



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2012
EMA/HMPC/26431/2012
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Rhodiola rosea* L., rhizoma et radix (EMA/HMPC/232091/2011)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Rhodiola rosea* L., rhizoma et radix as released for public consultation on 20 September 2011 until 15 December 2011

	Organisations and/or individuals
1	Prof. Dr Alexander Panossian, Swedish Herbal Institute (SHI)
2	Dr. Ulrich Mathes, Dr. Willmar Schwabe GmbH & Co.KG
3	The Association of the European Self-medication Industry (AESGP)
4	European Scientific Cooperative on Phytotherapy (ESCOP)



Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
ESCOP	ESCOP welcomes the draft Community herbal monograph on arctic rhizome and root prepared by the Committee on Herbal Medicinal Products (HMPC). ESCOP would like to comment on one particular issue of this monograph, i.e. the therapeutic indication.	
SHI	With reference to enclosed documentation and references, we would like the HPMC to review the herbal as well-established Herbal Medicinal Product. Some important non-clinical and clinical data supporting well establish use of Rhodiola in stress-induced fatigue related to published papers on pharmacodynamic and the mechanism of action of active ingredients as well as pharmacokinetic data have not been evaluated.	Well-established use is not endorsed, since no additional clinical data were submitted. The additional non-clinical data are acknowledged and implemented in the AR.
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Rhodiola roseae-containing products, should facilitate mutual recognition in Europe. We have the following specific comments.	
Schwabe	We are MAH of traditional herbal medicinal products approved in 6 EU member states (AT, ES, IT, NL, SE, UK) and applications in further EU member states (BE, DE, FR) are still pending. The active substance is a dry extract obtained from the underground parts of Rhodiola rosea L. [DER 1.5-5 : 1 ; extraction agent: ethanol 60 % (w/w)]. We welcome the draft Community herbal monograph [Doc. Ref. EMA/HMPC/232091/ 2011] and have the following specific comments.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
<p>2. Qualitative and quantitative composition</p>	<p>SHI</p>	<p>ii) Herbal preparations</p> <p>Definition of the genuine (native) extract: Rhodiola rosea root and rhizome extract.</p> <p>DERgenuine 2,5-5,0:1</p> <p>Extraction solvent: 1st extraction solvent - EtOH 70%, 2nd extraction solvent- potable water</p> <p>Composition of the herbal preparation: 79,8-79,9 % genuine extract.</p> <p>DER (Ratio of the herbal substance to the herbal preparation: (2,0 – 3,5) : 1.</p> <p>One tablet contains 144 mg of native extract. Daily dose: 1-2 tablets</p>	<p>Already considered in the AR.</p>
<p>2. Qualitative and quantitative composition</p>	<p>AESGP</p>	<p>The draft monograph mentions the following extract: Dry extract (DER 1.5-5:1), extraction solvent ethanol 67-70% v/v.</p> <p>As explained in the draft Assessment Report, the mentioned extract is based on the following data:</p> <p>1. Liquid extract, DER 1:1, extraction solvent ethanol 40% (V/V)</p> <p>In 1975 Rhodiola fluid extract was accepted in the former USSR as a 'Temporary Pharmacopoeial Article' which allowed the large-scale industrial production of a liquid extract (DER 1:1, extraction solvent ethanol 40%). The product is no longer marketed.</p>	<p>None of the medicinal products currently registered or authorised is at the moment more than 30 years in medicinal use. Therefore the definition of the herbal preparation in the monograph is rather broad in order to include all marketed products.</p>

SPECIFIC COMMENTS ON TEXT

		<p>2. Dry extract of root and rhizome, DER 2,5- 5:1, first extraction solvent ethanol 70%, second extraction solvent water.</p> <p>The product is marketed in Sweden since 1985/1987, the name according to the literature is 'SHR-5' in the literature. The product is still marketed today.</p> <p>3. Dry extract of root and rhizome, DER 1.5-5:1, extraction solvent ethanol 60% m/m (= approx. 67% (v/v).</p> <p>The extract is in the market as traditional herbal medicinal product according to Directive 2004/24/EC in Austria and the UK since 2008, in the Netherlands since 2009, in Sweden and Spain since 2010 and in Italy since 2011. The registrations were granted based on the traditional medicinal use of the herbal preparations A and B.</p> <p>As the extract mentioned in the draft monograph is apparently deduced from the 2nd and the 3rd extract we are wondering whether this extract is produced by a one-step procedure or whether it is produced (like the 2nd extract) in a two-step procedure using at first ethanol 70 % and then water. We would be happy for clarification and assume otherwise that both mentioned procedures are covered by the monograph.</p> <p>We would also propose to add the extraction solvent concentration in mass percent, as follows:</p> <p><i>"Dry extract (DER 1.5-5:1), extraction solvent ethanol 67-70% v/v [59-62% w/w]"</i></p>	<p>Not endorsed.</p> <p>The correlation between volume percent and mass percent of ethanol-water mixtures can be found in the European Pharmacopoeia. HMPC-monographs indicate one of these two options only.</p>
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SPECIFIC COMMENTS ON TEXT			
<p>2. Qualitative and quantitative composition</p>	<p>Schwabe</p>	<p>Proposed change:</p> <p><i>"ij) ... extraction solvent ethanol 67 – 70 % v/v [59 – 62 % w/w] ..."</i></p> <hr/> <p>Rationale:</p> <p>In favour of transparency and referring to our products on the market, we propose to add the extraction solvent concentration in mass percent.</p>	<p>Not endorsed.</p> <p>In the AR the extraction solvent for this herbal preparation is indicated in mass percent. For the monograph the characterisation of the herbal preparation for traditional use was widened in order to include all the very similar traditional extracts. Therefore the HMPC monograph does not only refer to the product of the Schwabe company. The correlation between volume percent and mass percent of ethanol-water mixtures can be found in the European Pharmacopoeia. HMPC-monographs indicate one of these two options only.</p>
<p>3. Pharmaceutical form Well-established use</p>	<p>SHI</p>	<p>Herbal preparation in solid or liquid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term</p>	<p>Not endorsed, see above.</p>
<p>4.1. Therapeutic indications</p>	<p>ESCOP</p>	<p>Proposed change:</p> <p>Replace "Traditional herbal medicinal product for relief of symptoms of asthenia such as fatigue and weakness" by:</p> <p>"Traditional herbal medicinal product for relief of mental and physical symptoms of stress, such as fatigue, weakness, exhaustion, irritability and slight anxiety"</p> <p>Rationale:</p> <p>The proposed therapeutic indication ("<i>THMP for relief of symptoms of asthenia such as fatigue and weakness</i>") does not cover properly the therapeutic indications attributed to arctic</p>	<p>Partly endorsed.</p> <p>After rediscussion the indication was modified to: Traditional herbal medicinal product for temporary relief of symptoms of stress, such as fatigue and sensation of weakness.</p> <p>The submitted reference Brown et al (2002) is acknowledged. As it is a review it does not contain original data and is therefore not included in the AR and list of references.</p>

SPECIFIC COMMENTS ON TEXT

root medicinal products based on its recognised longstanding use. According to the "Guideline on the assessment of clinical safety and efficacy for the preparation of community herbal monographs for well-established and for community herbal monographs / entries to the community list for traditional herbal medicinal products / substances / preparations" (EMA/HMPC/104613/2005), we cite "*An indication 'exclusively based upon longstanding use' may be plausible, even if no supporting scientific data are available*".

As mentioned in the draft assessment report on *Rhodiola rosea* L., rhizome et radix (EMA/HMPC/232100/2011, page 6/32), Herbal preparation B on the market in Sweden since 1987 (or 1985) is a "*THMP used as an adaptogen at decreased performance, such as fatigue and weakness*". Based on the same document, the indication given more recently by different national EU authorities to the Herbal preparation C is "*THMP for relief of mental and physical symptoms of stress, such as fatigue, weakness, exhaustion, irritability and slight anxiety*". Indeed, as reported in the literature "*registered preparations are extensively used in Sweden and other Scandinavian countries to increase mental work capacity during stress, as a psychostimulant, and as a general strengthener*" (Brown, 2002).

Accordingly, it appears appropriate, as suggested above, to reconsider the therapeutic indication, in order to fully cover the longstanding use of arctic root.

Literature reference. Brown RP, Gerbarg PL, Ramazanov Z. *Rhodiola rosea* A phytochemical overview. *Herbalgram* 2002;56:40-52.

<p>4.1. Therapeutic indications Well-established use</p>	<p>SHI</p>	<p>Herbal medicinal product for the relief of symptoms of stress, fatigue and mild depression. As adjuvant treatment in chronic fatigue syndrome (CFS) as diagnosed by physician. Clinical studies available:</p> <p>Panossian, A., and Wikman, G. (2010). Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress-Protective Activity. <i>Pharmaceuticals</i> 3, 188-224.</p> <p>Olsson EMG, von Schéele B, Panossian AG. A randomized double-blind placebo controlled Parallel group study of SHR-5 extract of <i>Rhodiola rosea</i> roots as treatment for patients with stress related fatigue. <i>Planta medica</i>. 2009 Feb; 75(2):105-12. Epub 2008 Nov 18.</p> <p>Summary of studies of anti-depressive activity of Rhodiola and proposal regarding the mechanism of action.</p> <p>Antidepressant activity of SHR-5 has been demonstrated in humans Darbinyan V., Aslanyan G., Amroyan E., Gabrielyan E., Malmström C. and Panossian A. Clinical trial of <i>Rhodiola rosea</i> L. extract SHR-5 in the treatment of mild to moderate depression. <i>Nordic Journal Psychiatry</i>, Vol 61, No. 5, 2343-348, 2007</p> <p>Antidepressant activity of SHR-5 and its active constituents (salidroside, etc.) has been demonstrated in animals. Panossian A., Nikoyan N., Ohanyan N., Hovhannisyan A., Abrahamyan H., Gabrielyan E., Wikman G. Comparative study</p>	<p>Well-established use not endorsed, see above.</p> <p>Panossian & Wilkman (2010): no additional clinical data Olsson et al (2009). Already considered in the AR. Darbinyan et al (2007): Already considered in the AR.</p> <p>Non-clinical data cannot be used to substantiate well-established use.</p>
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	<p>of Rhodiola preparations on behavioural despair of rats <i>Phytomedicine.</i> , 15 (1): 84-91, 2008</p> <p>The content of rosiridin, the main active inhibitor of MAO A (Van Diermen <i>et al.</i> 2009) in Rhodiola, is extremely low and obviously has no clinical significance. It was not detected in Rhodiola SHR-5 extract and found only in trace amounts in few Rhodiola preparations.</p> <p>It is very unlikely that rosiridin has any influence on antidepressant effect of SHR-5</p> <p>The mechanism of action of SHR-5 and salidroside is associated with activation of neuropeptide Y, but not with MAO A (where salidroside is inactive).</p> <p>First it should be mentioned that pathophysiology of depression is associated with many impairments in neuroendocrine system, where are many players, not only catecholamines and monoaminoxidases (MAO A). Pharmacological activity of some anti depressive drugs is due to inhibition of MAO, (unfortunately, all of them have numerous adverse effects)</p> <p>However, inhibition of MAO is not the only pharmacological target for the treatment of depression. There are some other alternatives.</p> <p>For example via neuropeptide Y (NPY), this is low in depression.</p> <p>Rhodiola is an antidepressant that stimulates biosynthesis of NPY in brain and therefore has anti depressive activity in humans and animals. Salidroside is found as an active substance stimulating</p>	
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		<p>NPY. http://www.frontiersin.org/neuroendocrine_science/abstract/17819</p> <p>NPY is known to play a role in the pathophysiology of depression (Heilig, M. et al., 1988). It has been shown that NPY displayed antidepressant-like activity in the rat forced swimming test (Redrobe, J. P. et al., 2002. Stogner, K. A. & Holmes, P. V., 2000).</p> <p>Human studies have revealed a role for NPY in adaptation to stress ("buffering" the harmful effects of stress) (Morales-Medina, J. C. et al., 2010; Morgan, C. A., 3rd et al., 2001; Morgan, C. A., 3rd et al., 2000). There is a plethora of pre-clinical and clinical evidence suggesting a mood and cognitive performance improving action for NPY (Fletcher, M. A. et al., 2010; Morgan, C. A., 3rd et al., 2000). Higher levels of NPY have been observed in soldiers who either present with reduced psychological distress or belong to the elite Special Forces branch (Morgan, C. A., 3rd et al., 2001; Morgan, C. A., 3rd et al., 2000). In contrast, decreased levels of NPY were observed in depression and in brain tissues of suicide victims (Morales-Medina, J. C. et al., 2010).</p>	
<p>4.1 Therapeutic indications</p>	<p>AESGP</p>	<p>Proposed change: <i>"Traditional herbal medicinal product for relief of mental and physical symptoms of asthenia stress and overwork, such as fatigue and weakness, exhaustion, asthenia, irritability, tenseness and mild anxiety"</i></p> <p>Rationale: We propose to word the indication more precisely, as "asthenia" is a condition that may be caused by stress as well as by organic or infectious diseases. We regard the above proposed indication as appropriate as it is more precise and corresponds much better to the specific pharmacological profile of <i>Rhodiola rosea</i>: It comprises the treatment of both</p>	<p>See above.</p>

		<p>mental and physical symptoms of stress, while asthenia means physical weakness. We see asthenia more as a stress symptom and have therefore included it in the list of symptoms in our proposed indication.</p> <p>The indication of all seven so far registered traditional herbal medicinal products includes "stress". In the meantime, the indication of the "Herbal Preparation B" in Sweden, mentioned under 2.2. in the Draft AR, has been changed to include "stress".</p> <p>We regard the plausibility of the pharmacological effects and the efficacy in the treatment of stress symptoms on the basis of long-standing use and experience as justified for the following reasons:</p> <ol style="list-style-type: none"> 1. The plausibility of the pharmacological effects and the efficacy in the indication "stress" can be derived from the numerous publications quoted in the draft assessment report that confirm the positive influence of <i>Rhodiola rosea</i> on mental and physical symptoms of stress (attachment 1) 2. As evidence for the "longstanding use", we would like to refer to the more recent edition of the monograph on <i>Rhodiola rosea</i> by Saratikov who performed extensive research on the efficacy of <i>Rhodiola rosea</i> preparations: Saratikov AS, Krasnov YA. <i>Rhodiola rosea</i> (Golden root). Fourth edition, revised and enlarged. Tomsk State University Publishing House 2004 Chapter VII: Adaptogenic properties of <i>Rhodiola</i> preparations (Saratikov AS), p. 189-219. (attachment 2A). In this 2004 edition, the author refers very often to "stress" as a condition which can be treated with <i>Rhodiola rosea</i>. This is supported by publications dated from 1951 until 2002 covering all decades in this time period (2 publications from the 1950s, 4 from the 1960s, 1 from the 1970s, 10 from the 1980s, 13 from the 1990s and 5 from 2000-2002). Above all chapter VII of this monograph contains lots of references which definitely confirm the longstanding successful use of this drug for the treatment of different symptoms of stress (attachment 2B). 	
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		<p>3. There are numerous other older publications on investigations of the pharmacological efficacy of Rhodiola in stress and similar indications. Some examples are compiled in attachment 3.</p> <p>The reason why the word "stress" is less frequently used in older publications may be caused by the fact that at that time other terms were used for what we would today describe as "stress" and the effects on health were less clear.</p>	
<p>4.1. Therapeutic indications</p>	<p>Schwabe</p>	<p>Proposed change:</p> <p><i>"Traditional herbal medicinal product for relief of mental and physical symptoms of stress and overwork, such as fatigue, exhaustion, asthenia, irritability, tenseness and mild anxiety"</i></p> <hr/> <p>Rationale:</p> <p>We propose to word the indication more precisely, as "asthenia" is a condition that may be caused by stress as well as by organic or infectious diseases. We regard the above proposed indication as appropriate as it is more precise and corresponds much better to the specific pharmacological profile of <i>Rhodiola rosea</i>: It comprises the treatment of both <u>mental</u> and <u>physical</u> symptoms of stress, while asthenia means <u>physical</u> weakness. We see asthenia more as a stress <u>symptom</u> and have therefore included it in the list of symptoms in our proposed indication.</p> <p>Correspondingly, the indication of all seven so far registered THMPs includes "stress". In the meantime, the indication of the "Herbal Preparation B" in Sweden, mentioned under 2.2. in the Draft AR, has been changed to include "stress".</p> <p>We regard the plausibility of the pharmacological effects and</p>	<p>See above</p>

		<p>the efficacy in the treatment of stress symptoms on the basis of long-standing use and experience as justified for the following reasons:</p> <ol style="list-style-type: none">1. The plausibility of the pharmacological effects and the efficacy in the indication "stress" can be derived from the numerous publications quoted in the draft assessment report that confirm the positive influence of <i>Rhodiola rosea</i> on mental and physical symptoms of stress (attachment 1)2. As evidence for the "longstanding use", we would like to refer to the more recent edition of the monograph on <i>Rhodiola rosea</i> by Saratikov whose remuneration is based on the fact that he was the first to perform extensive research on the efficacy of <i>Rhodiola rosea</i> preparations: Saratikov AS, Krasnov YA. <i>Rhodiola rosea</i> (Golden root). Fourth edition, revised and enlarged. Tomsk State University Publishing House 2004 (attachment 2C) Chapter VII: Adaptogenic properties of <i>Rhodiola</i> preparations (Saratikov AS), p. 189-219. (attachment 2A) In this 2004 edition, the author refers very often to "stress" as a condition which can be treated with <i>Rhodiola rosea</i>. This is supported by publications dated from 1951 until 2002 covering all decades in this time period (2 publications from the 1950s, 4 from the 1960s, 1 from the 1970s, 10 from the 1980s, 13 from the 1990s and 5 from 2000-2002). Above all chapter VII of this monograph contains lots of references which definitely confirm the longstanding successful use of this drug for the treatment of different symptoms of stress (attachment 2B).	
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		<p>3. There are numerous other older publications on investigations of the pharmacological efficacy of Rhodiola in stress and similar indications. Some examples are compiled in attachment 3.</p> <p>The reason why the word "stress" is less frequently used in older publications may be caused by the fact that at that time other terms were used for what we would today describe as "stress".</p>	
<p>4.2. Posology and method of administration Well-established use</p>	SHI	<p>Posology <i>Adults and Elderly</i> Single dose 144 - 200 mg Daily dose 144 – 400 mg The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').</p> <p>Duration of use If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p>Method of administration Oral use.</p>	Well-established use not endorsed, see above.
<p>4.3. Contra-indications Well-established use</p>	SHI	Patients with known hypersensitivity to the active substance should not use the preparation.	Well-established use not endorsed, see above.
<p>4.4. Special warnings and precautions for use</p>	SHI	The use of this product is not recommended in children below the age of 12 years. For preparations containing ethanol the appropriate labeling for ethanol, taken from the guideline on excipients, must be included.	Well-established use not endorsed, see above.

<p>4.4. Special warnings and precautions for use</p>	<p>AESGP</p>	<p>Proposed change: <i>"...If the symptoms persist longer than 2 weeks or worsen during the use of the medicinal product, a doctor or qualified health care practitioner should be consulted..."</i></p> <p>Rationale: We propose to add the same wording as included in section 4.2, but the case of symptoms worsening should be added here.</p>	<p>Not endorsed. The wording is in line with the template used for all HMPC monographs.</p>
<p>4.4. Special warnings and precautions for use</p>	<p>Schwabe</p>	<p>Proposed change: <i>"... If symptoms persist longer than 2 weeks or worsen during the use of the medicinal product, a doctor or qualified health care practitioner should be consulted. ..."</i></p> <hr/> <p>Rationale: We propose to add the same wording as included in section 4.2, but the case of symptoms worsening should be touched here additionally.</p>	<p>Not endorsed. The wording is in line with the template used for all HMPC monographs.</p>
<p>4.5. Interactions with other medicinal products and other forms of interaction Well-established use</p>	<p>SHI</p>	<p>Limited data on pharmacological interactions with other medicinal products are available. Clinically relevant interaction with drugs metabolized by the CYP 2C9, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway has not been observed. Study performed with warfarin and theophylline:</p> <p>Panossian A, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Pharmacokinetic and pharmacodynamic study of interaction of <i>Rhodiola rosea</i> SHR-5 extract with warfarin and theophylline in rats. <i>Phytother Res.</i> 2009 Mar; 23(3):351-7.</p>	<p>Well-established use not endorsed, see above. Non-clinical data already considered in the AR.</p>

		Panossian, A. Hovhannisyan, H. Abrahamyan, G. Wikman, Pharmacokinetics of active constituents of <i>Rhodiola rosea</i> L. special extract SHR-5. In: Comprehensive Bioactive Natural Products Vol. 2: Efficacy, Safety & Clinical Evaluation (Part-1) <i>Stadium Press LLC, USA, 2010.</i> pp. 1-23	
4.6. Fertility, pregnancy and lactation Well-established use	SHI	Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.	Well-established use not endorsed, see above.
4.7. Effects on ability to drive and use machines	SHI	Clin. Panossian A., V. Darbinyan , A. Kteyan, G. E. Gabrielian , G. Wikman <i>Rhodiola rosea</i> L. in stress induced fatigue – a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. <i>Drug Information Association, 36th Annual Meeting, June 11-15, 2000 Convention Center, San Diego, CA, USA</i>	Reference not submitted.
4.9. Overdose	SHI	No case of overdose has been reported.	Well-established use not endorsed, see above.
4.8. Undesirable effects Well-established use	SHI	None known. If adverse reactions occur, a doctor or a qualified health care practitioner should be consulted.	Well-established use not endorsed, see above.

<p>5.1. Pharmacodynamic properties Well-established use</p>	<p>SHI</p>	<p>Pharmacological data regarding isolated constituents: Salidroside and other phenylalkaloids:</p> <p>Effects on nervous system</p> <p>Panossian A., Nikoyan N., Ohanyan N., Hovhannisyan A., Abrahamyan H., Gabrielyan E., Wikman G. Comparative study of Rhodiola preparations on behavioural despair of rats <i>Phytomedicine.</i> , 15 (1): 84-91, 2008</p> <p>The antidepressant-like activity of rhodioloside (salidroside), rosavin, rosin, rosarin, tyrosol, cinnamic alcohol, cinnamaldehyde and cinnamic acid has been assessed in laboratory animals through application of the Porsolt behavioural despair assay.. A fixed combination of rhodioloside, rosavin, rosarin and rosin was more active than any of the individual components alone.</p> <p>Panossian A, Wikman G, Kaur P, Asea A. Adaptogens (ADAPT-232) stimulate neuropeptide Y expression in neuroglia cells. 59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research, 4th-9th September 2011, Antalya, Turkey. <i>Planta medica.</i> 2011;77 (12), 1248.</p> <p>Panossian A, Wikman G, Kaur P, Asea A. Adaptogens stimulate molecular chaperon Hsp70 expression in neuroglia cells. 59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research, 4th-9th September 2011, Antalya, Turkey. <i>Planta medica.</i> 2011;77 (12), 1420.</p> <p>Panossian AG, Wikman G, Kaur P, Asea A Adaptogens stimulate neuropeptide Y and Hsp72 expression and release in neuroglia cells. <i>Frontier in Neuroendocrine Science.</i> 2011. In</p>	<p>Well-established use not endorsed, see above.</p>
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	<p>press. http://www.frontiersin.org/neuroendocrine_science/abstract/17819</p> <p>ADAPT-232, a fixed combination of adaptogens Eleutherococcus senticosus root extract, Schisandra chinensis berry extract, Rhodiola rosea root extract SHR-5, and its active constituent salidroside, stimulated the expression of NPY and Hsp72 in isolated human neuroglia cells. The central role of NPY was validated in experiments in which pre-treatment of human neuroglia cells with NPY-siRNA and HSF1-siRNA resulted in the significant suppression of ADAPT-232-induced NPY and Hsp72 release. Taken together our studies suggest that the stimulation and release of the stress hormones, NPY and Hsp72, into systemic circulation is an innate defense response against mild stressors (ADAPT-232), which increase tolerance and adaptation to stress.</p> <p><i>Stress-protective effects:</i> Panossian A., Hambartsumyan M., Hovanissian A, Gabrielyan E., Wikman G. The Adaptogens Rhodiola and Schizandra Modify the Response to Immobilization Stress in Rabbits by Suppressing the Increase of Phosphorylated Stress-activated Protein Kinase, Nitric Oxide and Cortisol. <i>Drug Targets Insights</i>, 1, 39-54, 2007; http://www.la-press.com/the-adaptogens-rhodiola-and-schizandra-modify-the-response-to-immobili-a260</p> <p><u>Pharmacological data from combinations:</u> <i>Effects on nervous system</i> Panossian A, Wikman G, Kaur P, Asea A. Adaptogens (ADAPT-232) stimulate neuropeptide Y expression in neuroglia cells. 59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research, 4th-9th</p>	
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		<p>September 2011, Anatalya, Turkey. <i>Planta medica</i>. 2011;77 (12), 1248.</p> <p>Panossian A, Wikman G, Kaur P, Asea A. Adaptogens stimulate molecular chaperon Hsp70 expression in neuroglia cells. 59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research, 4th-9th September 2011, Antalya, Turkey. <i>Planta medica</i>. 2011;77 (12), 1420.</p> <p>Panossian AG, Wikman G, Kaur P, Asea A. Adaptogens stimulate neuropeptide Y and Hsp72 expression and release in neuroglia cells. <i>Frontier in Neuroendocrine Science</i>. 2011. In press. http://www.frontiersin.org/neuroendocrine_science/abstract/17819</p> <p>ADAPT-232, a fixed combination of adaptogens Eleutherococcus senticosus root extract, Schisandra chinensis berry extract, Rhodiola rosea root extract SHR-5, and its active constituent salidroside, stimulated the expression of NPY and Hsp72 in isolated human neuroglia cells.</p> <p>The central role of NPY was validated in experiments in which pre-treatment of human neuroglia cells with NPY-siRNA and HSF1-siRNA resulted in the significant suppression of ADAPT-232-induced NPY and Hsp72 release. Taken together our studies suggest that the stimulation and release of the stress hormones, NPY and Hsp72, into systemic circulation is an innate defense response against mild stressors (ADAPT-232), which increase tolerance and adaptation to stress.</p>	
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<p>5.2. Pharmacokinetic properties Well-established use</p>	<p>SHI</p>	<p>Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.</p> <p>The pharmacokinetic of tyrosol, salidroside and rosavin – the active constituents of <i>Rhodiola rosea</i> SHR-5 extract was studied by validated capillary electrophoretic in the blood and urine of rats, which had been administration SHR-5. Salidroside was found to be quickly and completely absorbed into the blood, distributed within organs and tissues, and rapidly metabolised to tyrosol following oral administration of SHR-5 at doses of 20 and 50 mg/kg. Many of the measured pharmacokinetic parameters of salidroside were significantly different when the pure compound was administered rather than the special extract. The basal level of tyrosol in blood plasma of rats increased following administration of SHR-5 as a result both of absorption of free tyrosol present in the extract and of biotransformation of salidroside into tyrosol, which occurred within the first 2 h.</p> <p>At least 68% of the administered salidroside was transformed into tyrosol and excreted in the urine. The pharmacokinetics and the rate of biotransformation of salidroside were essentially the same following single or multiple regimes of administration of SHR-5. Rosavin has very low bioavailability (20 - 26%) and was quickly eliminated from the blood of rats that have been administered SHR-5.</p> <p>Panossian, A. Hovhannisyan, H. Abrahamyan, G. Wikman, Pharmacokinetics of active constituents of <i>Rhodiola rosea</i> L. special extract SHR-5. In: Comprehensive Bioactive Natural Products Vol. 2: Efficacy, Safety & Clinical Evaluation (Part-1)</p>	<p>Well-established use not endorsed, see above.</p>
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		<p><i>Stodium Press LLC, USA,2010. pp. 1-23</i></p> <p>Abrahamyan H, Hovhannisyan A., Gabrielyan E. Panossian A., Pharmacokinetic study of salidroside and rosavin, active principles of <i>Rhodiola rosea</i> in rats by high performance capillary electrophoresis system. <i>Drugs and medicine</i>, No. 3, pp. 55-61, 2004.</p> <p>Abrahamyan H, Hovhannisyan A., Panossian A., Gabrielyan E. The bioavailability of salidroside and rosavin, active principles of <i>Rhodiola rosea</i> extract SHR-5 in rats. <i>Medical Science of Armenia</i>, 45 (1), 24-29, 2005.</p>	
<p>5.3. Preclinical Safety Data Well-established use</p>	SHI	<p>Preclinical studies performed:</p> <ul style="list-style-type: none"> -Acute toxicological study in rats (SHR-5 extract) -Sub-acute toxicological study in rats (SHR-5 extract) -Immunotoxicological study in rats (SHR-5 extract) -Subchronical toxicological study rats (SHR-5 extract) -Subchronical toxicological study piglets (SHR-5 extract) -CNS-toxicity in rats (SHR-5 extract) 	<p>Well-established use not endorsed, see above. The submitted non-clinical data will be considered in the AR.</p>

<p>Comments on the Draft Assessment Report</p>	<p>AESGP</p>	<p><i>2.2. Information on traditional/current indications and specified substances/preparations</i></p> <p>The indication of Herbal Preparation B (the Swedish THMP product Arctic root) has been changed in the meantime to:</p> <p><i>Traditionellt växtbaserat läkemedel använt som adaptogen vid stressrelaterad nedsatt prestationsförmåga med symptom såsom trötthet, svaghetskänsla, irritabilitet och lindrig oro.</i></p>	<p>Endorsed.</p> <p>According to information of the Swedish medicines agency the wording of the indication was changed to: "Traditional herbal medicinal product used as an adaptogen in case of stress related decreased performance ability with symptoms such as fatigue, sensation of weakness, irritability and mild anxiety. The indications of a traditional herbal medicinal product are based solely on experience and use during a long period of time."</p>
<p>Comments on the Draft Assessment Report</p>	<p>Schwabe</p>	<p><u>2.2. Information on traditional/current indications and specified substances/preparations</u></p> <p><u>The indication of Herbal Preparation B (the Swedish THMP product Arctic root) has been changed in the meantime to:</u></p> <p><i>Traditionellt växtbaserat läkemedel använt som adaptogen vid stressrelaterad nedsatt prestationsförmåga med symptom såsom trötthet, svaghetskänsla, irritabilitet och lindrig oro.</i></p>	<p>Endorsed. See above.</p>