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Expert opinion on the treatment of vulvovaginal atrophy with ospemifene based on new evidence

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ABSTRACT

Vulvovaginal atrophy (VVA) is an underdiagnosed and undertreated chronic condition resulting in physiological and histological changes in the genitourinary tract of postmenopausal women. Treatment of moderate to severe VVA includes local estrogens, dehydroepiandrosterone (DHEA) and oral ospemifene, a third-generation selective estrogen receptor modulator (SERM). Due to venous thromboembolism (VTE) safety concerns classically associated with the SERM class, and as part of its original marketing authorization approval (MAA), the European Medicines Agency (EMA) requested the performance of a 5-year post-authorization safety study (PASS) to study the incidence rate of VTE among women receiving ospemifene. The results have led to important regulatory changes to ospemifene's labeling, extending its indication and eliminating concerted risk management measures. A panel of experts discussed and reached consensus on the impact of these regulatory changes on clinical practice, reflecting on the reassurance of ospemifene's benefit–risk balance and recommending its positioning as a first-line pharmacological treatment option for moderate to severe VVA together with local therapies. In a scenario where different treatments present similar efficacy and safety profiles, a shared decision between clinician and patient, according to her needs and preferences over time, is fundamental to improve adherence and persistence with sequential treatment, contributing to the achievement of health outcomes.

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Introduction

Vulvovaginal atrophy (VVA) is an underdiagnosed and undertreated chronic and progressive condition [1] in which low estrogen levels result in physiological and histological changes in the lower genital and urinary tracts in menopausal women. The collection of VVA signs and symptoms associated with estrogen deficiency after menopause including loss of vaginal elasticity, dryness, decreased lubrication, irritation and dyspareunia, among others, have been grouped together as the genitourinary syndrome of menopause [1,2].

VVA signs and symptoms are linked with major psychosocial distress and under-reporting that lead to disease progression and a considerable impact on women's quality of life and sexual health [3] despite the currently available therapeutic options. Pharmacological treatment for VVA patients not responding to symptomatic measures like local moisturizers and lubricants includes treatments with demonstrated effect on vaginal trophism, such as local estrogens, dehydroepiandrosterone (DHEA) and ospemifene, as well as systemic estrogen therapy when other postmenopausal symptoms are observed [4,5].

Ospemifene is the only oral, non-steroidal selective estrogen receptor modulator (SERM) approved for the treatment of moderate to severe symptomatic VVA in postmenopausal women. The European Medicines Agency (EMA) restricted its original indication to patients who were not candidates for treatment with local vaginal estrogens [6].

The SERM class has been classically associated with venous thromboembolism (VTE) safety concerns [7]. Hence, as part of the initial European marketing authorization approval (MAA), the EMA mandated a 5-year post-authorization safety study (PASS) to examine the incidence of VTE among postmenopausal women receiving ospemifene compared to women who received other SERMs (raloxifene, bazedoxifene or tamoxifene) for non-cancer indications and breast cancer prevention, and women with untreated VVA [6].

The PASS results confirmed the EMA's Committee for Medicinal Products for Human Use (CHMP) adoption of a positive opinion in January 2022 recommending a change in ospemifene's indication, which was approved by the

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European Commission in February 2022, extending the indication as follows [8]:

> Ospemifene is indicated for the treatment of moderate to severe symptomatic VVA in post-menopausal women.

A panel of acknowledged experts in the field of genitourinary health in Italy and Spain discussed the impact of ospemifene's regulatory and label changes on clinical practice. The objective of this expert opinion article is to present the experts' reflections and reached consensus with the aim of guiding physicians in the pharmacological treatment of moderate to severe VVA in postmenopausal women, offering the current overarching options when starting the shared-decision treatment in their conversation with their patients.

Participants and methodology

An expert panel of five gynecologists from Italy and Spain with expertise in management of postmenopausal women with VVA and membership in relevant national and international scientific societies was reunited. A targeted literature review was performed specific to recommendations in clinical guidelines and treatment algorithms of moderate to severe VVA as well as the relative positioning of ospemifene in European countries where it is commercialized (Italy, Spain and the UK) [9], identifying medical and regulatory literature published since ospemifene's initial EU MAA in 2015 [6] until 21 March 2022 (Table 1).

The expert panel reviewed and validated the results from the literature review, complemented with personal experience, in order to provide a snapshot of the rationale for current positioning of ospemifene in clinical practice in their countries. Data from the PASS [10] and subsequent label changes were discussed, and consensus was reached on recommendations for pharmacological treatment of VVA in postmenopausal women, including specific considerations for ospemifene.

Current management of moderate to severe VVA in postmenopausal women

The objective of pharmacological treatment for VVA is the preservation of vaginal health, the absence of signs and symptoms, and the improvement in the quality of life and sexual health of postmenopausal women [11]. Clinical guidelines for the management of VVA in Italy and Spain emphasize the importance of early treatment to slow down progression, and consider the administration of local vaginal estrogens and DHEA and the use of oral ospemifene as equally valid options [11–14].

Adherence and persistence influence treatment effectiveness [11] and are required since symptoms recur on cessation due to the chronicity status of the VVA condition [5]. Nevertheless, adherence and persistence to vaginally applied pharmacological treatments are low in VVA [15,16]. In this sense, clinical guidelines advise clinicians to jointly decide with the patient the most appropriate pharmacological treatment according to her needs and preferences through empowered sequential treatment [11–14]; which involves the interchangeability of treatments over time [17], taking into account the frequency of follow-up and contributing to improving adherence and persistence and achievement of health outcomes [11–14].

Currently, there is no consensus between Italian and Spanish clinical guidelines on the relative therapeutic positioning of the different pharmacological alternatives for moderate to severe VVA [11–14] (Table 1). Local vaginal estrogens and DHEA were formerly positioned as the first-line pharmacological treatment options for moderate to severe VVA [11,12,14]. Ospemifene is usually positioned as a second-line treatment [12] according to its initial indication, limited to women who are not candidates for local vaginal estrogen therapy and the safety specifics detailed in its risk management plan [6].

Sequential treatment is sometimes used based on patients' specific requirements [11,13], although it is neither fully established in clinical practice nor reflected in all clinical

Table 1. Current positioning of ospemifene: results from the targeted literature review.

Country	*Ospemifene's positioning for the treatment of VVA*
European Union	The EMAS clinical guideline aims to provide an overview of topical estrogen and non-hormonal treatment options for VVA; thus, ospemifene is not included [4]
Italy	According to the SIM, the first-line treatments are local estrogens and ospemifene [14]
	The SIM and SIGiTE do not position ospemifene in any specific line of treatment [13]
Spain	In the MenoGuía, local estrogens and prasterone are the treatments of choice, and ospemifene is not positioned in any specific line of treatment [11]
	The SEGO recommends local estrogen therapy as the treatment of choice, and ospemifene is positioned as a second-line treatment [12]
	The TPR does not establish ospemifene's positioning, waiting for the results of the 5-year PASS [21]
UK	The NICE guideline does not establish ospemifene's positioning [22]
	The SMC adopted a positive opinion for the use of ospemifene within the Scottish National Health System (NHS Scotland) without positioning it in any specific line of treatment [23]

EMAS, European Menopause and Andropause Society; NICE, National Institute for Health and Care Excellence; PASS, post-authorization safety study; SEGO, Spanish Society of Obstetrics and Gynecology; SIGiTE, Italian Society of Third Age; SIM, Italian Society for Menopause; SMC, Scottish Medicines Consortium; TPR, therapeutic positioning report; VVA, vulvovaginal atrophy.

guidelines [12, 14]. There are special situations for which a particular pharmacological treatment is preferable versus others, as it is the case for breast cancer survivors (i.e. women with a history of breast cancer and who have completed their treatment, including adjuvant), for whom ospemifene represents the only approved option for treatment of their moderate to severe VVA [6,8].

Relevance of ospemifene's regulatory and label changes based on newly available safety evidence

The 5-year, real-world PASS analyzed the incidence of VTE in 8,977 postmenopausal women with moderate to severe VVA treated with ospemifene. The study was completed in March 2021. The incidence rate per 1,000 person-years of VTE was 3.39 (95% confidence interval [CI]: 1.55–6.43) in ospemifene users, 11.30 (95% CI: 8.81–14.28) among women receiving other SERMs and 10.92 (95% CI: 10.49–11.37) in women with untreated VVA. Thus, the incidence rate of VTE in ospemifene users was less than half the rate among women receiving other SERMs or women with untreated VVA. The PASS results showed no increased risk of VTE for ospemifene users compared to women receiving other SERMS (hazard ratio 0.40, 95% CI: 0.19–0.82) or women with untreated VVA (hazard ratio 0.47, 95% CI: 0.24–0.91), and they were consistent in all sensitivity analyses [10]. These results are consistent with findings reported during ospemifene's clinical development program, where the incidence rate per 1,000 person-years of VTE was 3.65 (95% CI: 0.44–13.19) in the ospemifene group and 3.66 (95% CI: 0.09–20.41) in the placebo group with no increased VTE risk for ospemifene patients (relative risk = 1.0) [6]. Altogether, the combined evidence from clinical trials [6] and the PASS [10] suggest that the SERM-associated elevated risk of VTE does not apply to ospemifene [8].

Results from the PASS were submitted to the EMA, ratifying its positive risk–benefit profile and led to important regulatory changes to the initial MAA, namely:

- the extension of the indication to first-line treatment:

  Ospemifene is indicated for the treatment of moderate to severe symptomatic VVA in post-menopausal women;

- and removal of the black inverted triangle, a measure imposed in Europe to label medicines subjected to 'additional monitoring' [8].

Management of moderate to severe VVA with ospemifene as a first-line treatment option

The newly available safety evidence [10] and the changes to the labeling [8] allow to position ospemifene as a first-line treatment option along with DHEA and local estrogens, increasing the choice of pharmacological treatment options for the management of moderate to severe VVA in postmenopausal women.

Ospemifene acts as an estrogen receptor agonist in the vagina exerting an estrogen-like effect, increasing cell maturation and mucification of the vaginal mucosa, restoring the trophism of the vulvovaginal area, reversing the symptoms of VVA [6] and possibly delaying the progression of the chronic condition. In this sense, a recent post-hoc analysis from two ospemifene pivotal 12-week phase III trials showed that early pharmacological treatment with ospemifene resulted in greater clinical benefits [18].

To date, ospemifene is the only oral treatment available for moderate to severe VVA [6,8,11–14]. As previously mentioned, treatment continuation conditions the effectiveness of the pharmacological therapy, and adherence to treatment for VVA is generally low [11]. A recent retrospective, observational study found that ospemifene users exhibited higher adherence and persistence rates than vaginal estrogen therapy users, excluding vaginal rings [15], revealing the importance of having the option of an oral treatment for moderate to severe VVA for patients who prefer this administration route. Recently, the CRETA (CRoss sectional European sTudy on Adherence), conducted in 29 hospitals and centers across Spain enrolling 831 postmenopausal women with VVA, reported higher satisfaction and adherence for ospemifene compared to vaginal estrogen therapy besides a lower number of missed doses in the treatment of moderate to severe VVA [19]. Since patient's preference is a major driver for long-term treatment adherence and persistence [11,12], informing patients about available treatment options and shared decision-making between clinician and patient is critical when selecting the most appropriate treatment for moderate to severe VVA.

Nevertheless, certain patient subpopulations cannot benefit from the availability of all therapeutic options, as in the case of breast cancer survivors [11–14]. The latest publications show no difference in the incidence and recurrence of breast cancer between ospemifene users and untreated VVA patients [20], reassuring the safety profile of ospemifene for women with breast cancer who have completed adjuvant treatment and its position as the first and only pharmacological treatment option in these patients, although consensus between oncologists and gynecologists is fundamental.

Conclusions

The newly available safety results [10] and the changes to the labeling, which include the extension of indication and the elimination of the black inverted triangle [8], provide evidence and reassurance on the safety profile upon which to consider ospemifene as a first-line pharmacological treatment option together with local vaginal estrogens and DHEA for the management of moderate to severe VVA in postmenopausal women, ospemifene being the only oral first-line therapeutic option.

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R. E. Nappi has had financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Gedeon Richter, HRA Pharma, Merck, Procter & Gamble, TEVA and Zambon. At present, she has an ongoing relationship (research grants and/or consulting fees) with Astellas, Bayer, Exeltis, Fidia, Novo Nordisk, Organon, Palatin Technologies, Pfizer, Shionogi and Theramex.

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