbal drug with lower hyperforin content as well as in case of herbal tea, pressed juice, oily extract and other extracts with very low hyperforin content.

2. Studies with ciclosporin

In a study which examined the interaction potential on hyperforin-free samples of Hypericum preparations on ciclosporin A, even with an extremely high dose of 4 g powdered drug daily, no relevant interactions were seen [Klinischer Bericht der Studie Nr. 774: Bericht der klinischen Studie: "Pilotstudie zur Dosisfindung der Interaktion von Johanniskraut mit Ciclosporin A", Studiennr. 774, Institut für Klinische Pharmakologie Rostock, 11.09.2002]

The results of a cross-over study in seven patients [Mai et al. 2004] receiving ciclosporin A as permanent medication after kidney transplantation as well as a commercial hyperforin-rich Hypericum extract or the corresponding de-hyperforinised extract, respectively, demonstrate that hyperforin-free preparations do not cause clinically relevant interactions.

3. Studies with midazolam

A pilot study with midazolam showed that the extent of an interaction depends on the daily dose of hyperforin. The most pronounced interaction with a reduction of the AUC of midazolam by 79 % was observed in the group taking the highest daily dose of hyperforin (42 mg/day). In all other groups the reduction of the AUC of

midazolam was less pronounced but increased with hyperforin-containing powdered drug to maximum -48 % at a daily dose of 2700 mg Hypericum. The same daily dose of a hyperforin-free preparation (daily dose of hyperforin 0,09 mg) lead to a reduction of only 21 % of the AUC of midazolam. From a further pilot study it was concluded that the threshold dose of a relevant interaction caused by Hypericum is lower than 1800 mg Hypericum/ 2 mg hyperforin [Studien-Nr. 786 Pilotstudie I: Midazolam-Interaktion. Studien-Nr. 824 Pilotstudie II Interaktion von Johanniskraut mit geringem Hyperforingehalt mit Cytochrom P450-3A4-Substraten]

In the corresponding pivotal study (Mueller, Majcher-Peszynska et al 2006) in 20 non-smoking volunteers a potential influence of a co-medication consisting of a traditional Hypericum preparation at a daily dose of 1 g (hyperforin < 1 mg/day) on a pharmacokinetic interaction (induction of CYP3A4) was examined. For the primary target parameter midazolam AUC a significant but only slight decrease was shown with hypericum. For midazolam C_{max} , midazolam $t_{1/2}$ and midazolam t_{max} the intake of Hypericum did not lead to significant alterations. Thus the intake of Hypericum does not cause clinically relevant alterations in therapy of drugs which undergo metabolism by the CYP3A4 system. This has been confirmed by Mueller et al. 2009.

All in all it can be shown that for hypericum preparation up to 1000 mg herbal drug equivalent daily and preparations with a low hyperforin content as well as for herbal tea, pressed juice from fresh plants and oily preparations ("Rotöl") clinically relevant interactions do not exist.

4. Study Arold

From the experiments published by Arold [2005] it can be concluded that the intake of a Hypericum preparation containing up to 3,5 mg hyperforin per day does not cause a statistically significant decrease of the AUC for the respective marker substances. Thus it can be demonstrated that low-dose Hypericum preparations (daily dose up to around 4 mg hyperforin) do not cause interactions.

5. Expert Statement Derendorf

A detailed expert statement on the clinical relevance of Hypericum

preparations with chemical drugs written by Prof. Dr. Hartmut Derendorf, Gainesville/Florida [2004], comes to the following conclusions:

- According to an FDA Guideline [Bjornsson 2003, Huang 2003] the clinical relevance of drug interactions can be assessed by models based on experiences with the CYP3A4 system which represents one of the most important ways of interactions. With the highly sensitive model substance midazolam an AUC increase by 200-500 % is classified as a medium increase, an increase of less than 200 % as a weak and an increase of more than 500 % as a strong increase.
- Based on these assumptions the expert proposes to classify a decrease of the midazolam AUC by less than 50 % as a weak and a decrease of more than 50 % as a strong interaction.
- Interactions and their clinical relevance have to be assessed in the context of all other parameters of the patients' life which also might have a strong influence. For this reason interactions which are to be assessed as relevant have to exceed individual changes markedly.
- Information on potential or existing interactions have to be communicated in an appropriate manner. For this reason it is more important to inform patients who receive a medicines which is influenced than to inform patients who take a potentially influencing medicinal or food product.
- In case of Hypericum products a clear differentiation has to be made between products with a high or low content of hyperforin.

6. Publications Schulz and Butterweck

Schulz [2004b] comes to the conclusion that potential dangers are due to chemical drugs with a narrow therapeutic index. For this reason preventive measures have to be performed for drugs with such a high potential of being influenced and not for herbal medicinal products. Butterweck et al. [2004] describe that in vitro tests conducted so far lead to contradictive results due to the lack of validation data. Furthermore food, beverages and lifestyle products can cause interactions. Preventive measures should therefore be taken

	<p>for drugs with a narrow therapeutic index.</p> <p>For further details see statement of BAH on behalf of German companies submitted on 23 January 2006 as justification of the formal objections of these companies to the BfArM decision in the risk assessment ("Stufenplanverfahren") on Hypericum [BAH 2006].</p>	
<p>4.5.</p>	<p>Proposed change:</p> <p>We propose to change “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.”</p> <p>into</p> <p>“Regarding potential interactions with medicinal products used during general and regional anaesthesia please refer to 4.5 Interactions.”</p> <p>Comments:</p> <p>We consider the statement “The product should be discontinued at least 10 days prior to elective surgery due to the potential for interactions with medicinal products used during general and regional anaesthesia.” as too broad and not scientifically justified.</p> <p>Some drugs potentially used during anaesthesia like alprazolam or midazolam for sedation are listed under 4.5 (Interactions). However, there is no prove for the entirety of anaesthetics to trigger interactions with St. John’s Wort (SJW), thus the range in the proposed wording is too extensive. Anyhow, even if an effect on pharmacokinetics or pharmacodynamics of single benzodiazepines might have been found in in-vitro or in-vivo-studies, a clinical relevance is not a logical consequence, since it appears possible that regardless of a hypothetic certain alteration of blood plasma levels of benzodiazepines by SJW, the sedative effect of the benzodiazepines might stay uninfluenced.</p>	<p>No such wording in 4.5, traditional use.</p>

	<p>In a hospital survey published in 2000 (1) a total of 1017 surveys were submitted over a period of 5 months out of which 755 surveys were assessed as valid surveys. 30% of the patients took a SJW preparation. The anaesthetic consideration for SJW indicates the “pseudoephedrine, MAOIs (monoamine oxidase inhibitor), SSRIs (selective serotonin reuptake inhibitor) should be avoided.” The survey did not reveal any risk within anaesthesiology practice for the concomitant intake of SJW and benzodiazepines.</p> <p>An article published in The Lancet by Marilyn Larkin (2) apparently reports about research from various centres in the USA which warns the patients who use herbal remedies may suffer from herb-anaesthesia interactions (3). However, the evidence of this article is rather weak, since there is no scientific basis for the statement that “SJW: May prolong effects of some narcotics and anaesthetics”. Neither narcotics nor anaesthetics are closer specified, there is no background given for this statement.</p> <p>Marilyn Larkin published another article in 2001 (4) in which she specifies the aspect of a “safe use of herbal products before surgery” for, amongst others, SJW: “Major concerns: Diminished effects of other drugs such as ciclosporin, warfarin, steroids &c. Stop before surgery: At least 5 days”. Narcotics and anaesthetics are not listed here.</p>	
<p>4.6.</p>	<p><u>Traditional use</u></p> <p>In the absence of sufficient data, the use during pregnancy and lactation is not recommended.</p>	<p>Exact wording of draft monograph.</p>
<p>4.7.</p>	<p>Comments:</p> <p>We suggest to substitute the following sentences:</p> <p><u>Traditional use</u></p> <p>No studies on the effect on the ability to drive and use machines have been performed.</p>	<p>The wording will be changed to:</p> <p>Indications 1, 3: No adequate studies on the effect on the ability to drive and use machines have been performed.</p>

	<p>There is no evidence for a possible influence on the ability to drive and use machines.</p> <p>Rationale:</p> <p>There is a published study showing that there is no negative effect on the ability to drive and use machines investigating preparation B (2) (Herberg 1994). In this study there were no clinically relevant impairments of motor performance or loss of vigilance observed. We therefore suggest replacing the wording in the draft by the proposed sentence.</p>	<p>Indication 2: Not relevant.</p> <p>In the mentioned study of Herberg (1994) the impact of the combination of Hypericum and alcohol on motor performance and vigilance was tested. There are no data for hypericum alone.</p>
<p>4.7.</p>	<p><u>Traditional use</u></p> <p>No effects on the ability to drive and use machines are to be expected. No studies on the effect on the ability to drive and use machines have been performed.</p> <p>Comment:</p> <p>1) The draft monograph states that no studies on the effect on the ability to drive and use machines have been performed. However, a study has been published (Herberg 1994), in which the herbal preparation C* was tested. No clinically relevant impairment of motor performance or loss of vigilance were observed (steady state assessment after 9 days of 3 times daily 180 mg of herbal preparation C*).</p> <p>2) 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 (Friede et al. 1998).</p> <p>The effects on visual and acoustic evoked potentials, the time to appearance of amount of REM sleep, and the effects on theta- and alpha-activities of the EEG, suggested that some of the effects on the CNS are similar to those documented for synthetic antidepressants, whilst sedation does not occur (Boettcher et al. 2000).</p> <p>With other SJW preparations a lack of an impairment of vigilance was likewise demonstrated. Johnson et al. (1992) found an improved</p>	<p>See above.</p>

	<p>vigilance in psychometric tests 2.5 hours post application of the SJW extract LI 160 in a pharmacodynamic randomized double-blind study in 12 healthy volunteers.</p>	
4.8	<p>Comments:</p> <p>Due to the potential seriousness of serotonergic syndrome, an information on the risk is of major interest for the user of <i>Hypericum perforatum</i></p> <p>Proposed change</p> <p>Well-established use and Traditional use, indication1</p> <p>Cases of serotonergic syndrome have been reported in elderly patients in case of concomitant treatment with ISRS. Symptoms have decreased after discontinuation of <i>Hypericum perforatum</i>.</p> <p>Gastrointestinal disorders, allergic reactions of the skin, fatigue and restlessness may occur. The frequency is not known.</p> <p>Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight.</p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>	<p>Interaction with serotonergic drugs already included in the monograph.</p>
4.8.	<p><u>Traditional use</u></p> <p>Indication 1:</p> <p>Gastrointestinal disorders, allergic reactions of the skin, fatigue and restlessness may occur. The frequency is not known.</p> <p>Fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight.</p> <p>If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.</p>	<p>Change not endorsed.</p> <p>There are no data available from studies designed to detect a frequency of adverse reactions. Moreover, from the traditional preparations no data from clinical trials are available.</p>

Indication 2:

Skin reactions may occur. ~~The frequency is not known.~~

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

Comments: Within a recently compiled PSUR, a total of 27 cases with adverse events during treatment with St. John's wort have been identified in the literature during the period under review, i.e. from 26/Apr/2004 to 26/Mar/2007. A detailed description of the case reports is attached (encl. 2).

In summary, a total of 27 case reports in connection with Hypericum were retrieved from the literature within the report period. One fatal case was reported following SJW intake and bone marrow depression. However, this case is poorly documented. Several other factors which may have been responsible for the fatal outcome were not discussed. This case is consequently considered to be not relevant for other authorized SJW products. 4 case reports are related to different drug-drug interactions of SJW with synthetic drugs. Two case reports of suspected drug/drug interactions with cyclosporine and digoxin respectively, have been published which involved concomitant ingestion of hypericum tea. However, in one case (Alscher and Klotz 2003) the patient consumed a tea mixture containing an unspecified amount of St. John's Wort besides unspecified other herbs. The second case (Andelic 2003) describes an 80-year old man who started consuming SJW herbal tea in an amount of 2000 ml/d. This 2nd case as well is not adequately reported. The information given about a dosage of SJW for preparation of the tea is not sufficient. The product is not specified. Both case reports are clearly contradictory to clinical findings with hypericum tea as described by L'Homme (2006), Mai et al (2004), Mueller, Uehleke et al (2004) and Mueller, Majcher-Peszynska et al. (2006). 3 cases of a serotonin syndrome were reported. However, even though some of the cases are formally possible, the overall documentation is poor. However, most of the cases are not well described and causality of the respective hypericum preparation is not stringently demonstrated in any of the cases. No cases of phototoxicity were retrieved from the

	<p>literature in the reporting period. All other reactions described in the case reports are at maximum formally possible.</p> <p>However, a final assessment can often not be made because several severe shortcomings of the reports. None of these reports is considered to qualify for further measures. Overall, no change of the safety profile of SJW preparations is seen. In conclusion, for both modern extract preparations and traditional Hypericum preparations the risk/benefit balance is adequate in their respective indications.</p>	
5.2.	<p><u>Traditional use</u></p> <p>Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.</p> <p>Hyperforin is a strong enzyme inducer and may interact with many medicinal products. This is not relevant in traditional preparations corresponding to less than 1000 mg herbal drug, as in these the hyperforin content is low and does not cause clinically relevant interactions.</p> <p>Comments: The 2nd sentence should be deleted in preparations corresponding to less than 1000 mg extract, because it is not relevant for almost all traditionally used preparations, as these have a low hyperforin content; moreover they have a much lower dose. For further explanation see our comments on paragraph 4.5, traditional use.</p>	<p>Not endorsed.</p> <p>At the moment there is no limit of the hyperforin uptake established below which no interactions occur.</p> <p>For safety reasons the patients should get a clear message that some precautionary measures should be considered when taking hypericum preparations independent of the actual hyperforin content.</p>
5.3.	<p><u>Traditional use</u></p> <p>Studies on acute toxicity and repeated dose toxicity did not show signs of toxic effects.</p> <p>The weak positive results of an ethanolic extract in the AMES-test (Salmonella typhimurium TA 98 and TA 100 with and without metabolic activation) could be assigned to quercetin. No signs of mutagenicity could be detected in further in vitro and in vivo test systems.</p> <p>No adverse effects have been observed in reproduction toxicity testing.</p>	<p>Genotoxicity: wording modified</p> <p>Reproduction toxicity: according to the data in literature modified to: Tests on reproduction toxicity revealed equivocal results.</p>

~~No adequate testes on reproduction toxicity have been performed.~~

No genotoxicity was observed in corresponding test models.

Tests on the carcinogenic potential have not been performed.

Phototoxicity:

After oral application of dosages of 1800 mg of an extract per day for 15 days the skin sensitivity against UVA was increased, and the minimum dose for pigmentation was significantly reduced. In the recommended dosage no signs of phototoxicity are reported.

Comments: The same applies. Furthermore it should be mentioned that traditional herbal medicinal products are normally much lower dosed.

Superseded