Does the vaginal microbiome drive cervical carcinogenesis?

DOI:
10.1111/1471-0528.15867

Document Version
Accepted author manuscript

Senshio®▼

Ospemifene **60mg**
Oral Tablets

Empowering women through choice[1-3]

The first oral prescription treatment that does not contain hormones, **for post-menopausal women with moderate to severe symptomatic vulvovaginal atrophy (VVA) who are not candidates for local vaginal oestrogen therapy.**[4-6]

Senshio works on the underlying cause of VVA [6-10] to **significantly reduce both dyspareunia and vaginal dryness by 12 weeks vs. placebo**[7]

For more information, a visit or call: **Senshio.co.uk**

Find out more ›

Please refer to the SPC for full details of any special warnings and precautions for use.

▼**Senshio® (ospemifene) 60 mg tablets**
Refer to full Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each film-coated tablet contains 60 mg ospemifene. **Indication:** Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy. **Posology and method of administration:** The recommended dose is one 60 mg tablet once daily with food taken at the same time each day. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. Active or previous venous thromboembolic events (VTEs), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis. Unexplained vaginal bleeding. Suspected or actively treated breast cancer, active or suspected sex-hormone dependent malignancy. Signs or symptoms of endometrial hyperplasia. **Warnings and precautions:** For the treatment of vulvar and vaginal atrophy, Senshio should only be initiated for symptoms that adversely affect quality of life e.g. dyspareunia and vaginal dryness. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually taking into consideration other menopausal symptoms, effects on uterine and breast tissues, thromboembolic and cerebrovascular risks. Senshio should only be continued as long as the benefit outweighs the risk. Endometrial thickening has been observed; Risk of VTE is increased with other selective oestrogen receptor modulators (SERMs) and cannot be excluded with Senshio, discontinue 4 to 6 weeks prior to and during prolonged immobilisation, major trauma or major surgery. Advise patients to seek immediate help if they experience potential thromboembolic symptoms. Risk of cerebrovascular events is possibly increased with other SERMs and cannot be excluded with Senshio; take into consideration in postmenopausal women with history of stroke or other significant risk factors. Use only after treatment of breast cancer, including adjuvant therapy, has been completed. May increase incidence of hot flushes. Caution when co-administering with fluconazole, carbamazepine, phenytoin, St John's wort, rifabutin, metformin, acyclovir, ganciclovir, oxaliplatin or orlistat. Concurrent use with oestrogens or other SERMs not recommended. Contains lactose. **Pregnancy & lactation:** Not to be used in women of child-bearing potential. If pregnancy occurs during treatment with ospemifene, ospemifene should be withdrawn immediately. Senshio is not indicated during breast-feeding. **Undesirable effects:** Common; Vulvovaginal candidiasis / mycotic infections, hot flush, muscle spasms, vaginal discharge, genital discharge, headache, rash. Uncommon; Endometrial hypertrophy, drug hypersensitivity, hypersensitivity, swollen tongue, pruritus, urticaria. Prescribers should consult the SmPC in relation to other side effects. **Legal classification:** Prescription only medicine. **MA number:** EU/1/14/978/002. **Pack sizes and Cost: 28 tablets £39.50. MA Holder:** Shionogi B.V., Kingsfordweg 151, 1043GR, Amsterdam, Netherlands. **Date of preparation:** March 2019.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk. Adverse events should also be reported to SHIONOGI.

Shionogi, 33 Kingsway, London, WC2B 6UF, UK +44(0)20 3053 4190
contact@shionogi.eu

References: 1. Neves-e-Castro M, et al. *Maturitas* 2015; 81(1): 88-92. **2.** Stuenkel C, et al. *JCEM* 2015; 100(11): 3975-4011. **3.** Palacios S, Cancelo M. *Int J Women's Health* 2016; 8: 617-626. **4.** Senshio Summary of Product Characteristics. **5.** NICE. Menopause: diagnosis and management. NICE guideline [NG23] November 2015. https://www.nice.org.uk/guidance/ng23/resources/menopause-diagnosis-andmanagementpdf-1837330217413 [Accessed January 2019]. **6.** Portman D, et al. *Maturitas* 2014; 78: 91-98. **7.** Bachmann G, et al. *Menopause* 2010; 17: 480-486. **8.** Cancelo M, et al. *Prog Obstet Ginecol* 2016; 59(3): 141-150. **9.** Alvisi A, et al. *Gynecological Endocrinology* 2017; 31: 1-5. **10.** Nappi R, et al. *Climacteric* 2015; 18: 233-240.

March 2019 PP-EU-FDC-0001

SHIONOGI

EMMA CROSBIE (Orcid ID : 0000-0003-0284-8630)

Article type : Mini commentary

Mini-commentary on BJOG-19-0278.R1: The vaginal microbiota, HPV and cervical dysplasia: a systematic review and network meta-analysis

Does the vaginal microbiome drive cervical carcinogenesis?

Kelechi Njoku[1], Emma J Crosbie[1]

[1]Division of Cancer Sciences, University of Manchester, School of Medical Sciences, Faculty of Biology, Medicine and Health, 5th Floor Research, St Mary's Hospital, Oxford Road, Manchester M13 9WL

Correspondence: Emma Crosbie
Email: emma.crosbie@manchester.ac.uk

Since the discovery of lactic acid producing bacteria in the vagina by Albert Dodelein in 1892, multiple studies have explored the relationship between the vaginal microbiota and various physiological, infectious and malignant conditions (Łaniewski et al, *Sci Rep*. 2018;8(1):7593). Whether the vaginal microbiome influences the association between human papillomavirus (HPV) infection and cervical cancer is one example with several, albeit small studies assessing whether vaginal dysbiosis influences HPV acquisition, persistence and progression to cervical dysplasia and malignancy. Whilst findings from these studies have been consistent and highly suggestive of an altered vaginal microbiome (Brusselaers at al., *Am J Obstet Gynaecol*

2019: 221(1):9-18), compelling evidence for the specific bacterial community state type (CST) species linked with cervical disease is lacking.

Genital HPV infections, though common in young sexually active women, are mostly transient and resolve without ever causing disease. Factors that influence their acquisition and especially persistence are not yet fully understood although smoking, the pathogenicity of specific HPV subtypes and immunological factors are important (Crosbie et al., *Lancet* 2013;382:889–99). It is indeed plausible that women with certain vaginal microbiome CST groups are more prone to acquiring and failing to clear high risk HPV and therefore identifying these CSTs is important to 1). Predict cervical cancer risk 2). Develop targeted prevention strategies, and 3). Test novel therapeutic strategies based on pre/probiotics.

Norenhag et al. in a systematic review and network-analysis of eleven cross sectional and longitudinal studies sought to explore what subtypes of CST, defined by molecular techniques, are linked with HPV-infection and cervical disease and report that non-lactobacillus species or Lactobacillus iners had 3-5 times higher odds of any prevalent HPV and 2-3 times higher odds for high risk HPV, cervical dysplasia and cervical cancer in comparison to Lactobacillus crispatus (Norenhag et al, *BJOG* 2019). These findings stem from a well-designed systematic review addressing a clearly focused question and conducted according to the PRISMA guidelines. Nevertheless, they should be interpreted with caution given the substantial methodological and population heterogeneity across included studies and the ever present possibility of reverse causation, especially with the inclusion of cross sectional studies. The variability in the composition of CSTs across studies, lack of consensus on methods of CST classification, omission of CSTs not fitting with authors' categories and use of varying terminologies for different disease stages are important limitations.

Importantly, quality assessment of included studies did not address how confounding variables including co-infection with HIV were addressed, especially for those studies involving high risk women (sex workers), nor was there clarity on how decisions on the overall quality of included studies were made. Despite these shortcomings, however, the study does provide a unique perspective into the role of specific CTS subtypes in cervical carcinogenesis. Well-designed longitudinal studies with adequate sample sizes and using standardized sampling and analytical methods are now needed to provide robust evidence on what CST subtypes are linked with high risk HPV and cervical cancer and importantly, to confirm causality.

Funding: K. Njoku is supported by a Cancer Research UK Manchester Cancer Research Centre Clinical Research Fellowship. E. Crosbie is supported by the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007).

Disclosure of interests: None declared. Completed disclosure of interest forms are available to view online as supporting information.