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Summary of the risk management plan (RMP) for Senshio (ospemifene)

This is a summary of the risk management plan (RMP) for Senshio, which details the measures to be taken in order to ensure that Senshio is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Senshio, which can be found on Senshio's EPAR page.

Overview of disease epidemiology

Senshio is a medicine used to treat moderate to severe symptoms of vulvovaginal atrophy (dryness, irritation and soreness around the genital area, and painful sexual intercourse) in women who have been through the menopause. In these women, vulvovaginal atrophy is usually caused by falling levels of the sex hormone oestrogen which lead to a thinning of the tissues in and around the vagina and to reduction in the amount of mucus that keeps the vaginal environment moist. This can cause dryness, leading to painful sexual intercourse, and irritation and soreness around the genital area.

The percentage of postmenopausal women who have symptoms from vulvovaginal atrophy has been reported to be around 50%.

Summary of treatment benefits

Senshio contains the active substance ospemifene, which stimulates the receptors for oestrogen in some tissues in the body such as the vagina, helping to reverse the symptoms of vulvovaginal atrophy.

Senshio has been compared with placebo (a dummy treatment) in two main studies involving over 1,700 postmenopausal women with vulvovaginal atrophy. The main measure of effectiveness was related to the change in symptoms such as pain associated with sexual activity as well as vaginal dryness using a validated questionnaire. Women also received a non-hormonal vaginal lubricant for use as needed. In the first study, 66% of women using Senshio reported relief from vaginal dryness (mild or no symptoms) after 12 weeks' treatment compared with 49% in the placebo group. In the second study, 62% of women using Senshio reported relief from vaginal dryness after 12 weeks (compared with 53% in the placebo group). Regarding pain during sexual activity, 58% of women using Senshio reported relief in the first study (compared with 42% using placebo) and 63% reported relief during the second study (compared with 48% using placebo). The studies also showed that Senshio was effective in restoring the vaginal environment including its acidity and tissue thickness.

Unknowns relating to treatment benefits

There are limited data from clinical studies on the effectiveness of Senshio beyond 12 months.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increase in uterine (womb) diagnostic procedures	Investigation of the womb such as a transvaginal ultrasound (scan of the womb using a probe inserted in the vagina) was performed in a greater number of patients who received Senshio and experienced vaginal bleeding compared with women on placebo.	Patients with unexplained vaginal bleeding must not take Senshio. Bleeding or spotting that occurs after taking Senshio, or continues after Senshio has been stopped, should be investigated.

Important potential risks

Risk	What is known
Blood clots in the arteries leading to stroke (cerebrovascular events)	Blood clots in the arteries may lead to a stroke. In the Senshio clinical studies, the number of strokes observed with Senshio was not significantly different from the number of strokes observed in patients receiving placebo and none of the strokes had a fatal outcome. However, stroke is a recognised risk with other medicines from the same therapeutic class (called selective oestrogen receptor modulator - SERMs).
Blood clots in the veins (venous thromboembolic events)	Blood clots in the veins of the legs may lead to a painful swelling of the legs (deep vein thrombosis) and, very occasionally, to life threatening or fatal events if the clots are dislodged and travel to the lungs (pulmonary embolism). In the Senshio clinical studies, the number of venous thromboembolic events observed with Senshio was no greater than in the patients receiving placebo, and there were no cases of pulmonary embolism. However, as a risk of blood clots in the veins has been identified with other SERMs, the possibility of venous thromboembolic events occurring during treatment with Senshio cannot be ruled out.
Vaginal bleeding	Some medicines from the same therapeutic class as Senshio are known to have effects that are similar to the hormone oestrogen, such as stimulating abnormal growth of the womb lining which could lead to vaginal bleeding. The number of patients in the clinical studies who had vaginal bleeding when taking Senshio was comparable to the number who experienced this when taking placebo. However, if vaginal bleeding occurs whilst taking Senshio, it is essential that the cause is further investigated.
Cancer of the lining of the womb (endometrial cancer)	No cases of endometrial cancer occurred in the Senshio clinical studies. A few cases of non-cancerous polyps (small growths) of the womb and one case of hyperplasia (abnormal thickening) of the womb occurred 3 months after treatment with Senshio in clinical studies. Some medicines from the same therapeutic class as Senshio are known to have effects that are similar to the hormone oestrogen, such as stimulating abnormal growth of the womb lining which could lead to cancer.
Bulging of the womb,	An increased risk of pelvic organ prolapse has been seen with some other

Risk	What is known
bowel or bladder into the vagina (pelvic organ prolapse) / unintentional passing of urine (urinary incontinence)	SERMs and is therefore a potential risk with Senshio. Pelvic organ prolapse can lead to urinary incontinence. However, in clinical studies with Senshio the rate of bladder prolapse with Senshio was lower than that seen in patients receiving placebo.
Cholecystitis (inflammation of the gallbladder) and gallbladder events	Inflammation of the gallbladder (a small organ underneath the liver that stores bile) is usually caused by gallstones. An increased risk of gallstones has been seen with some other SERMs. In clinical studies with Senshio the number of patients developing gallstones with Senshio was lower than that seen with placebo.
Atrial fibrillation (heart condition that causes an irregular and often abnormally fast heart rate)	No increased risk of atrial fibrillation has been seen in the Senshio clinical trials. However, an increased risk of atrial fibrillation has been observed with another SERM.
Increased amounts of triglycerides (fatty substance) in the blood	An increased risk of raised triglycerides in the blood has been seen with some SERMs. However, no increased risk has been seen in the Senshio clinical trials.
Liver tumours	No cases of liver tumours have been observed with Senshio in clinical trials. Liver tumours have been seen in experimental models with Senshio, however, this finding is not thought to be relevant to post-menopausal women.
Thymic epithelial tumours (cancer of the thymus gland – a small organ located in the upper portion of the chest)	No cases of thymic epithelial tumours have been observed with Senshio in clinical trials. Thymic epithelial tumours have been seen in experimental models with Senshio, however, this finding is not thought to be relevant to post-menopausal women.
Renal carcinoma and adenoma (cancer of the kidney)	Kidney cancer was seen in experimental models with another SERM. However, as kidney cancer is known to occur spontaneously the significance of this is not known. One case of cancer of the urinary tract was found in a patient receiving Senshio in a clinical trial but this was not thought to be caused by the medicine.
Renal failure (kidney failure)	No cases of kidney failure or worsening kidney failure were seen in clinical trials with Senshio. However, nephrocalcinosis (calcium deposits in the kidney) and kidney failure were seen in experimental models with a SERM other than Senshio.
Use of Senshio for conditions other than the approved use of the product (off label	Senshio has been approved to treat moderate to severe symptoms of vulvovaginal atrophy in post-menopausal women who are not able to use oestrogen products that are applied locally in the vagina.

Risk	What is known
use)	Senshio is not effective in treating other symptoms of the menopause such as hot flushes. There is a risk that Senshio may be prescribed to patients in whom its use is not approved (such as postmenopausal women suffering from hot flushes).

Missing information

Risk	What is known
Long-term safety information	Only a small number of patients received Senshio for more than 12 months in the clinical studies and so it is not known if use beyond this time would cause any problems. For this reason doctors should assess patients taking Senshio at least once a year to check that it is safe for the patient to continue treatment.
Women with diseases of the reproductive system other than signs of thinning of the vagina	Women with diseases of the female reproductive system other than symptoms of thinning of the vagina were excluded from the clinical studies, so experience of using Senshio in such patients is limited. Therefore, it is recommended that such conditions are investigated and treated appropriately.
Women with breast cancer	Women with breast cancer were excluded from the Senshio clinical studies, so there is limited experience of using Senshio in women with breast cancer. There is also no experience of using Senshio together with breast cancer treatments. For this reason, Senshio should be used only after the treatment of breast cancer has been completed.
Use of Senshio together with medicines such as SERMs, oestrogens or other medicines with oestrogenic/ antioestrogenic actions	The use of SERMs, oestrogen-containing medicines or medicines that have oestrogen-like or opposing effects was not permitted together with Senshio in the clinical studies. For this reason, use of these medicines together with Senshio is not recommended.
Side effects due to increase in blood levels of Senshio's active substance, ospemifene, when used together with medicines that decrease the activity of liver enzymes	Studies investigating interactions of Senshio with other medicines have shown that levels of the active substance ospemifene may increase when given together with medicines that block certain enzymes in the liver which are responsible for the way ospemifene is processed in the body. Caution is recommended if the antifungal medicine fluconazole is given together with Senshio because it significantly increases ospemifene levels and may lead to side effects. Treatment with Senshio may have to be stopped while treatment with fluconazole lasts. Caution is recommended when taking Senshio with certain medicines known as strong inhibitors of liver enzymes because patients taking such medicines were not included in the main clinical studies and the clinical consequences have not been established.
Risk of lack of effect due to decrease in blood levels of	A study has shown that the medicine rifampicin decreases the levels of Senshio due to its ability to increase the activity of enzymes in the liver that metabolise Senshio. Administration of Senshio together with medicines that

Risk	What is known
ospemifene when used together with medicines that increase the activity of liver enzymes	increase the activity of certain enzymes in the liver known as CYP3A4 and CYP2C9 (e.g. carbamazepine, phenytoin, St John's wort and rifabutin) would be expected to decrease the amount of Senshio, which may decrease the clinical effect.
Severe hepatic (liver) impairment	The safety and efficacy of Senshio in patients with severe liver impairment were not evaluated in clinical trials and its use in such patients is not recommended. No dose adjustment is required in patients with mild to moderate liver impairment.
Patients who often suffer severe allergic reactions	Patients who often suffer from severe allergic reactions were excluded from the Senshio clinical trials. Therefore there is no experience of Senshio use in such patients. Patients who are allergic to Senshio or to any of the other inactive substances in the tablets must not take Senshio.
Limited amount of data in the elderly (over 65 years old)	Approximately 19% of the patients who took Senshio in the clinical studies were over 65 years old. Although no specific problems were observed in these elderly patients compared with younger patients the number of elderly patients taking part was relatively small. For this reason, the safety of Senshio in elderly patients will continue to be assessed closely.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Senshio can be found on Senshio's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A post-marketing safety study of Senshio using information from health databases in Germany, Italy, Spain, and the United States.	To find out the number of certain side effects of interest occurring in women taking Senshio for treatment of vaginal dryness or	Long-term safety assessing risks of: • venous thromboembolic events • cerebrovascular events	Planned.	Annual study progress reports and interim reports will be provided for each individual country from 2016 to 2020.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	painful sex compared with 1) the number of side effects experienced in post-menopausal women not receiving treatment for this condition ; and 2) in post-menopausal women taking other similar medications to Senshio (SERMs) for other oestrogen-deficiency conditions or breast cancer prevention.	• increase in medical tests relating to the vagina or womb • pelvic organ prolapse/urinary incontinence • cholecystitis and gallbladder events • atrial fibrillation • increased blood levels of triglycerides • liver tumours • cancer of the thymus • kidney cancer and kidney failure or worsening kidney failure • off label use.		Final report (planned): Feb 2021.
A study to investigate whether the blood levels of a medicine called midazolam are affected by repeated doses of Senshio	To find out if multiple doses of Senshio affect the blood levels of midazolam in postmenopausal women. To check the safety of taking Senshio together with midazolam.	Experimental models found Senshio to weakly increase the activity of the enzyme. Whilst this is not expected to be a safety concern for Senshio it is not known if Senshio will increase the activity of this enzyme and reduce the effects of medicines like midazolam in humans. This study is being carried out to find out if this is the case or not.	Planned	Planned Dec 2016

Studies which are a condition of the marketing authorisation

The post-marketing safety study listed above is a condition to the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 12-2014.