EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of comments received on Community herbal monograph on *Vitis vinifera* L., folium (EMEA/HMPC/16635/2009)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Vitis vinifera* L. folium as released for public consultation on 12 November 2009 until 15 April 2010.

	Organisations and/or individuals
1	AESGP
2	Boehringer Ingelheim GmbH
3	Diapharm Regulatory Services GmbH
4	Kooperation Phytopharmaka
5	ESCOP
6	Indena

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Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
AESGP	AESGP welcomes the preparation of the above-mentioned Community herbal monograph which should facilitate mutual recognition in Europe by harmonising the assessment criteria. In particular we welcome that the well-established use as well as the traditional use have been reflected.	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Title of Monograph (and all throughout the monograph)	AESGP	**Comments**: We suggest deleting "Var. Tinctoria" in the title for the monograph. **Proposed change (if any)**: COMMUNITY HERBAL MONOGRAPH ON VITIS VINIFERA L., Folium **Justification**: "VITIS VINIFERA L., Folium" is the correct botanical term. "Var. Tinctoria" was occasionally used in the literature to underline the use of dyer grapes. It is not a name for a variety.	**Endorsed** The French Pharmacopoeia X edition refers to the vigne rouge "teinturier" and the title of the monograph is "Vitis vinifera".
Table on page 1	AESGP	**Proposed change (if any)**: The German word for this plant is ***"Rotes Weinlaub"***	**Not endorsed.** According to BfArM 'Rote Weinrebenblätter' is preferred.
2. Qualitative and quantitative composition	AESGP	**Well established-use**: A clinical efficacious and safe extract preparation is achieved by the selection of an appropriate quality of red vine leaves and a specific manufacturing procedure. The active ingredient, which is the herbal preparation, is characterised by the drug to	**Endorsed**

SPECIFIC COMMENTS ON TEXT			
		extract ratio of 4-6:1 and the solvent used. *Therefore "quantified to flavonoids content 3-7% should be deleted".* **<u>Traditional use</u>**: The dry extract (3:1) should be given with a range. A DER of 3:1 without a range is not realistic and does not correspond to the HMPC Declaration guideline.	Although the company was contacted, complete information on this extract is not available so this extract was deleted.
4.1 Therapeutic indication	AESGP	**<u>Well established-use</u>**: **Comments**: We suggest including "prevention" in the indication. **Proposed change (if any)**: Herbal medicinal product for treatment and prevention of symptoms of chronic venous insufficiency, which … **Justification**: In clinical studies all <u>objective</u> efficacy parameters investigated (leg volume, calf circumference, cutaneous microcirculation, transcutaneous oxygen pressure) improved as early as after two to six weeks of therapy. A statistically significant and clinically relevant reduction of the leg oedema was measured after 6 weeks, with further improvement until 12 weeks of treatment. A re-occurrence of subjective symptoms or an increase in leg volume was not observed in patients treated with a Vitis vinifera-containing product, whereas this was the case in those subjects treated with placebo. These observations in clinical studies support the claim that Vitis vinifera prevents the occurrence of symptoms of chronic venous insufficiency when used as indicated. [1,2,3]	**Not endorsed** The clinical studies available were performed in patients suffering from CVI, grade I, II, or III according to Widmer classification, with the objective of demonstrating the effective treatment of symptoms associated to this condition. The observations in clinical studies were the basis for the acceptability of efficacy in the treatment of CVI, but were not proposed for the evaluation of prevention of CVI.

SPECIFIC COMMENTS ON TEXT			
		Further support for the prevention claim has been gained in *in vitro* studies of human venous endothelial cells. Certain release products from simultaneously activated blood platelets and polymorphonuclear granulocytes, which are released in venous hypostasis, lead to local edema, arteriolar constriction and venular thrombosis. Vitis vinifera has been shown to prevent the deleterious effect of the release products on the venular endothelial monolayers and is able to repair damage of the endothelium caused by these release products.[4] A clinical study with a Vitis vinifera-containing product in CVI patients demonstrated its ability to enhance skin microcirculation and improve transcutaneous partial pressure of oxygen. These findings are assumed to prevent CVI deterioration. [2]	
4.2 Posology and method of administration Posology	AESGP	**Traditional use:** Indication a) **Comments**: We suggest deleting the timing (for more than 2 weeks) and **including instead "or worsen"** **Proposed change (if any)**: If the symptoms persist or worsen for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Justification**: This gives a clearer guidance to the patients to consult a doctor in the case of persisting or worsening of symptoms.	**Not endorsed** 2 weeks is the recommended duration of use for symptoms related to minor venous circulatory disturbances without medical supervision.
4.2 Posology and method of administration Posology	AESGP	**Well-established use**: **Comments**: We suggest adding also 720 mg as single dose. The current wording ("single dose: 360 mg") indicate that	**Endorsed** The single dose of 720 mg has also been proposed by Germany:

SPECIFIC COMMENTS ON TEXT			
		single dose is 360 mg exclusively. **Proposed change (if any):** Single dose: 360mg ***to 720mg*** **Justification**: Single doses of 720 mg have been used in clinical studies [1]	1 x (1-2 caps) containing 360 mg extract.
4.2 Posology and method of administration Duration of use	AESGP	**<u>Traditional use</u>**: Soft extract (4-6:1; extraction solvent water; not quantified) which is marketed in Austria as Pedopur Tropfen, we propose to include the posology for internal use (not only cutaneous use). Product information can be found under: http://www.pharmazie.com/graphic/A/86/0-12486.pdf	**Not endorsed** There is not clear information on this product. The information as proposed by AESGP refers to a content of 1.2 mg of aesculin, and vitamin P complex. It is unclear if it is a combination product. Pedopur oral drops, contain in 1 ml, 73.5 mg of extract (corresponding 1.2 mg aesculin) in ethanolic solution (DER not declared) and is on the market since 1993 (Austria). AMIS Bfarm Data Base: (1974) PEDOPUR TROPFEN has been a solution for oral use. 20 ml contained 1.2 g of Extr. Fol. Vitis viniferae aquos (1:4.5) and 0.02 g of aesculin. (1978) 10 ml containing 0.6 g of grapevine leaf extract DER (5-7:1) (extraction solvent: water) and 0.01 g aesculin. (1999) Aesculin has been removed. DER of the grapevine leaf dry extract is (4-6:1; solvent water). Following the information provided by Hungary **Pedopur drops** consist of 81.4 mg Vitis viniferae rubrae folii extr. spissum(4-6:1), corresponding to 1.2 mg aescin /ml.

SPECIFIC COMMENTS ON TEXT			
4.2 Posology and method of administration Duration of use	AESGP	**<u>Well-established use:</u>** **Comments:** We suggest deleting "the recommended duration of use is 6 weeks" **Proposed change (if any):** ~~The recommended duration of use is 6 weeks~~ **Justification**: To mention 6 weeks is incorrect and misleading for the patient, as there is no basis for this statement. In clinical studies red vine leaf extracts were administered over 12 weeks. During that period a steady decrease of oedema was observed. The continuous progression of oedema reduction allows the conclusion to be drawn that further treatment would result in an even better effect**. Based on this and its good safety profile, no limit on the use of red vine leaf extract is necessary.**	**Partly endorsed** We accept to extend the recommended duration of use to 12 weeks. The medicinal product has a good safety profile, but it is not enough to recommend no limitation of use. The following information will be stated in the monograph: "the recommended duration of use is 12 weeks". Nevertheless clear information to the patient was already in the monograph: "Long term use is possible in consultation with a doctor".
4.2 Posology and method of administration Duration of use	AESGP	**<u>Well-established use:</u>** **Comments**: The onset of action as minimum of 4 weeks does not appropriately reflect the results of the clinical studies. Therefore we suggest changing "At least 4 weeks of treatment may be required before any beneficial effect is observed… " to "Two to three weeks of treatment may be required before beneficial effects are observed". **Proposed change (if any):** ~~At least 4 weeks of treatment may be required before any beneficial effect is observed~~ ***"Two to three weeks of treatment may be required before beneficial effects are observed".***	**Endorsed** "Two to three weeks of treatment may be required before beneficial effects are observed".

SPECIFIC COMMENTS ON TEXT			
		Justification: The therapeutic effect, measured objectively or felt subjectively, is present 2 to 3 weeks after start of treatment. This could be demonstrated in clinical studies.[2][3]	
4.4 Special warnings and precautions for use	AESGP	**<u>Traditional use:</u>** Indication a) **Comments**: We suggest a rewording of the warning in order to highlight the possible event of thrombophlebitis and better describe the symptoms. **Proposed change (if any):** ~~If there is inflammation of the skin, thrombophlebitis, or subcutaneous induration ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, a doctor should be consulted~~. We suggest to put a warning as to the possible acute event of thrombophlebitis: "If there appears, especially in one leg, a sudden swelling, reddening of the skin, feeling of tension, heat and pain, a doctor should be consulted. These symptoms may be due to thrombophlebitis, which is a sign of an aggravation of the underlying disease. This is not due to the treatment with red vine leaf extract, which may be continued." **Justification**: The warning statement for thrombophlebitis as now proposed gives a clear guidance to patients in which situation they have to consult a doctor. - Subcutaneous induration is often seen as a later sign of thrombophlebitis. It seems advisable to give a warning as to	**Not endorsed** The information on the monograph is more complete than the proposal. The deletion of the reference to subcutaneous induration ulcers, cardiac and renal insufficiency is not acceptable; these warnings should be kept for better information of patients, particularly, taking in to account the use of these medicinal products without medical supervision.

SPECIFIC COMMENTS ON TEXT			
		the initial symptoms, as proposed. - There is no risk in administering red vine leaf extract to patients suffering from venous ulcers as rather a beneficial effect than a negative influence can be expected from the medication. - Cardiac or renal insufficiency is not any risk factors known during treatment with red vine leaf extract. (Preclinical studies with red vine leaf flavonols and metaanalysis from epidemiological studies even show a beneficial effect of flavonols on the heart).	
4.4 Special warnings and precautions for use	AESGP	**Well-established use:** **Comments**: We suggest deleting "varicosis" in special warnings. **Proposed change (if any):** See next comment for complete rewording of the warning statement. **Justification:** Red vine leaf products are indicated for patients with varicosis. Varicosis is often present in CVI patients. Many patients included in the clinical studies with red vine leaf extract had moderate to severe varicosis and could be successfully treated. With the proposed OTC posology there is no need to consult a doctor prior to start treatment.	**Endorsed** In this case the evolution could be supervised by the doctor and the treatment of varicose veins is included in the therapeutic indication.
4.4 Special warnings and precautions for use	AESGP	**Well-established use:** **Comments**: We suggest a rewording of the warning in order to delete "subcutaneous induration, ulcers and cardiac or renal insufficiency" and to highlight the possible event of	**Not endorsed** The warning corresponds to an accepted standard statement which has been adopted in other monographs on products intended for similar treatments.

SPECIFIC COMMENTS ON TEXT			
		thrombophlebitis. **Proposed change (if any):** ~~If there is inflammation of the skin, thrombophlebitis, varicosis or subcutaneous induration ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, a doctor should be consulted~~. We suggest to put a warning as to the possible acute event of thrombophlebitis: ***"If there appears, especially in one leg, a sudden swelling, reddening of the skin, feeling of tension, heat and pain, a doctor should be consulted. These symptoms may be due to thrombophlebitis, which is a sign of an aggravation of the underlying disease. This is not due to the treatment with red vine leaf extract, which may be continued."*** **Justification:** The warning statement for thrombophlebitis as now proposed gives a clear guidance to patients in which situation they have to consult a doctor. - Subcutaneous induration is often seen as a later sign of thrombophlebitis. It seems advisable to give a warning as to the initial symptoms, as proposed. - There is no risk in administering red vine leaf extract to patients suffering from venous ulcers as rather a beneficial effect than a negative influence can be expected from the medication. - Cardiac or renal insufficiency is no known risk factors during	The advice about to consult the doctor in case of cardiac or renal insufficiency has to be given.

SPECIFIC COMMENTS ON TEXT			
		treatment with red vine leaf extract. (Preclinical studies with red vine leaf flavonols and metaanalysis from epidemiological studies even hint to a beneficial effect of flavonols on the heart).	
4.4 Special warnings and precautions for use	AESGP	**Well-established use:** **Comments**: We suggest changing the whole paragraph: "In the event of inadequate or unsatisfactory symptomatic response within 2 weeks, a doctor should be consulted as oedema may have alternative causes" to the below given sentence: **Proposed change:** ~~"In the event of inadequate or unsatisfactory symptomatic response within 2 weeks, a doctor should be consulted as oedema may have alternative causes. "~~ "If symptoms aggravate or if there is no improvement within 6 weeks a doctor should be consulted". **Justification:** The available clinical studies demonstrated the efficacy of a Vitis-vinifera containing product in reducing oedema and subjective symptoms of CVI grade I and grade II (according to Widmer classification). All objective efficacy parameters investigated (leg volume, calf circumference, cutaneous microcirculation, transcutaneous oxygen pressure) improved as early as after two to six weeks of therapy. A statistically significant and clinically relevant reduction of the leg oedema was measured after 6 weeks at the latest time point with further improvement until 12 weeks of treatment. Therefore it is justified to use Vitis vinifera for at least 6 weeks until a judgement can be made if or if not there is an improvement.	**Not Endorsed** This sentence is a standard wording reflected in other monographs with similar indications.

SPECIFIC COMMENTS ON TEXT			
4.6 Pregnancy and lactation	AESGP	**<u>Traditional use:</u>** **Comments**: We suggest adding "but may be considered in consultation with a doctor for topical applications". **Proposed change (if any):** Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended, ***but may be considered for topical application in consultation with a doctor*** **Justification:** During the longstanding use no harmful feto/neonatal effects during pregnancy nor lactation have been detected. Animal data do not indicate any effect on embryo-fetal development.	**Not Endorsed** In the absence of sufficient data, the use during pregnancy and lactation is not recommended. This is the standard sentence already used in many monographs, also in case of cutaneous use.
4.8. Undesirable effects	AESGP	**<u>Well-established use:</u>** **Comments:** We suggest deleting "headache and vertigo". **Proposed change (if any):** Nausea, gastrointestinal complaints, ~~headache~~ and ~~vertigo~~, may occur. **Justification:** Headache and vertigo have not been reported as side effects for red vine leaf products.	**Partly endorsed** Headache adverse effect reported in clinical studies [Schaefer, 2002]. Nausea, gastrointestinal complaints and headache, may occur.
5.1. Pharmacodynamic properties	AESGP	**<u>Well-established use</u>:** **Comments**: We suggest adding at the end of this section: "Red vine leaf extract improves the microvascular blood flow in	**Endorsed**

		CVI patients". **Proposed change (if any):** Red vine leaf extract improves the microvascular blood flow in CVI patients. **Justification:** The red vine leave extract excerts an antioedematous and antiinflammatory effect thus protecting the microcirculation. Clinically this could be proven in a study with CVI patients. [2]	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Title of monograph	Boehringer Ingelheim GmbH	**<u>Well-established use:</u>** **Comments:** We suggest deleting "Var. Tinctoria" in the title for the monograph. **Proposed change (if any):** COMMUNITY HERBAL MONOGRAPH ON ***VITIS VINIFERA* L., Folium** **Justification**: "*VITIS VINIFERA* L., Folium" is the correct botanical term. "Var. Tinctoria" was occasionally used in the literature to underline the use of dyer grapes. It is not a name for a variety.	**Endorsed** See the outcome on a similar comment by AESGP.
2. Qualitative and quantitative composition	Boehringer Ingelheim GmbH	**<u>Well-established use:</u>** **Comments:** We suggest deleting "Var. Tinctoria", folium **Proposed change (if any): *VITIS VINIFERA* L., Folium** **Justification**: "*VITIS VINIFERA* L., Folium" is the correct	**Endorsed**

		botanical term. "Var. Tinctoria" was occasionally used in the literature to underline the use of dyer grapes, but is not a variety.	
2. Qualitative and quantitative composition ii) Herbal preparation	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** To delete "quantified to flavonoids content 3-7%" **Proposed change (if any): -** **Justification:** A clinical efficacious and safe extract preparation is achieved by the selection of an appropriate quality of red vine leaves and a specific manufacturing procedure. The active ingredient, which is the herbal preparation, is characterised by the drug to extract ratio of 4-6:1 and the solvent used.	**Endorsed** See the outcome on a similar comment by AESGP.
4.1 Therapeutic indication	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** We suggest including "prevention" in the indication. **Proposed change (if any):** Herbal medicinal product for treatment **and prevention of symptoms** of chronic venous insufficiency, which … **Justification:** In clinical studies all objective efficacy parameters investigated (leg volume, calf circumference, cutaneous microcirculation, transcutaneous oxygen pressure) improved as early as after two to six weeks of therapy. A statistically significant and clinically relevant reduction of the leg oedema was measured after 6 weeks, with further improvement until 12 weeks of treatment. A re-occurrence of subjective symptoms or an increase in leg volume was not observed in patients treated	**Not endorsed** See the outcome on a similar comment by AESGP.

		with Antistax, whereas this was the case in those subjects treated with placebo. These observations in clinical studies support the claim that Antistax prevents the occurrence of symptoms of CVI when used as indicated. Kiesewetter H, Koscielny J, Kalus U, Vix JM, Peil H, Petrini O, Toor BSJ van, De Mey C. Efficacy of orally administered extract of red vine leaf AS 195 (*folia vitis viniferae*) in chronic venous insufficiency (stages I-II). A randomized, double-blind, placebo-controlled trial. Arzneim Forsch/Drug Res 2000; 50(2):109-117. Kalus U, Koscielny J, Grigorov A, Schaefer E, Peil H, Kiesewetter H. Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS 195: a randomised, double-blind, placebo-controlled, crossover study. Drugs Res Dev 2004;5(2):63-71 Monsieur R, Snick G van. Efficacy of the red vine leaf extract AS 195 in chronic venous insufficiency. Schweiz Rundsch Med Prax 2006;95:187-190 Further support for the prevention claim has been gained in *in vitro* studies of human venous endothelial cells. Certain release products from simultaneously activated blood platelets and polymorphonuclear granulocytes, which are released in venous hypostasis, lead to local edema, arteriolar constriction and venular thrombosis. Antistax has been shown to prevent the deleterious effect of the release products on the venular endothelial monolayers and is able to repair damage of the endothelium caused by these release products. Nees S, Reichenbach-Klinke E, Rampp F, Weiss DR. Venular	

		endothelial cells (VEC) as preferred targets in inflammatory edema: influence of thrombin (T), platelets (P), polymorphonuclear leukocytes (PMN), and flavonoid extracts of red vine leaves (ERVL). FASEB Cong, San Diego, 11-15 Apr 2003 (Poster). 2003 A clinical study with Antistax in CVI patients demonstrated its ability to enhance skin microcirculation and improve transcutaneous partial pressure of oxygen. These findings are assumed to prevent CVI deterioration. Kalus U, Koscielny J, Grigorov A, Schaefer E, Peil H, Kiesewetter H. Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS 195: a randomised, double-blind, placebo-controlled, crossover study. Drugs Res Dev 2004; 5(2):63-71.	
4.2 Posology and method of administration Posology	Boehringer Ingelheim GmbH	**<u>Well-established use:</u>** **Comments:** We suggest adding also 720 mg as single dose. The current wording ("single dose: 360 mg") indicate that single dose is 360 mg exclusively. **Proposed change (if any):** "Daily dose is 360 to720 mg. This should be taken in a single dose". **Justification**: Single doses of 720 mg have been used in clinical studies. Kiesewetter H, Koscielny J, Kalus U, Vix JM, Peil H, Petrini O, Toor BSJ van, De Mey C. Efficacy of orally administered extract of red vine leaf AS 195 (*folia vitis viniferae*) in chronic venous insufficiency (stages I-II). A randomized, double-blind, placebo-controlled trial. Arzneim Forsch/Drug Res 2000;	**Endorsed** See the outcome on a similar comment by AESGP.

		50(2):109-117.	
4.2 Posology and method of administration Duration of use	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** We suggest deleting "the recommended duration of use is 6 weeks". **Proposed change (if any):** ~~The recommended duration of use is 6 weeks~~ **Justification**: To mention 6 weeks is incorrect and misleading for the patient, as there is no basis for this statement. In clinical studies red vine leaf extracts were administered over 12 weeks. During that period a steady decrease of oedema was observed. The continuous progression of oedema reduction allows the conclusion to be drawn that further treatment would result in an even better effect**. Based on this and its good safety profile, no limit on the use of red vine leaf extract is necessary.**	**Endorsed** Duration of use extended to 12 weeks.
4.2 Posology and method of administration Duration of use	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** The onset of action as minimum of 4 weeks does not appropriately reflect the results of the clinical studies. Therefore we suggest changing "At least 4 weeks of treatment may be required before any beneficial effect is observed…" to "Two to three weeks of treatment may be required before beneficial effects are observed". **Proposed change (if any):** ~~At least 4 weeks of treatment may be required before any beneficial effect is observed~~ "Two to three weeks of treatment may be required before beneficial effects are observed".	**Endorsed** The onset of the action has been modified accordingly in the monograph. "Two to three weeks of treatment may be required before beneficial effects are observed".

		Justification: The therapeutic effect, measured objectively or felt subjectively, is present 2 to 3 weeks after start of treatment. This could be demonstrated in clinical studies. Kalus U, Koscielny J, Grigorov A, Schaefer E, Peil H, Kiesewetter H. Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS195. A randomised, double-blind, placebo-controlled, cross-over study. Drugs R&D 2004; 5(2):63-71. Monsieur R, Snick G van. Efficacy of the red vine leaf extract AS 195 in chronic venous insufficiency. Schweiz Rundsch Med Prax 2006; 95:187-190.	
4.4 Special warnings and precautions for use	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** We suggest deleting "varicosis" in special warnings**.** **Proposed change (if any):** If there is inflammation of the skin, thrombophlebitis, ~~varicosis~~ or subcutaneous induration*ulcers*, sudden swelling of one or both legs, cardiac or renal insufficiency*, a doctor should be consulted. [*: see next comment for a rewording of the warning statement] **Justification:** Red vine leaf products are indicated for patients with varicosis. Varicosis is often present in CVI patients. Many patients included in the clinical studies with red vine leaf extract had moderate to severe varicosis and could be successfully treated.	**Endorsed** In case of WEU the evolution could be supervised by the doctor and the treatment of varicose veins is recommended as part of the therapeutic indication.

		With the proposed OTC posology there is no need to consult a doctor prior to start treatment.	
4.4 Special warnings and precautions for use	Boehringer Ingelheim GmbH	**<u>Well-established use:</u>** **Comments:** We suggest a rewording of the warning in order to delete "subcutaneous induration, ulcers and cardiac or renal insufficiency" and to highlight the possible event of thrombophlebitis **Proposed change (if any):** ~~If there is inflammation of the skin, thrombophlebitis, varicosis or subcutaneous induration ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, a doctor should be consulted~~. We suggest to put a warning as to the possible acute event of thrombophlebitis: "If there appears, especially in one leg, a sudden swelling, reddening of the skin, feeling of tension, heat and pain, a doctor should be consulted. These symptoms may be due to thrombophlebitis, which is a sign of an aggravation of the underlying disease. This is not due to the treatment with red vine leaf extract, which may be continued." **Justification:** The warning statement for thrombophlebitis as now proposed gives a clear guidance to patients in which situation they have to consult a doctor. - Subcutaneous induration is often seen as a later sign of thrombophlebitis. It seems advisable to give a warning as to the initial symptoms, as proposed. - There is no risk in administering red vine leaf extract to patients suffering from venous ulcers as rather a beneficial	**Not endorsed** See the outcome on a similar comment by AESGP.

		effect than a negative influence can be expected from the medication. - Cardiac or renal insufficiency are no known risk factors during treatment with red vine leaf extract. (Preclinical studies with red vine leaf flavonols and metaanalysis from epidemiological studies even hint to a beneficial effect of flavonols on the heart).	
4.4 Special warnings and precautions for use	Boehringer Ingelheim GmbH	***Well-established use:*** **Comments:** We suggest changing the whole paragraph: "In the event of inadequate or unsatisfactory symptomatic response within 2 weeks, a doctor should be consulted as oedema may have alternative causes." to the below given sentence: ***Proposed change:*** ~~"In the event of inadequate or unsatisfactory symptomatic response within 2 weeks, a doctor should be consulted as oedema may have alternative causes. "~~ "If symptoms aggravate or if there is no improvement within 6 weeks a doctor should be consulted". **Justification:** The available clinical studies demonstrated the efficacy of Antistax in reducing oedema and subjective symptoms of CVI grade I and grade II (according to Widmer classification). All objective efficacy parameters investigated (leg volume, calf circumference, cutaneous microcirculation, transcutaneous oxygen pressure) improved as early as after two to six weeks of therapy. A statistically significant and clinically relevant reduction of the leg oedema was measured after 6 weeks at the latest timepoint with further improvement until 12 weeks of treatment. Therefore it is justified to use Antistax for at least 6	**Not endorsed** Not according to the terminology already accepted for other similar monographs.

		weeks until a judgement can be made if or if not there is an improvement.	
4.8. Undesirable effects	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** We suggest deleting "headache and vertigo". **Proposed change (if any):** Nausea, gastrointestinal complaints, ~~headache~~ and ~~vertigo~~, may occur. **Justification:** Headache and vertigo have not been reported as side effects for red vine leaf products.	**Partly endorsed** Headache is an adverse effect reported in clinical studies [Schaefer, 2002]. Nausea, gastrointestinal complaints and headache may occur.
5.1. Pharmacodynamic properties	Boehringer Ingelheim GmbH	**Well-established use:** **Comments:** We suggest adding at the end of this section: "Red vine leaf extract improves the microvascular blood flow in CVI patients". **Proposed change (if any):** Red vine leaf extract improves the microvascular blood flow in CVI patients. **Justification:** The red vine leave extract excerts an antioedematous and antiinflammatory effect thus protecting the microcirculation. Clinically this could be proven in a study with CVI patients. (Kalus U, Koscielny J, Grigorov A, Schaefer E, Peil H, Kiesewetter H. Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS195. A randomised, double-blind, placebo-controlled, cross-over study. Drugs R&D 2004; 5(2):63-71).	**Endorsed**

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	Diapharm Regulatory Services GmbH	**<u>Well-established use</u>** ii) Herbal preparation We suggest to delete the wording "quantified to flavonoids content 3-7%". There is no evidence that any product on the market really contains such a quantified extract. Sources: SPC´s of several products in France, Germany, UK, Austria, AMIS database (BfArM). In case HMPC would like to stay with this quantified extract under well-established use, we suggest to add under traditional use as follows (see next comment).	**Endorsed** See the outcome on a similar comment by AESGP.
2. Qualitative and quantitative composition	Diapharm	**<u>Traditional use</u>** We suggest to add: Dry extract of red vine leaves (4-6:1; extraction solvent water) Note: Unlike the dry extract described under Well-established use, this extract is not quantified to a certain content of flavonoids. There is evidence of 30 years traditional use in line with Directive 2004/24 EC for a product containing such a non-quantified aqueous extract. (Evidence is given in the Annex provided together with this comment to HMPC.)	**Not endorsed** This dry extract has been considered of well established use.
4.2. Posology	Diapharm	**<u>Traditional use</u>**	**Not endorsed**

		Posology Indication a) Oral use We suggest to re-uptake as it has been correctly stated in the first HMPC draft of Vitis vinifera monograph, published on 12 November 2009 (EMA/HMPC/16635/2009): • Soft extract (4-6:1; extraction solvent water) 6 ml up to 2 times a day (60 mg liquid extract/ml) There is no reason to delete this soft extract under oral use as has been done in Rev. 1. Such a product (Antistax Venentropfen) is on the German market since at least 1976, see AMIS database, BfArM.	The information on this product is not complete. The preparation is unstable and has to be stabilised with ethanol. *Antistax Venentropfen has WEU marketing authorisation in Germany.* This medicinal product was also proposed by Germany in the exchange of information between MS as: Soft extract (4-6:1), extraction solvent: water, for oral use in adults; at least marketed since 1976. Posology: 1 x daily 6 ml liquid if necessary 1 x daily 12 ml liquid 10 ml (= 11.013 g) liquid contain 0.6 g soft extract (60 mg soft extract/ml)
4.2. Posology	Diapharm	**Traditional use** Posology Indication a) Oral use We suggest to add: Dry extract of red vine leaves (4-6:1; extraction solvent water) 180 mg, 2 capsules a day. There is evidence of 30 years traditional use in line with Directive 2004/24 EC for a product containing such a non-quantified aqueous extract. (Evidence is given in the Annex provided together with this comment to HMPC.)	**Not endorsed** This product has been already included under WEU.
4.2. Duration of	Diapharm	**Traditional use**	**Not endorsed**

use		We suggest to add for the oral products, Indication a) under Traditional use the same wording as under Well-established use: "The recommended duration of use is 6 weeks. At least 4 weeks of treatment may be required before any beneficial effect is observed." There is no scientific reason to believe that traditional us products would act faster and more efficacious than well-established use medicines. Patients should be clearly informed that pharmacological and beneficial effects will take a certain time to occure (ca. 4 weeks). Of course this information should be followed by the wording: "If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted." as stated by the rapporteur. This combination of important information for the patient will prevent inadequate or unsatisfactory use.	The use of THMP is intended without medical supervision, after 2 weeks of treatment a doctor should be consulted. Nevertheless, duration of use of 4 weeks has been accepted by the MLWP. Added to the monograph: The recommended duration of use is 4 weeks.
5.3. Preclinical safety data	**Diapharm**	**<u>Traditional use</u>** The wording under <u>Well-established</u> use for the quantified aqueous dry extract 4-6:1 should apply as well to the following extracts for oral administration: • Soft extract (4-6:1; extraction solvent water) • Dry extract of red vine leaves (4-6:1; extraction solvent water) There is no scientific reason to make any difference between a quantified and a non-quantified extract; an extract not quantified to high amounts of flavonoids would even be less	**Not endorsed** Both preparations were not accepted for oral use in the TU monograph.

		harmful. And the soft extract is the direct precursor of the dry extract, only containing some more water.	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	Koop Phytopharmaka	Under **"well established medicinal use**" a specific "quantified extract" is mentioned, quantified to a content of flavonoids of 3-7% without mentioning the analytical method. As a Pharmacopoeia monograph does not yet exist at the moment, it is necessary to mention the analytical method together with the single constituents of the group of flavonoids that have to be calculated in the HMPC monograph. From our point of view it would be most useful to establish a Pharmacopoeia monograph for the quantified extract of red vine leaves. Under „**Traditional use"** ii) the terms should be chosen in accordance with the new monograph „herbal drug preparations (Ph. Eur. 6.8). ~~Comminuted~~ herbal substance = cut herbal substance Furthermore an extract with an DER native of **3:1** is not in accordance with the *"Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products".* The DER has not to be given as a fixed value, but always as a range.	**Endorsed** See the outcome on a similar comment by AESGP. **Not endorsed** We usually refer to comminuted herbal substance*.*

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
	ESCOP	ESCOP in principle welcomes the preparation of the above-mentioned Community herbal monograph which may provide harmonised assessment criteria for herbal medicinal products in Europe. As a general comment, the botanical name *Vitis vinifera* var. *tinctoria* seems unsatisfactory. Although the term "var. *tinctoria*" has appeared in a few publications [1,2] we are not convinced that a specific "var. *tinctoria*" has been botanically defined and it would be inappropriate to imply that pharmaceutical red vine leaf is obtained from only one variety (or cultivar) of *Vitis vinifera*. It is obtained from "teinturier" (or "dyer") varieties of *Vitis vinifera*, such as Alicante Bouschet and Gamay Fréaux, which are characterized by black grapes with red pulp and leaves that turn red in autumn [3-5]. **We propose the following definition for the herbal substance**: *Vitis vinifera* L., folium (red vine leaf) obtained from varieties known as "teinturiers" (dyers) and characterized by black grapes with red pulp. We only have few comments with regard the "well established use" and the "traditional use".	**Endorsed** See the outcome on a similar comment by AESGP.
2. Qualitative and quantitative composition	ESCOP	**<u>Well established use</u>** **Comment:** Quantification to flavonoids (3 to 7%) given in the definition of the herbal preparation is not specified in the literature. So,	**Endorsed** See the outcome on a similar comment by AESGP.

		there is no known published information to correlate pharmacological or clinical studies with a specified chemical composition. In consequence, it does not seem appropriate to include a specified chemical composition in the definition of the active substance. **Proposed change:** Read: "Dry extract ~~of red vine leaves~~ (4-6:1; extraction solvent water) ~~quantified to flavonoid content 3-7%~~. **<u>Traditional use</u>** **Proposed change:** Under ii) Herbal substance, "Soft extract (4-6:1; extraction solvent water)" should be replaced by "Dry extract (4-6:1; extraction solvent water)".	**Not endorsed** This product has been considered of WEU.
4.2. Posology and method of administration Traditional use	ESCOP	**Proposed change:** Read "Dry extract (4-6:1; extraction solvent water)".	**Not endorsed** This product has been considered of WEU.
5.3. Preclinical safety data	ESCOP	**Proposed change:** Read "Dry extract (4-6:1; extraction solvent water)".	**Not endorsed** **This product has been considered of WEU.**

Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	Indena	**Proposed change:** **<u>Traditional use:</u>** *Dry extract (3:1; water) and*	**TU** Although the company was contacted, complete information on the extract Dry extract (3:1; water) is

			not available.
		Soft extract (4-6:1; water): This is not correct, furthermore it's impossible, the drug/extract ratio of the soft extract must be lower than the dry one since a soft extract has a dry residue between 50 and 70%: If Dry extract is 4-6:1 => a Soft extract should be around 2-4:1.	**Endorsed** According to further information provided by Germany, DER for the soft extract has been corrected to (2.5-4:1).

[1] AMIS database is the official database of the German authority (BfArM) which includes all approved registrations (AMIS = Arzneimittel Information System = Drug Product Information System)