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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Serenoa repens* (W. Bartram) Small (*Sabal serrulata* (Michaux) Nichols), fructus

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HMPC decision on review of monograph *Serenoa repens* (W. Bartram) Small (*Sabal serrulata* (Michaux) Nichols), fructus adopted on 24 November 2015	25 September 2019
Call for scientific data (start and end date)	From 1st August 2020 to 31st October 2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	7 July 2021

Review of new data on *Serenoa repens* (W. Bartram) Small (*Sabal serrulata* (Michaux) Nichols), fructus

Periodic review (from 2015 to 2021)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

- ☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)
- ☒ Scientific databases: Embase, PubMed. Keywords: *sabal, serenoa, sabal serrulata, serenoa repens, saw palmetto*.
- ☐ Other

Regulatory practice

- ☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)
- ☒ New market overview (including pharmacovigilance actions taken in member states)
- ☐ Referral

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☐ Ph. Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☐ Public statements or other decisions taken by HMPC

☐ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Market overview

No new products on the market.

Pharmacovigilance

A search in the EudraVigilance database was done from 2015 until March 2021. It resulted in 641 hits on '*Serenoa*'. '*Serenoa*' was solely mentioned in 302 cases, in a combination with an extract of *Urtica dioica,* radix in 167 cases and in the other cases other agents were also involved.

Among the most frequently cited undesirable effects reported were gastro-intestinal disorders (abdominal pain, nausea, diarrhoea…), skin and subcutaneous tissue disorders (pruritus, rash

pruritic…), nervous system disorders (headache) and endocrine disorders (gynecomastia). These undesirable effects are already in the current HMPC monograph.

The pharmacovigilance information obtained does not reveal any need to revise the monograph on *Serenoa repens* for safety reasons.

Summary and conclusions on the review

During the review, 316 new references not yet available during the first assessment were identified.

20 references were provided by Interested Parties during the Call for data.

16 reference were considered to be relevant for the assessment.

No references justify a revision of the monograph.

Revision is not recommended because there are no new data/findings of relevance for the content of the monograph.

Analysis of the scientific data

To what extent are there new clinical efficacy data?

(The references are alphabetically listed)

Alcaraz *et al*. (2020) made a subset analysis of patients with an International Prostate Symptom Score score (IPSS) of ≥ 12 treated with tamsulosin (0.4 mg per day) or a hexane extract of *Serenoa repens,* fructus (320 mg per day) alone or in combination. They confirmed the added value of the hexane extract when combined with tamsulosin and the safety of the hexane extract of *Serenoa repens,* fructus during a study period of 6 months. The posology is in accordance with the existing monograph. This study does not justify a revision of the monograph.

Boeri *et al*. (2017) did a cross sectional cohort study comparing silodosin alone (8 mg per day) with a combination of silodosin + *Serenoa repens* hexane lipidosterolic extract (8 mg and 320 mg per day respectively). The authors concluded that the study provides new clinically-relevant evidence that a combination therapy of silodosin + *Serenoa repens* leads to greater clinically meaningful improvements in lower urinary tract symptoms (LUTS) severity, compared to SIL as a monotherapy, after at least 12 months of treatment in men with moderate-to-severe LUTS/ benign prostate hyperplasia (BPH). The posology of the hexane extract is the same as in the existing monograph. No serious adverse events occurred. The results of this study do not justify a revision of the monograph.

A review by Görne *et al*. (2017) deals with articles, which are already in the assessment report. This review does not justify a review of the monograph.

Gurzhenko and Spyrydonenko (2020) followed BPH patients with erectile and ejaculatory function disorders during 12 months. The exact nature of the *Serenoa repens* preparation is unknown. Most probably it was made from the fruit, but this is not specified. This open study does not justify a revision of the monograph.

Kaplan *et al*. (2015) randomly assigned BPH patients to either tamsulosin 0.2 mg per day plus *Serenoa repens* fructus hexane extract 320 mg per day or tamsulosin 0.2 mg per day only. The results of this 6

months open randomised clinical trial are in line with the WEU of hexane extracts, as included in the actual monograph. Drug related adverse reactions did not differ between both groups. This study does not trigger a revision of the monograph.

Saidi *et al*. (2017) studied the efficacy of a commercially available extract from *Serenoa repens,* fructus versus no treatment with outcome measurement after 6 and 12 months. The soft extract (DER 9-11:1), made with ethanol 96% V/V is covered by the monograph under traditional use. The data are not sufficient to accept a well-established use as the low number of patients was not justified by a power calculation. The results do not trigger a revision of the monograph.

Samarinas *et al*. (2020) reported a positive effect of a hexane extract on prostatic inflammation. As this use of *Serenoa repens* is not well established in the EU, the study does not justify a change the existing monograph.

The study by Sekikawa *et al*. (2020) has several weaknesses. The patient characteristics are not very specific (awaking $\geq$ twice at night to urinate), the description of the extract is not appropriate, and the follow-up period of eight weeks is relatively short. The difference between saw palmetto (most probably fruit) and placebo is not significant. This publication does not lead to a change of the monograph.

The open non-comparative observational study by Vinarov *et al*. (2019) reports on the continuous use of *S. repens* ethanolic plant extract at a dosage of 320 mg once a day for 15 years. The ethanolic *Serenoa repens* extract is included in the traditional use part of the monograph. The long-term use (15 years) of the extract without serious adverse events supports the safe traditional use covered by the monograph. The study does not support well-established use of the extract, because of the open design and the limited number of patients. There is no reason to change the existing monograph.

Ye *et al*. (2019) selected patients with LUTS/BPH for a treatment with an ethanolic extract of *Serenoa repens,* fructus. There are doubts about the exact composition and the source of the extract used in the study. Hence, the study does not trigger a revision of the monograph.

A meta-analysis by Zong *et al*. (2019) includes studies with different *Serenoa repens* extracts (hexane and ethanol) and with different study design (placebo controlled as well as open). Most of the studies are already described in the existing assessment report or are included in this review report. Based on the results of this meta-analysis, there is no need for a revision of the monograph.

To what extent are there new clinical safety data?

New clinical safety data do not trigger a revision of the monograph because the available reports lack details of the extracts, patients were using co-medications and/or reported side effects are already included the monograph. Gammoudi *et al*. (2020), Jacobsson *et al*. (2009), Jipescu *et al*. (2017) Svedlund *et al*. (2017) and Wadood *et al*. (2019)

References

a) References relevant for the assessment:

Alcaraz A, *et al*. Clinical Benefit of Tamsulosin and the Hexanic Extract of *Serenoa Repens*, in Combination or as Monotherapy, in Patients with Moderate/Severe LUTS-BPH: A Subset Analysis of the QUALIPROST Study. *J. Clin. Med.* 2020, 9, 2909; doi:10.3390/jcm9092909

Boeri L, *et al*. Clinically Meaningful Improvements in LUTS/BPH Severity in Men Treated with Silodosin Plus Hexanic Extract of *Serenoa Repens* or Silodosin Alone. *Scientific Reports* 2017, 7:15179 | in press doi 10.1038/s41598-017-15435-0

Gammoudi R, *et al*. Fixed drug eruption to *Serenoa repens*: First case report and consideration of the use of herbal medicine. *Dermatologic Therapy* 2020, 33:e14247

Görne RC, *et al*. Randomized double-blind controlled clinical trials with herbal preparations of *Serenoa repens* fruits in treatment of lower urinary tract symptoms. *Wien. Med. Wochenschr.* 2017, 167:177–182

Gurzhenko I, Spyrydonenko V. HP-4-1 Improvement of Sexual Functions in Men With Benign Prostatic Hyperplasia With Long-Term Use of the *Serenoa Repens* Extract. *Journal of Sexual Medicine* 2020; 17 (6) Supplement 2 (S160-S161)

Jacobsson I, *et al*. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. *Pharmacoepidemiology and Drug Safety* 2009, 18:1039–1047

Jipescu D, *et al*. Rare case of saw palmetto induced complete heart block. *Journal of the American College of Cardiology* 2017; 69:11 Supplement 1 (2310)

Kaplan SA, *et al.* Comparison of Tamsulosin plus Serenoa repens with Tamsulosin in the Treatment of Benign Prostatic Hyperplasia in Korean Men: 1-Year Randomized Open Label Study. *Urol. Int.* 2015, 94:187–193

Saidi S, *et al.* Effects of Serenoa repens alcohol extract on benign prostate hyperplasia. Contributions. *Sec. of Med. Sci*., XXXVIII 2, 2017

Samarinas M, *et al.* The Clinical Impact of Hexanic Extract of Serenoa repens in Men with Prostatic Inflammation: A Post Hoc Analysis of a Randomized Biopsy Study. *J. Clin. Med.* 2020, 9, 957; doi:10.3390/jcm9040957

Sekikawa T, *et al.* Verification study on the effects of saw palmetto fruit extract on urination issues. *Japanese Pharmacology and Therapeutics* 2020, 48(3):429-440

Svedlund E, *et al.* Spontaneously Reported Adverse Reactions for Herbal Medicinal Products and Natural Remedies in Sweden 2007-15: Report from the Medical Products Agency. *Drugs Real World Outcomes* 2017, 4(2):119-125

Vinarov AZ, *et al.* 15 years' survey of safety and efficacy of Serenoa repens extract in benign prostatic hyperplasia patients with risk of progression. *Urologia Journal* 2019, 86(1):17–22

Wadood R, *et al*. A case of acute liver injury caused by an herbal supplement containing saw palmetto: Good for the prostate but not for the liver? *American Journal of Gastroenterology* 2019, 114:S1342

Ye Z, *et al*. Efficacy and Safety of *Serenoa repens* Extract Among Patients with Benign Prostatic Hyperplasia in China: A Multicenter, Randomized, Doubleblind, Placebo-controlled Trial. *Urology* 2019, 129:172−179

Zong H.-T, *et al*. Efficacy and safety of *Serenoa repens* extract combined with α-receptor blocker in the treatment of benign prostatic hyperplasia. *National Journal of Andrology* 2019, 25(6):553-558

b) References that justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on *Serenoa repens* (W. Bartram) Small (*Sabal serrulata* (Michaux) Nichols), fructus, by consensus.