24 November 2015
EMA/HMPC/278488/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Serenoa repens* (W. Bartram) Small, fructus (EMA/HMPC/280079/2013

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Serenoa repens* (W. Bartram) Small, fructus as released for public consultation on 22 December 2014 until 15 March 2015.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	European Scientific Cooperative on Phytotherapy (ESCOP)
3	PIERRE FABRE MEDICAMENT, France (PFM)
4	Indena S.p.A., Italy
5	Kooperation Phytopharmaka (KOOP Phyto)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
ESCOP	ESCOP welcomes the draft Community herbal monograph on *Serenoa repens* (W. Bartram) Small, fructus, accompanied with companion documents (draft assessment report and draft reference list), prepared by the Committee on Herbal Medicinal Products (HMPC). We propose to take into consideration the following specific comments which relate to the inclusion of the ethanolic extracts (mentioned under "traditional use") into the "well-established use" column.	The question by ESCOP is taken into consideration. See below.
PFM	**Pierre Fabre Medicament (PFM) is the Marketing Authorisation Holder (MAH) of a hexanic extract of *Serenoa repens* containing medicinal product.** This medicinal product is registered with a Marketing Authorisation, with different trade names (PERMIXON, LIBEPROSTA, CAPISTAN, SEREPROSTA), in the following European member states : France, Bulgaria, Czech Republic, Greece, Italy, Luxembourg, Portugal, Spain. **On the basis on the comments provided, PFM will comment on the Well-established Use part of the monograph for the hexanic extract of *Serenoa repens* (DER 7-11:1).** MAH comments are presented in the table below. Bibliographic references are presented at the end of each section; Bibliographic data are presented in a separate file. Overall, the assessor proposes different status (WEU/TU) for each different extract (hexan, C02, ethanol), this proposal was approved by the HMPC. PFM fully agrees with this HMPC position on the basis of the following points :	**Partially endorsed** This information is taken into consideration. The commercial names of the registered medicines are important to verify the tested material in the studies underneath. However as a general policy commercial names will not be withheld in the assessment report or the monograph. **Endorsed** Notice is taken of the position of PFM as WEU use is concerned as well as of the possible differences between extracts. Additional information is added to the assessment report as justification under the following headings: 3.1.1.1.8. Comparative analysis of extracts 3.4. Overall conclusions on non-clinical data 6. Overall conclusions

Interested party	Comment and Rationale	Outcome
	-The majority of the publications used to prepare the EMA monograph came from hexanic extract of *Serenoa repens* (DER 7-11:1) registered by Pierre Fabre Medicament. - Each herbal medicinal product is defined by the name of the plant, the extraction solvent and the Drug Extract Ratio (EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1). - Each herbal medicinal product is also defined by this production process and specifications (EMA/HMPC/201116/2005 Rev. 2 section 3 – Directive 2004/24/EC article 1, 32. Herbal preparations). - Each herbal preparation is assessed individually as available information may vary from one preparation to another (EMA/HMPC/402684/2013). - To demonstrate comparability, an applicant would need to address the same extraction solvent with an identical strength and the same or comparable DER (R7 - EMA/HMPC/345132/2010 Rev.2). That is why, to support a non clinical / clinical part, a pharmaceutical bridge is not sufficient. The comparability between two extracts which a different extraction solvent may require bridging studies to address issues relating to non-clinical toxicology and clinical safety/efficacy Overview on the basis of bibliographic data : Hexanic extract of *Serenoa repens* is one of the most widely investigated and used products for the treatment of BPH. It is a very complex mixture of free (90%) and esterified (7%) long chain fatty acids. More than 90% of fatty acids in the extracts consist of oleic, lauric, myristic and palmitic acid. It also contains several phytosterols and various polyprenic compounds.	**Partially endorsed** The data provided by Habib and Wyllie (2004) are now included in the assessment report. Attention is paid to the important fraction of free fatty acids (FFA) and the differences between different extracts with regard to this fraction However it should be noticed that the results obtained by Habib & Wyllie (2004) do not confirm 90% of free fatty acids. The maximum the authors report is 80.7% (see below).

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	A plant extract can vary according to the method of extraction. On the market 3 types of extracts are marketed: ethanol extract, CO2 extract, and hexanic extract. The compositions of all extracts are different and we cannot extrapolate one's efficacy or safety to the other because it is not the same product.	**Endorsed** Additional information is added to the assessment report, taking into account the differences in chemical composition (Habib and Wyllie 2004) as well as in biological activity (Scaglione *et al.* 2008).
	Recommendations regarding the use of plant-derived medications for the treatment of LUTS associated with BPH state that every brand should be fully evaluated and considered separately (International Consultation on BPH, 2000). Disparity between a number of brands in terms of their stated and actual doses has been recently highlighted.	**Endorsed** See below.
	In 2004, a study was performed aiming at fully quantifying the variations in *Serenoa repens* extracts commercially available ("Not all brands are created equal: a comparison of selected components of different brands of *Serenoa repens* extract" by FK HABIB, ref 40). To this end, 14 brands of Serenoa repens were compared in terms of concentrations in free fatty acids, methyl and ethyl esters, long-chain esters and glycerides. The analysis revealed marked differences between brands despite their common origin.	**Endorsed** *Habib FK & Wyllie MG. Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract. Prostate Cancer and Prostatic Diseases 2004; 7: 195-200.* The authors specify the brands by their commercial names. Hexane (a.o. the one of PMF) and ethanolic extracts were tested. Details of the extraction procedure as well as the results of the analysis are included in the assessment report. It is seen that there are considerable differences between hexane and ethanolic extracts with regard to free fatty acids (FFA) and esterified fatty acids (methyl and ethyl esters). Also the glycerides revealed to be considerable different from one preparation to another.

Interested party	Comment and Rationale	Outcome
		Quote from the reference: *… The differences in content between the 14 brands analysed here is further evidence of the 5th International Consultation on BPH's recommendation that plant-derived pharmaceuticals be analysed separately and considered as distinct entities. The potential benefits of such medication, with symptom improvement equal to that of synthetically derived drugs and a much improved side-effect profile, when accompanied by a complete range of successful large-scale clinical trials, are manifold …*
	Moreover, metabolomic analysis performed by two authors (Booker et al, and De Combarieu et Al, ref 41-42) confirm the chemical differences of all the analysed products. Both conclude to difference in finger print of the hexanic and ethanolic and CO_2 extract. De Combarieu indicated that "these differences were not significant" but, without clinical comparison, chemical differences, even minor, must be taken into consideration. Booker determined that the pattern of fatty acids determined by gas chromatography for hexane extract is slightly different from to the one of the ethanol extract. It is to note that the active ingredients of *Serenoa repens* extract, even different, are not only fatty acids. Finally, Booker summarized his study with the capability of NMR to differentiate several types of extracts.	**Partially endorsed** The products investigated by Booker et al. (2014) are not characterised with regard to their commercial names. No conclusions can be drawn without detailed information on the type of the extracts. From the study by De Combarieux et al. (2015) no conclusions can be drawn with regard to the position of the PFM hexane extract of *Serenoa repens*. Ethanolic extracts revealed to cover a more distinct area when constructing 95% confidence clusters based upon 2-dimensional multivariate analysis.
	Very recently, in 2014, De Monte et al (ref 43) demonstrated chemical differences of different types of extract of S repens, using modern analytical methods. He concluded saying that "the variety of the extractive techniques and strategies makes one extract different from another in terms of bioactives composition".	**Not endorsed** This reference has a general character and no direct conclusions for the hexane PFM extract can be drawn.

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	As indicated by De Monte, the disparity between the extracts supports the difference in pharmacological activities of the extracts, as described 5 alpha reductase inhibition in Scaglione et al (ref 44). Indeed, the activity of different extracts of Serenoa repens were compared by Scaglione et al in a co- culture model of epithelial and fibroblast cells. The mean proportion of free fatty acids ranged from 80.7% to 40.7%, methyl and ethyl ester content ranged from 16.7% to 1.5% while long chain ester ranged from 1.36 to 0.7%. Furthermore, 2 different batches for each brand were evaluated. All extracts tested were able to inhibit both isoforms of 5a-reductase. However, the potency of the extracts appears to be very different. Therefore the clinical benefits derived from different extracts will vary depending on the solvent used for extraction of *Serenoa repens* and results from different clinical trials must be compared strictly according to the same validated extraction technique. **[40]. HABIB, WYLLIE** *Not all brands are created equal : a comparison of selected components of different brands of Serenoa repens extract* Prostate Cancer and Prostatic Diseases, 2004 **[41] Booker A, Suter A, Krnjic A, Strassel B, Zloh M, Said M, Heinrich M.** *A phytochemical comparison of saw palmetto products using gas chromatography and (1) H nuclear magnetic resonance spectroscopy metabolomic profiling*. J Pharm Pharmacol. 2014 Jun;66(6):811–22 **[42.] de Combarieu E, Martinelli EM, Pace R, Sardone N.** *Metabolomics study of Saw palmetto extracts based on (1)H NMR spectroscopy.* Fitoterapia. 2015 Feb 21;102C:56-60	**Endorsed** In the AR (3.1.1.1.8.) the studies of Scaglione et al. (2008)(2012) are included. There is a difference in biological activity between different extracts. However the authors apparently did only 1 analysis per batch of extract. This hampers statistical evaluation as no standard errors where determined. **Endorsed**

Interested party	Comment and Rationale	Outcome
	[43.] **De MONTE et Al BMC** Urology 2014 [44.] **Scaglione and al** European Review for Medical and Pharmacological Sciences 2012	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition ii) Herbal preparations	AESGP	**Comment:** We propose to add the ethanolic extract to the preparations with well-established use status. The available clinical data do support the fact that medicinal products containing ethanolic *Serenoa repens (*SR) extracts as active substance possess a recognised efficacy and acceptable level of safety. Ethanolic preparations are on the market at least since 1976; authorized in many European member states as well-established use products (Austria, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia, Sweden). Moreover, it has been demonstrated that ethanolic extracts and the hexane SR extract are pharmaceutically and pharmacologically equivalent. Details are provided in the proposed additions to the drafted assessment report (EMA/HMPC/137250/2013). **Proposed revision:** ii) Herbal preparations a) Soft extract (extraction solvent hexane: DER 7-11:1)	**Not endorsed** See general comments for details.

Section number and heading	Interested party	Comment and Rationale	Outcome
		b) Soft extract (DER 7.5-14.3:1), extraction solvent: ethanol 90 % to 96 % m/m	
2. Qualitative and quantitative composition ii) Herbal preparations	Indena S.p.A.	In the considered European Union herbal monograph, the herbal preparations of *Serenoa repens* are reported as “soft extracts”. We would like to point out that this can create unclarity due to the fact that in Ph. Eur. monograph 01/2014:2579 saw palmetto extracts are reported just as “extracts” and described as “oily liquids”. It seems not easy to define saw palmetto extracts considering the definitions reported in Ph. Eur. general monograph “Herbal Drug Extracts” (07/2015:0765), as demonstrated by the fact that for the herbal preparations contained in pharmaceutical products currently on the market (see paragraph 2.2 of the assessment report EMA/HMPC/137250/2013), many different terms were used (“dry extract”, “spissum extract”, “soft extract”, “lipophilic extract”, “extractum”, “lipido-sterolic extract”). In order to avoid unclarity, we suggest to delete the word “soft” from the European Union herbal monograph or to ask for an amendment to the Ph. Eur. monograph.	**Not endorsed** *Ph. Eur. 8.5 Herbal drug extracts* and *Ph.Eur. 8.5 Saw Palmetto Extract* are provided by the Company Standardisation of the name(s) of the extract(s) is needed. As ‘soft extracts’ are still described in the monograph about herbal drug extracts. For the time being it is proposed to keep ‘soft extract’ and to use this term throughout the AR and the Monograph. The comment will be transmitted to the respective Ph. Eur. working group for further elaboration.
2. Qualitative and quantitative composition ii) Herbal preparations	ESCOP	Comment: We welcome the decision of granting well-established medicinal use for some of the *Serenoa repens* preparations. However, from our point of view the ethanolic extracts should be attached to the “well-established use” category as well, because in our opinion the similarity of information on the extracts as demonstrated in the HMPC monograph leads to the conclusion that the ethanolic extracts have a “well-established use” like the hexane extract:	**Not endorsed.** See rationale below.

Section number and heading	Interested party	Comment and Rationale	Outcome
		1. Indication: The wording of the indications for “traditional use”and “well-established use” is very similar.	There is still a difference in approach between the indication for WEU and TU. The former is pointing to a medical diagnosis (BPH), whereas the latter focuses on symptoms. For this reason the therapeutic indications are not supporting a transfer of the ethanolic extracts from TU to WEU.
		2. Posology: The recommended daily intake in both preparations is the same, regardless of extraction solvent. This would not be the case if there was a difference in the constituents or potency. *In vitro* studies show only marginal differences in the inhibition concentration between the hexane and the ethanolic extract.	Scaglione *et al.* (2008) and Scaglione *et al*. (2012) report considerable differences in inhibition of two types of alpha-reductase activity between extracts.
		3. The section “Special warnings and precautions for use” and “Undesirable effects” contain the same wording. Similarity in risks of a medicinal product may suspect similarity in benefit.	Sections 4.8 has been revised and despite similarities in WEU and TU part has not anymore the same wording. The logical approach to conclude simply from a comparable risks to a comparable benefit cannot be followed and is not in line with the detailed separate assessment in the AR.
		4. For the reasons above and the argument of separating a medicinal product strictly from food supplements the ethanolic extract should be granted well-established use.	This reasoning is acknowledged, but not substantial enough, because the approach is too general, and not in line with the factual evidence.
		5. In a systematic review, Görne (2014) comes to the conclusion that ethanolic of *Serenoa repens* extracts are effective in the reduction of lower urinary tract complaints caused by BPH.	A part of the studies incorporated by Görne are already in the AR (Mattei 1990; Löbelenz 1992; Barry 2011). The study by Argirovic (2013) in which *Serenoa repens* and tamsulosin are compared and combined, is similar to the one of Glémain (2002) and is be incorporated in

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		6. Proposed change (if any): We therefore suggest to move preparation a) into the left column "well-established medicinal use"	the AR. Ethanolic extracts fulfil only the requirements for traditional use, until more clinical evidence is generated.
2. Qualitative and quantitative composition ii) Herbal preparations	KOOP	ii) Herbal preparations a) Soft extract (extraction solvent hexane: DER 7-11:1) Comment: We recommend to ad ethanolic extracts to the preparations with well-established use status. There are further controlled and open studies, contributing to the evidence of use of SR extracts, yet not listed in the list of references (Alliaev et al. 2013, Argirovic & Argirovic 2013, Breza et al. 2005, Sinescu et al. 2011). A review paper analyses the available data from controlled and open studies with ethanolic extracts (Goerne 2014). Various extracts of Serenoa repens, including ethanolic extracts, have demonstrated clinical efficacy particularly in the short-term treatment (up to 6 months) of lower urinary tract symptoms (LUTS) accompanied by a remarkable low number of side effects. Thus, the available evidence supports the well-established use of saw palmetto extracts in patients with LUTS in daily practice (Statement I, Kooperation Phytopharmaka 2015). The available clinical data do support the fact that medicinal products containing ethanolic Serenoa repens (SR) extracts as API possess a recognised efficacy and acceptable level of safety.	**Not endorsed** Open clinical trials are indeed contributing to the evidence of use of ethanolic extracts of *Serenoa repens* in different European countries. However they do not contribute to the WEU of the extracts. It should also be remarked that the study reported by Aliaev et al. (2002) is done with an hexane extract doses 320 mg twice daily, and not an ethanolic extract. Nevertheless the references have been incorporated in the assessment report.

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		It has been demonstrated that ethanolic extracts and the hexane SR extract are analytically and under pharmaceutical criteria equivalent. Details are provided in the enclosed statetment (Statement II, Kooperation Phytopharmaka 2015)..Both extract qualities – hexane as ethanolic SR - are described together in one single European monograph for Saw palmetto extracts since 2014 (European Pharmacopeia 8.0). Based on the comparable extraction force for lipohilic substances using hexane or ethanol 90-96% m/m, the characteristic substances are also on the same level: min 80% fatty acids, min 23% lauric acid, min 0.2% sterols, min. 0.1% beta-sitosterol. Editorial, we would like to point out that the range of the ethanolic SR extracts starts with 90% v / v ethanol instead of 90% m/m ethanol; e.g. in assessment report listed for Austria product no. 2, for Germany products no.11, 21, 30, 35, for Hungary product no.1, Editorial, we would like to point out that the DER for hexane extracts is broader as mentioned yet. The assessment report listed for Czech republic, product no.1a DER 6-12: 1. **Proposal for revised monograph:** ii) Herbal preparations a) Soft extract (extraction solvent hexane: DER 6-12:1) b) Soft extract (DER 7.5-14.3:1), extraction solvent: ethanol 90% v/v to 96% m/m	

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		It has been demonstrated that ethanolic extracts and the hexane SR extract are analytically and under pharmaceutical criteria equivalent. Details are provided in the enclosed statement (Statement II, Kooperation Phytopharmaka 2015). Both extract qualities – hexane as ethanolic SR - are described together in one single European monograph for Saw palmetto extracts since 2014 (European Pharmacopeia 8.0). Based on the comparable extraction force for lipophilic substances using hexane or ethanol 90-96% m/m, the characteristic substances are also on the same level: min 80% fatty acids, min 23% lauric acid, min 0.2% sterols, min. 0.1% beta-sitosterol. Editorial, we would like to point out that the range of the ethanolic SR extracts starts with 90% v / v ethanol instead of 90% m/m ethanol; e.g. in assesment report listed for Austria product no. 2, for Germany products no.11, 21, 30, 35, for Hungary product no.1, Editorial, we would like to point out that the DER for hexane extracts is broader as mentioned yet. The assesment report listed for Czech republik, product no.1: DER 6-12: 1. **Proposal for revised monograph:** ii) Herbal preparations a) Soft extract (extraction solvent hexane: DER 6-12:1) b) Soft extract (DER 7.5-14.3:1), extraction solvent: ethanol 90% v/v to 96% m/m	

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Section 2. Qualitative and quantitative composition Well-established use ii) Soft extract (extraction solvent hexane:DER 7-11:1)[3] [3] : containing 97% of fatty acids (free or esterified) and 3% of an unsaponifiable part	PFM	This information came from an old version of the SmPC of the hexanic extract of *Serenoa repens* containing products approved in France. This mention was deleted during the last update of Product Information submitted in March 2014 to the French Authorities (ANSM) and approved in October 2014. The Marketing authorisation holder agrees to add the specifications of fatty acids and unsaponifiable matter should be added in section 2 of the monograph, in the foot note page n°3. However the percentages of fatty acids (free or esterified) and of the unsaponifiable part proposed do not correspond to their average composition in the soft extract (extraction solvent hexane: DER 7-11:1). In this context, based on **historical data*** of a significant number of industrial batches (159 batches over 10 years of production), representative percentages are proposed to be mentioned as followed: *** With an average content of 92% of fatty acids (free or esterified) and 2% of an unsaponifiable part."** ***These data are available and submitted in a separated file.** **Please to be informed that this data should be considered and kept confidential.**	**Endorsed** The footnote in the monograph has been adapted according to the analytical data provided.
4. Clinical particulars **4.2. Posology and method of administra-**	KOOP	**Traditional use** 320 mg once daily Comment: The common posology of traditional marketed products since 1976 up today for medicinal products with ethanolic SR	**Endorsed** The product on the market since more than 30 years has a posology of 160 mg two times daily. There is enough more recent evidence for therapeutic equivalence between 320 mg once daily and 160 mg two times daily. This posology can be accepted.

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tion		extracts is 2-times 160 mg daily. Parallel an 320mg single dosage regimen was established. This dosage regimen should be added to the monograph. The use of this dosage is documented in several open studies under the conditions of daily practice (Alliaev et al. 2013, Argirovic & Argirovic 2013, Barry 2011, Breza et al. 2005, Sinescu et al. 2011; see also Goerne 2014 and Statement I, Kooperation Phytopharmaka 2015). **Proposal for revised monograph:** 320 mg once daily or 160 mg 2-times daily	
Section 4.3. Contraindications Well-established use Hepatic disease	PFM	**The monograph includes hepatic disease as a contraindication:** Preclinical animal data did not identify hexanic extract of *Serenoa repens* (DER 7-11:1) as hepatotoxic drug, nor the liver as a target organ. No specific studies have been performed specifically in patients suffering from hepatic disease. During more than 30 years of marketing, and while there was no warning in SmPCs regarding this population, pharmacovigilance did not evidence any specific signal or risk in patients suffering from hepatic disorders and treated with hexanic extract of *Serenoa repens*. **MAH proposes then not to add hepatic disease as contraindication in the *Serenoa repens* monograph** **Moreover, the product information of hexanic extract of**	**Endorsed** On one hand there is no evidence for enhanced risk in case of hepatic disease, on the other no clinical studies were performed with patients who suffered from an impaired hepatic function. It is acceptable to eliminate the contra-indication in order to put the monograph in line with the actual status of the SmPC content.

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		***Serenoa repens*, more particularly safety sections of the SmPC, was recently updated (without hepatic disease contraindication) by all Member States where the medicinal product is registered.** **In this context, the MAH proposes to present in the EMA monograph the same section as approved in the current EU SmPCs of *Serenoa repens* hexanic extract containing medicinal products** **(SmPCs can be made available through the MAH or directly through the competent authorities):** **"4.3. Contraindications** **Hypersensitivity to the active substance or to any of the excipients listed in section 6.1"**	
Section 4.8: Undesirable effects Well-established use Cases of acute hepatitis have been reported very rarely	PFM	**<u>The monograph includes cases of acute hepatitis as undesirable effect justified by two published cases and 24 cases from vigilyze database:</u>** **-Assessment of the two published cases of hepatitis: Lapi et al. 2010[1] and Jibrin et al. 2006[2]** The two cases are questionable: The event of the first case occurred in a context of overdose. The patient took three times the recommended dose in the proposed monograph. Moreover, the patient age can be considered as a risk factor[3] and even he denied alcohol abuse, an unknown moderate alcohol drink above 3 can be also considered as a second risk	**Endorsed** The most important reason to eliminate the cases of acute hepatitis from the monograph is the fact that both cases are not related to the hexane extract described. Jibrin et al. (2006) and Lapi et al. (2010) are examples of the better reporting, with detailed information about the patient, the possible causes of hepatic disease and the outcomes. In Jibrin et al. (2006) the circumstances of medication are described as follows: *… A 55-year-old reformed alcoholic, sober for greater than 15 years, presented with severe non-radiating epigastric pain associated with nausea and vomiting. His only significant comorbidity is BPH for which he intermittently took Saw*

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		factor[3].The patient abdominal ultrasound scan revealed a patchy steatosis. This imaging finding is a very common condition of fat accumulation in the liver with a prevalence of 20–30% in the adult population and 70% in diabetes patients[4]. The laboratory analysis excluded the presence of contaminants. However, even denied by the patient a punctual co-administration of another herbal product, food or drug cannot be definitely excluded. To be noted, the product taken by the patient was not the same extract than the MAH containing hexanic extract of *Serenoa repens* (HESr). The second case concerned a patient who was taking saw palmetto for four (4) years. Chronologically, hepatoxicity occurs in an interval of 5 to 90 days after the first administration of the suspected herb[3]. Moreover, the patient with a history of alcohol abuse was at risk because of his age[3] and even there was no alcohol abuse, an unknown moderate alcohol drink above 3 was a second risk factor[3]. As the first case, a punctual co-administration with another herbal product, food or drug was unknown. No laboratory analyses were performed to exclude definitely the presence of contaminants which may have caused this event. The author reported that there was no established cause of acute hepatitis apart from the fact that the patient was taking saw palmetto. Based on the provided information, and the unknown genetic predisposition, there is no strong evidence of a causal	*palmetto for about four years …* Neither preparation nor the posology are specified. There is a considerable time lapse between taking the medication and the first symptoms. Lapi *et al*. (2010) characterise the preparation as follows: *… he (= 58 year old male patient) had taken during the last week a commercially available preparation of S. repens to ease the symptoms of BHP, at the dose suggested by the producer of 3 capsules per day, equal to 900 mg of dried extract and 660 mg of berry powder …* Nothing is mentioned about the exact nature of the preparation. Moreover it seems like the patient might have taken an overdose. As there is also no relation with ethanolic extracts, hepatotoxicity is removed from the traditional use side as well. The assessment report is amended accordingly.

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		relationship between *Serenoa repens* and the two events. **-Assessment of the 24 cases of Vigilyze database :** When analysing cases entered in Vigilyze, at the same time as cases registered in a company database, one must take into account the high probability of duplicate cases, especially from those originated from the Competent Authority (and in France cases documented by French regional pharmacovigilance centers). **The overview presented from Vigilyze, only give a number of reported cases in the liver SOC: 24 reports of Liver and biliary system disorders: increase of hepatic enzymes, cholestatic hepatitis and jaundice**. These hepatic disorders were all grouped together without specifying the number of each ADR. Therefore, we have no information on the number of hepatitis cases. Taking into account the average age of patients treated for prostate hyperplasia, the causal relationship can only be suspected further to an analysis of the data included in the cases. Moreover, hepatitis is spontaneously reported by notificators while only biological symptoms are registered and no histological neither clinical signs confirm the diagnosis of hepatitis. Moreover, there is no available assessment on the causal relationship between the reported events and *Serenoa repens*. According to Teschke and Al[3] on a recent published article	

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		discussing the causality assessment of herbal hepatotoxicity, the causality confirmation was surprisingly rare for individual cases of suspected herbal hepatotoxicity, which often were published as narrative and anecdotal reports without valid and transparent data collection that require stringent efforts for causality attribution. A valid causality assessment of assumed herbal induced liver injury (HILI) cases is required for further case evaluations, otherwise speculations and fruitless discussions will emerge. The WHO method does not take into account relevant data like uncertainties in daily dose, temporal association, start, duration and end of herbal use, time to onset of ADR, and course of liver values after herbal discontinuation. Insufficiently considered or ignored are co-medication, pre-existing liver diseases, numerous alternative explanations, and exclusion of virus infections by hepatitis A, B, C and E, CMV, EBV, HSV, and VZV. Since only a few raw data are evaluated, case duplications and retracted cases remain undetected by the WHO method to a higher degree than by other methods. **Additional information from MAH sources:** The analysis of the database retrieved: -15 serious cases reported as hepatitis, 8 were assessed as doubtfully related to HESr, 3 not assessable and 3 were not related. Only one (1) published[5] case in a 35 year-old patient was considered as possibly related by the author. A punctual co-administration with another herbal product, food or drug was unknown and laboratory analyses to exclude definitely the presence of contaminants which may have caused the event	

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		were not performed. -One (1) case of Hepatic insufficiency assessed as not related to HESr as the alternative explanation was a Salmonellosis infection. -One (1) case of Liver injury assessed as doubtfully related to HESr. A concomitant medication Xatral (alfusozine) was also suspected. **Based on the analysis of the cases registered no definite case of documented hepatitis has been reported.** **Moreover, none of the authorized products in the EU countries include hepatitis as undesirable effect.** **Hepatitis should therefore be removed from the list of undesirable effets in the *Serenoa repens* monograph.** **LITTERATURE REFERENCES** **[1]LAPI F et al.** *Acute liver damage due to Serenoa repens: a case report* Br J Clin Pharmacol 2010; 69: 558-560. **[2]JIBRIN I, ERINLE A, SAIDI A, ALIYU Z** *Saw palmetto-induced pancreatitis* Southern Med J 2006; 99: 611-612. **[3]TESCHKE R, FRENZEL C, SCHULZE J, EICKHOFF A.** *Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods.* World J Gastroenterol. 2013 May 21; 19(19):2864-82. Review.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		[4]**DECARIE P-O, LEPANTO L, BILLIARD J-S, et al.** *Fatty liver deposition and sparing: a pictorial review.* Insights into Imaging 2011; 2 (5):533-538. [5]**G. BUONI O DEL BUONO, G. BRUSCO, P. CAVALLO, F. GABBA, M. GHELFI** *Serenoa repens induced acute cholestatic hepatitis* L. MagnaniItalian Journal of Medicine 2014; 8(s2)	
4.8. Undesirable effects Well-established use	PFM	**The monograph does not include Gamma-Glutamyltransferase increased, transaminases increased as undesirable effect.** **<u>Analysis of MAH the databases of the company owning the MA shows that:</u>** Twenty-nine (29) cases of hepatic enzyme increased. Only one (1) case was associated with a reported diagnosis of hepatitis. The majority of the cases were not serious. **Moreover, the product information of hexanic extract of *Serenoa repens*, more particularly section 4.8 of the SmPC, was recently updated and approved (with Gamma-Glutamyltransferase increased and transaminases increased as undesirable effect) in all Member States where the medicinal product is registered.** **Based on this analysis, the following biological symptoms are proposed for inclusion in the *Serenoa repens* monograph :**	**Endorsed** Increase of liver enzymes has been added under 'Undesirable effects'.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Transaminases increased: (uncommon) **Gamma-glutamyltransferase increased: (uncommon)**	
4.8. Undesirable effects Well-established use Intra-operative floppy iris syndrome can occur during cataract extraction. The frequency is not known.	PFM	**The monograph includes Intra-operative floppy iris syndrome can occur during cataract extraction as undesirable effect.** This undesirable effect was only mentioned in the German product information labelling which corresponds to an ethanolic extract of *Serenoa repens*. Intra-operative floppy iris syndrome (IFIS) is a relatively rare syndrome, reported in approximately 2% of cataract surgery cases. It has been observed during cataract surgery in some patients currently or previously treated with the alfa 1 adrenoceptor (AR) antagonist tamsulosin. Although the precise mechanism by which tamsulosin can lead to IFIS remains unknown. Chang et al.[6] suggest that tamsulosin has a high affinity and specificity for the alfa 1A adrenergic receptor, which is thought to be the dominant receptor in the iris. While often associated with the use of systemic α-blockers, particularly tamsulosin, it can be observed with other systemic α-blockers and related to diseases that influence dilator muscle tone[7]. Two (2) cases of intra-operative floppy iris syndrome (IFIS) were reported in 2 patients taking saw palmetto for BPH who had cataract surgery[8]. The first was a 49-year-old man who had been taking saw palmetto for approximately 2 years . During cataract surgery, the patient demonstrated moderate **Intra-operative floppy iris syndrome (IFIS)**. There were	**Endorsed** Intra-operative floppy iris syndrome is now eliminated from the WEU part of the monograph as causal relationship with *Serenoa repens* is not established.

Section number and heading	Interested party	Comment and Rationale	Outcome
		no surgical complications, and the outcome was good. The second patient was a 74-year-old man who had taken saw palmetto for approximately 5 years. During cataract surgery and experienced moderate IFIS. As a result, there was segmental loss of iris pigment epithelium, visible by transillumination only. Despite this, the surgical outcome was excellent. These two patients were taking saw palmetto for many years, but potential risk factors were not identified Based on the known pharmacologic mechanism for this adverse drug reaction (ADR) linked to the systemic activity on Alfa-blockers, there is no evidence to link *Serenoa repens* (having no systemic alpha blocker activity) and this disorder. In the two reported cases there was no search for alternative etiologies mentionned (patients seems to have been only questioned on hypertrophy benign of prostate (HBP) drugs intake) **No cases of Intra-operative floppy iris syndrome (IFIS) have been reported during the extensive post marketing period (post marketing history of 34 years).** **Moreover, the product information of hexanic extract of *Serenoa repens*, more particularly section 4.8 of the SmPC, was recently updated and approved (without this ADR) in all Member States where the medicinal product is registered.** **Concerned MAH proposes to remove Intra-operative floppy iris syndrome from the list of undesirable effects**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		in the *Serenoa repens* monograph. **LITTERATURE REFERENCES** **[6]CHANG DF, BRAGA-MELE R, MAMALIS N, MASKET S, MILLER KM, NICHAMIN LD, PACKARD RB, PACKER M;** *ASCRS Cataract Clinical Committee. ASCRS White Paper: clinical review of intraoperative floppy-iris syndrome.* J Cataract Refract Surg. 2008 Dec; 34 (12):2153-62. **[7]FLACH, A. J. (2009).** *Intraoperative Floppy Iris Syndrome: Pathophysiology, Prevention, and Treatment.* Transactions of the American Ophthalmological Society, 107, 234–239 **[8]YEU E, GROSTERN R.** *Saw palmetto and intraoperative floppy-iris syndrome.* J Cataract Refract Surg. 2007 May;33(5):927-8	
Section 4.8: Undesirable effects Well-established use **Frequencies**	PFM	**The EMA HMPC template for a European Union herbal monograph (EMA/HMPC/107436/2005 Rev. 7) stipulates that "*when available, frequencies of cited adverse reactions should be stated according to the convention laid down in the SmPC guideline*".** **In order to reflect the content of the current SmPCs of *Serenoa repens* hexanic extract containing medicinal products authorised in the EU, MAH proposes to include the frequencies of undesirable effects as recommended by the SmPC guideline in the EU monograph.**	**Endorsed** Changes have been made in the WEU part of the monograph and the assessment report.

Section number and heading	Interested party	Comment and Rationale	Outcome
		- Frequency of Gastro-intestinal disorders (nausea, abdominal pain) was reported as not known in the monograph. **MAH proposes to maintain the frequency for nausea and abdominal pain as follows in the *Serenoa repens* monograph:** **-Abdominal pain (≥ 1/100 to < 1/10) : Frequency common** **-Nausea (≥ 1/1000 to < 1/100) : Frequency uncommon** -Frequency of Reversible gynecomastia cases was reported as not known in the monograph**.** **MAH proposes to maintain the frequency of Reversible gynecomastia as (≥ 1/1000 to < 1/100) frequency uncommon in the *Serenoa repens* monograph.** -Frequency of Skin rash and oedema was reported as rare in the monograph. **MAH proposes to maintain the frequency of Reddening of the skin (rash) as (≥ 1/1000 to < 1/100) frequency uncommon and oedema as frequency unknown in the *Serenoa repens* monograph.**	
Section 4.8: Undesirable effects Well-established use	PFM	Many cases of headache were reported to the concerned company and in the literature[9*10] **The product information of hexanic extract of *Serenoa repens*, more particularly section 4.8 of the SmPC, was recently updated and approved (with Headache as undesirable effect) in all Member States where the**	**Endorsed** The information is taken to the WEU part of the monograph and an explanatory paragraph is inserted in the assessment report.

Section number and heading	Interested party	Comment and Rationale	Outcome
		medicinal product is registered. **Concerned MAH proposes to maintain headache as undesirable effect in the *Serenoa repens* monograph :** **Headache (≥ 1/100 to < 1/10) : Frequency common** **LITTERATURE REFERENCES** **[9]AVINS AL, LEE JY, MEYERS CM, BARRY MJ** *CAMUS Study Group. Safety and toxicity of saw palmetto in the CAMUS trial.* J Urol. 2013 Apr;189 (4):1415-20. **[10]AGBABIAKA TB, PITTLER MH, WIDER B, ERNST E.** *Serenoa repens (saw palmetto): a systematic review of adverse events* Drug Safety 2009; 32(8): 637-647. **Finally and on the basis of the previous comments on section 4.8, the concerned MAH proposes to present in the EMA monograph of *Serenoa repens* the same section as approved in the current European SmPCs (SmPCs available through the MAH or directly through the competent authorities):** **"4.8. Undesirable effects** **The undesirable effects classified by organs or systems (according to MedDRA) are listed below as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000),**	**Partially endorsed**. The assessment report already comments upon the limitations of the reporting. Increase of hepatic enzymes is mentioned in the monograph (see previous comments).

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>very rare (< 1/10,000) and frequency unknown (it cannot be estimated on the basis of the data available).

No adverse drug reactions were “very rare”, “rare” or “very common” in frequency and therefore these columns were not presented in the table.
<table>
<tr><th>Common >=1% to 10%</th><th>Uncommon >=0.1% to 1%</th><th>Unknown frequency</th></tr>
<tr><td colspan="3">08- Nervous system disorders</td></tr>
<tr><td>Headaches</td><td></td><td></td></tr>
<tr><td colspan="3">14- Gastrointestinal disorders</td></tr>
<tr><td>Abdominal pain</td><td>Nausea</td><td></td></tr>
<tr><td colspan="3">15- Hepatobiliary disorders</td></tr>
<tr><td></td><td>Increase in gamma-glutamyltransferases</td><td></td></tr>
<tr><td></td><td>Increase in transaminases</td><td></td></tr>
<tr><td colspan="3">16- Disorders of the skin and subcutaneous tissue</td></tr>
<tr><td></td><td>Rash</td><td>Oedema</td></tr>
<tr><td colspan="3">20- Disorders of the reproductive organs and breasts</td></tr>
<tr><td></td><td>Gynecomastia</td><td></td></tr>
</table></td><td></td></tr>
<tr><td>Section 4.9
Well-established use</td><td>PFM</td><td>A total of 11 spontaneous case reports of overdose in male patients aged from 61 to 91 years old, of 2 or 3 times the recommended dosage with a maximum overdose at 960 mg per day, three (3) cases were serious, two (2) patients with underlying cardiovascular diseases and one (1) intentional overdose of multiple drugs (Seresta, Neurontin, doxazosine) associated with coma. The patient had fully recovered. In four serious cases, unspecified gastrointestinal disorders were</td><td>Partially endorsed
Referred information is now included in the assessment report, but not in the monograph, because there is too few factual evidence that cannot be transformed into a clear instruction.</td></tr>
</table>

Section number and heading	Interested party	Comment and Rationale	Outcome
		associated. Three relevant articles[1*11*12] with other *Serenoa repens* extracts and reported ADRs after high doses of *Serenoa repens* intake were identified. These cases concerned patients who took *Serenoa repens* as herbal supplements without supervision and at a dose superior to the recommended one. Moreover, it was not the same extract than concerned MAH hexanic extract of *Serenoa repens* (HESr); and in one publication, it was associated with many other herbal extracts. **Taking into account the safety analysis of overdose, concerned MAH proposes adding the following sentence in the section 4.9. of the *Serenoa repens* monograph :** **"4.9 Overdose** **In the event of overdose, the patient may show transient gastrointestinal disorders."** **Moreover, the product information of this product, more particularly safety sections of the SmPC, was recently updated by all Member States where the medicinal product is registered (modification approved or process on-going).** **In this context, the MAH proposes to present in the EMA monograph of *Serenoa repens* the same section as approved in the current SmPCs (SmPCs available through the concerned MAH or directly through the competent authorities).**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		LITTERATURE REFERENCES **[1]LAPI F et al.** Acute liver damage due to *Serenoa repens*: a case report. Br J Clin Pharmacol 2010; 69: 558-560. **[11]VILLANUEVA S, GONZÁLEZ J.** Coagulopathy induced by saw palmetto: a case report. Bol Asoc Med P R. 2009 Jul-Sep;101(3):48-50. **[12]WEINROBE MC, MONTGOMERY B.** Acquired bleeding diathesis in a patient taking PC-SPES. N Engl J Med. 2001 Oct 18;345(16):1213-4.	
Section 5. Pharmacological properties **5.1. Pharmacodynamic properties** Well-established use Pharmacotherapeutic group: benign prostatic hyperplasia. Proposed ATC code:	PFM	According to the conclusion of EMA assessment report on *Serenoa repens* (W. Bartram) Small, fructus, (EMA/HMPC/137250/2013), several experimental findings support the use of *Serenoa repens* in BPH. From in vitro experiments the following properties were identified: (1) inhibition of 5-alpha-reductase; (2) influence on androgen-receptor binding; (3) inhibition of alpha-receptor binding; (4) inhibition of eicosanoid synthesis; (5) spasmolytic effects and (6) anti-inflammatory effects. The activity can differ from one extract to another, dependent upon the composition of the extracts. Anti-androgenic and anti-inflammatory effects were confirmed in *in vivo* experiments. The pharmacological effects of hexanic extract of *Serenoa repens* (HESr) have been studied for several decades because they are widely used. Most of the studies have been conducted in the 80's.	**Not endorsed** As the clinical relevance of the preclinical data in the symptomatic treatment of benign prostatic hyperplasia is not known, it has been decided not to include any mechanism of action.

Section number and heading	Interested party	Comment and Rationale	Outcome
G04CX02.		All these *in vitro* and *in vivo* studies using validated and currently approved models are concordant to demonstrate that in addition to a well-documented anti-androgenic activity through the inhibition of 5α-reductase types I and II and the reduction of dihydrotestosterone (DHT) concentration in the prostate tissue, *Serenoa repens* extracts have also anti-proliferative and anti-inflammatory effects and are able to bind to autonomic receptors in the lower urinary tract. **<u>Anti-androgenic effects</u>** *In vitro* studies conducted on different models were concordant to show that *Serenoa repens* extracts*:* - Inhibited the conversion of testosterone into DHT in cultured human foreskin fibroblasts. In addition, it was shown to strongly inhibit the formation of 5α-androstane-3α, 17β-diol up to 90%, thus inhibiting the 5α-reductase and the 3-ketosteroid reductase [[33]SULTAN Ch, 1984]. In primary cultures of stroma and epithelial cells derived from BPH and prostate cancer tissues, HESr inhibited the formation of all testosterone metabolites studied while 5α- reductase inhibitors (4-MA and finasteride) inhibited DHT formation [[16]DELOS S, 1995]; - Markedly inhibited both iso-enzymes of 5α-reductases while finasteride and turosteride were shown to be selective inhibitors of the type II isoform [[22]IEHLE C, 1995]; - Displayed non-competitive inhibition of the type I isozyme and uncompetitive inhibition of the type II	

Section number and heading	Interested party	Comment and Rationale	Outcome
		isozyme in DU 145 cell line and in a baculovirus-directed insect cell system (Sf9 insect cells expressing 5α-reductases) [[22]IEHLE C, 1995; [16]DELOS S, 1994]. The inhibitory activity of HESr on 5α-reductase types I and II was shown to be prostate-specific, by an effect on the nuclear membrane, thus disrupting the micro-environment of the 5α-reductase enzyme and thereby inhibiting its activity [[14]BAYNE CW, 2000]. The inhibition of 5α-reductase types I and II activity was only observed with some components of *Serenoa repens* extracts such as free fatty acids. In addition, a specificity of the fatty acids in 5 α-reductase type I or type II inhibition has been found. The dual inhibitory activity of HESr on 5α-reductases can be attributed to its high content in free fatty acids [[30]RAYNAUD JP, 2002]; - Did not influence the secretion of PSA [[13]BAYNE CW, 1999; [20]HABIB FK, 2005]. - Competitively inhibited the binding to the cytosolic androgenic receptor of the rat prostate [[15]CARILLA E, 1984, [18]EL-SHEIKH M., 1988]. - Could affect 5 α-reductase isoforms with different extents. Recently, [[31]SCAGLIONE F, 2008] showed the superiority of HESr compared to other extracts of *Serenoa repens* on the 5 α-reductase activity inhibition on co-cultured epithelial and fibroblast cells by a 5 α-reductase activity assay.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Anti-androgenic effects were confirmed in, *in vivo* studies, conducted on castrated mice and rats. *Serenoa repens* extracts: - Significantly inhibited the prostate enlargement due to exogenous androgen stimulation (testosterone) in mice and rats [[32]STENGER A, 1982] and due to oestradiol and testosterone treatment in rats [[27]PAUBERT-BRAQUET M, 1996]. - Significantly counteracted in a consistent manner the increase in prostate weight, seminal vesicles, preputial glands following endogenous androgen stimulation (gonadostimulin) in rats [[32]STENGER A, 1982]. The anti-androgen effect of *Serenoa repens* extracts was also assessed in comparison to a well known 5-α reductase inhibitor (finasteride) on an androgen-induced prostatic enlargement in rats [[34]TALPUR N, 2003]. Both treatments decreased the size of the prostate to roughly the same size as in the non-castrated rats, a size that was significantly smaller than castrated rats treated with testosterone under the same conditions. No oestrogen or gestagen properties in mice were observed with *Serenoa repens* extracts and no effect on pituitary system in rats was found with these extracts whatever the method used. **Anti-proliferative effects** *In vitro* studies conducted on different models were concordant to show the anti-proliferative effects of *Serenoa repens*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		extracts with or without apoptotic effects. *Serenoa repens* extracts: - Inhibited the prolactin-induced growth by acting on several steps of prolactin receptor signal transduction in transfected Chinese hamster ovary cells [36VACHER P, 1995]. - Affected the proliferative response of prostate cells (from biopsies of human prostate) to ß- FGF more than their basal proliferation [24PAUBERT-BRAQUET M, 1998] and the response to IGF in prostate epithelial cell line P69 [39WADSWORTH TL, 2004]. - Induced apoptosis in some models in addition to an anti-proliferative effect. [28PETRANGELI E, 2009] showed induction of apoptosis and inhibition of the proliferation by *Serenoa repens extract* in an androgen-independent PC3 cell line. Complex changes in cell membrane organization and fluidity of prostate cancer cells that have progressed to hormone-independent status were observed after treatment with *Serenoa repens* extracts [28PETRANGELI E, 2009]. However, other results failed to evidence the induction of apoptosis by these extracts in prostatic cancer cell lines but confirmed its effects on cell growth [21HILL B, 2004]. These anti-proliferative effects of *Serenoa repens* extracts were confirmed in, *in vivo* models of rat prostate hyperplasia induced by hyperprolactinemia in comparison with finasteride (inhibitor of 5- alpha reductase) [37VAN COPPENOLLE F, 2000].	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Anti-inflammatory effects *In vitro* studies were concordant to show the effects of *Serenoa repens* extracts on inflammation. *Serenoa repens* extracts: - Inhibited in a dose-dependent manner the activity of phospholipase extracted from snake venom and from pig pancreas. The extract induced a dose-dependent inhibition of membrane phospholipid hydrolysis in rat prostatic cell cultures (essentially fibroblasts) and in primary human prostate tissue cultures (fibroblasts and epithelial cells) previously incubated with 14C-arachidonic acid with a decrease in the release of arachidonic acid and of the concentration of prostaglandin E2 in the medium [29RAGAB A, 1988]. - Significantly inhibited the production of 5-lipoxygenase metabolites (5-HETE, 20-COOH LTB4 and 20-OH LTB4) at concentrations as low as 5 µg/mL in human polymorphonuclear neutrophiles stimulated with a calcium ionophore [26PAUBERT-BRAQUET M, 1997]. - Stimulated macrophage phagocytosis and NK cell synthesis of interferon-gamma [19GROOM, 2007]. - Impeded key steps of monocyte and T cell attraction and adherence by inhibiting cytokine MCP-1/CCL2 and VCAM-1 expression by human prostate and vascular cells in an inflammatory environment [23LATIL A, 2012].	

Section number and heading	Interested party	Comment and Rationale	Outcome
		These *in vitro* results on the anti-inflammatory effects of *Serenoa repens* extracts were confirmed by *in vivo* studies demonstrating their inhibitory effects on: - Different models of oedema (generalized dextran oedema in rat and tail oedema in mouse). No effect was observed on carrageenan induced oedema in rat. - Capillary permeability using wheals created by injections of various inflammatory mediators including histamine and the 2 histamine releasing agents (compound 48/80, dextran) in rat. No effect was found on wheals induced by serotonin and bradikynin. - Passive IgG-dependent cutaneous anaphylaxis in rats adrenalectomized or not. - UV induced erythema in guinea pig. These results demonstrated the anti inflammatory effects of *Serenoa repens* extracts mainly *via* the histamine pathway as characterized by an oedema reduction effect [[35]TARAYRE JP, 1983]. In addition, *Serenoa repens* extracts significantly reduced mast cell accumulation and provoked epithelium atrophy within the central area of the rat ventral prostate. These phenomena may participate in the clinical activity of the drug [[24]MITROPOULOS D, 2002]. The BPH inflammatory hypothesis was also tested in humans in a pilot study [[38]VELA NAVARRETE 2003]. This study showed a significant reduction of some inflammatory parameters in	

Section number and heading	Interested party	Comment and Rationale	Outcome
		prostatic tissues of patients treated with hexanic extract of *Serenoa repens.* **<u>Conclusion:</u>** **In conclusion, concerned MAH proposes to add the following information in the section 5.1. Pharmacodynamic properties of the European Union herbal monograph on *Serenoa repens* (W. Bartram) Small, fructus :** **"The hexanic extract of *Serenoa repens* has anti-inflammatory, antiandrogenic and antiproliferative properties that act on benign prostatic hyperplasia.** **Anti-inflammatory properties are expressed by an inhibition** **- of phospholipase A2 (reduction of arachidonic acid synthesis),** **- of cyclooxygenase (reduction of prostaglandins)** **- of lipoxygenase (reduction of leukotrienes.)** **This action on the arachidonic acid cascade and the effect observed on some inflammatory cytokines explain the anti-inflammatory activity found both in animal models and benign prostatic hyperplasia.** **Antiandrogenic properties are mainly due to an inhibition of the 5 alpha reductases responsible for transforming testosterone into its active metabolite dihydrotestosterone (DHT). This antiandrogenic activity**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		is also increased by a reduction of the prolactin-dependent penetration of testosterone into the cell, an inhibition of oestrogen-dependent androgen receptor formation and finally an inhibition of DHT binding to its receptors. **This activity has been confirmed in an experimental rat model of benign prostatic hyperplasia.** **Antiproliferative properties are explained by the fact that the hexanic extract of *Serenoa repens* slows the proliferation of the glandular epithelium (estimated using the tritium-labelled thymidine index) induced by growth factors in human prostate organotypic cells.** **It reduces protein synthesis in prostate cell cultures, stimulated by a combination of testosterone and prolactin, the latter of which regulates prostatic volume."** **LITTERATURE REFERENCES** **[13]BAYNE CW, DONNELLY F., ROSS M. et al.** *Serenoa repens (Permixon®): A 5α-Reductase Types I and II Inhibitor-New Evidence in a coculture model of BPH* The Prostate, 1999, 40:232-241 **[14]BAYNE CW, ROSS M., DONNELLY F. et al.** *The selectivity and specificity of the actions of the lipido-sterolic extract of serenoa repens (Permixon®) on the prostate* The Journal of Urology, 2000, 164, 876–881.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		[15]**CARILLA E, BRILEY M, FAURAN F et al.** *Binding of Permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate* J.Steroid Biochem., 1984, 20(1) 521-523 [16]**DELOS S, CARSOL JL, GHAZAROSSIAN E et al.** *Testosterone Metabolism in Primary Cultures of Human Prostate Epithelial Cells and Fibroblasts* J.Steroid Biochem. Molec. Biol., 1995, 55(3/4) 375-383 [17]**DELOS S, IELHE C, MARTIN PM et al.** *Inhibition of the Activity of 'Basic' 5α-Reductase (Type 1) Detected in DU 145 Cells and Expressed in Insect Cells* J.Steroid Biochem. Molec. Biol., 1994, 48(4) 347-352 [18]**EL-SHEIKH M., DAKKAK M.R. and SADDIQUE A.** *The effect of permixon and androgen receptors.* Acta Obstet Gynecol Scand., 1988, 67, 397-399. [19]**GROOM SN, JOHNS T, OLDFIELD PR,** *The potency of immunomodulatory herbs may be primarily dependent upon macrophage activation.* J Med Food 2007, 10 (1), 73-79 [20]**HABIB FK, ROSS M, HO CK et al.** *Serenoa repens (Permixon) inhibits the 5 alpha-reductase activity of human prostate cancer cell lines without interfering*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		with PSA expression. Int J Cancer. 2005, 114(2), 190-194. **[21]HILL B, and KYPRIANOU N.** *Effect of Permixon on Human Prostate Cell Growth:Lack of Apoptotic Action* The Prostate, 2004, 61:73-80 **[22]IEHLE C, DELOS S, GUIROU O. et al.** *Human Prostatic Steroid 5α-Reductase Isoforms-A comparative Study of Selective Inhibitors* J.Steroid Biochem. Molec. Biol., 1995, 54(5/6) 273-279 **[23]LATIL A, LIBON C, TEMPLIER M, JUNQUERO D, LANTOINE-ADAM F, NGUYEN T.** *Hexanic lipidosterolic extract of serenoa repens inhibits the expression of two key inflammatory mediators, MCP-1/CCL2 and VCAM-1, in vitro.* BJU INTERNATIONAL, 2012, doi : 10.1111/j.1464-410X.2012.11144.x **[24]MITROPOULOS D, KYROUDI A, ZERVAS A, PAPADOUKAKIS S, GIANNOPOULOS A, KITTAS C, KARAYANNACOS P,** *In vivo effect of the lipido-sterolic extract of Serenoa repens (Permixon) on mast cell accumulation and glandular epithelium trophism in the rat prostate.* World J Urol, 2002, 19: 457–461	

Section number and heading	Interested party	Comment and Rationale	Outcome
		[25]PAUBERT-BRAQUET M, COUSSE H, RAYNAUD JP et al. *Effect of the Lipidosterolic Extract of Serenoa Repens (Permixon®) and its major Components on Basic Fibroblast Growth Factor-Induced Proliferation of Cultures of Human Prostate Biopsies* Eur. Urol., 1998, 33:340-347 **[26]PAUBERT-BRAQUET M, MENCIA HUERTA JM, COUSSE H et al.** *Effect of the lipidic lipidosterolic extract of Serenoa repens (Permixon®) on the ionophore A23187-stimulated production of leukotriene B4 (LTB4) from human polymorphonuclear neutrophilis* Prostaglandins, Leukotrienes and Essential Fatty Acids, 1997, 57(3), 299-304 **[27]PAUBERT-BRAQUET M, RICHARDSON FO, SERVENT-SAEZ NGORDON WC,** **MONGE MC, BAZAN NG, AUTHIE D and BRAQUET P.** *Effect of Serenoa repens extract (Permixon®) on estradiol/testosterone-induced experimental prostate enlargement in the rat* Pharmacological Research, 1996, 34, ¾, 171-179. **[28]PETRANGELI E, LENTI L, BUCHETTI B,** *Lipido-sterolic extract of Serenoa repens (LSESr, Permixon®) treatment affects human prostate cancer cell membrane organization* Journal of Cellular Physiology 2009, 219, Issue 1, 69–76.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		[29]**RAGAB A, RAGAB-THOMAS JMF, DELHON A et al.** *Effects of Permixon® (Sereprostat® in Spain) on phospholipase A2 activity and on arachidonic acid metabolism in cultured prostatic cells* Acta Medica, 1988 [30]**RAYNAUD JP, COUSSE H and MARTIN PM** *Inhibition of type 1 and type 2 5 alpha-reductase activity by free fatty acids, active ingredients of Permixon®* Journal of Steroid Biochemistry & Molecular Biology, 2002, 82, 233–239. [31]**SCAGLIONE F, LUCHINI V, PANNACCI M et al.** *Comparison of the potency of different brands of Serenoa repens extract on 5alpha-reductase types I and II in prostatic co-cultured epithelial and fibroblast cells* Pharmacology, 2008, 82, 270-275 [32]**STENGER A, TARAYRE JP, CARILLA E, DELHON A, CHARVERON M, MORRE M and LAURESSERGUES H.** *Pharmacologic and biochemical study of the hexane extract of Serenoa Repens B (PA 109*)* GAZ MED FR, 1982, 89, 2041-2048 [33]**SULTAN Ch, TERRAZA A, DEVILLIER C et al.** *Inhibition of androgen metabolism and binding by a liposterolic extract of "Serenoa Repens B" in human foreskin fibroblasts* J.Steroid Biochem., 1984, 20(1) 515-519	

Section number and heading	Interested party	Comment and Rationale	Outcome
		[34]TALPUR N, ECHARD B, BAGCHI D, BAGCHI M, PREUSS HG Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats. Molecular and Cellular Biochemistry, 2003, 250: 21–26 **[35]TARAYRE JP, DELHON A, LAURESSERGUES H, STENGER A** *Action anti-oedémateuse d'un extrait hexanique de drupes de Serenoa repens Bartr.* Ann. Pharmaceutiques Françaises, 1983, 41, 6, 559-570 **[36]VACHER P, PREVARSKAYA N, SKRYMA R et al.** *The Lipidosterolic Extract from Serenoa repens Interferes with Prolactin Receptor Signal Transduction* J Biomed Sci, 1995, 2:357-365 **[37]VAN COPPENOLLE F, LE BOURHIS X, CARPENTIER F et al.** *Pharmacological Effects of the Lipidosterolic Extract of Serenoa repens (Permixon®) on Rat Prostate Hyperplasia Induced by Hyperprolactinemia: Comparison with Finasteride* The Prostate, 2000, 43:49-58 **[38]VELA-NAVARRETE R., GARCIA CARDOSO J.V., BARAT A. et al.** *BPH and Inflammation: Pharmacological Effects of Permixon on Histological and Molecular* *Inflammatory Markers. Results of a Double Blind Pilot Clinical*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Assay European Urology, 2003, 44:549-555 **[39]WADSWORTH TL, CARROLL JM, MALLINSON RA, ROBERTS CT, JR., AND ROSELLI CE,** *Saw palmetto extract suppresses insulin-like growth factor-I signaling and induces stress activated protein kinase/C-jun N-terminal kinase phosphorylation in human prostate epithelial cells* Endocrinology, 2004, 145(7): 3205–3214	