SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Senshio 60 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg ospemifene.

Excipient with known effect

Each film-coated tablet contains 1.82 mg lactose as monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Oval biconvex, white to off-white, film-coated tablets of dimensions 12 mm x 6.45 mm, debossed with “60” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Senshio is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women.

4.2 Posology and method of administration

Posology

The recommended dose is one 60 mg tablet once daily with food taken at the same time each day.
If a dose is missed it should be taken with food as soon as the patient remembers. A double dose should not be taken in the same day.

Elderly
No dose adjustment is necessary in patients above the age of 65 years (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild, moderate or severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Ospemifene has not been studied in patients with severe hepatic impairment, therefore Senshio is not recommended for use in such patients (see section 5.2).

Paediatric population
There is no relevant use of ospemifene in the paediatric population for the indication of the treatment of moderate to severe symptomatic VVA in post-menopausal women.

Method of administration

Oral use.

One tablet should be swallowed whole once daily with food and should be taken at the same time each day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active or past history of venous thromboembolic events (VTEs), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
- Unexplained vaginal bleeding.
- Patients with suspected breast cancer or patients undergoing active treatment (including adjuvant therapy) for breast cancer (see section 4.4).
- Suspected or active sex-hormone dependent malignancy (e.g. endometrial cancer).
- Patients with signs or symptoms of endometrial hyperplasia; safety in this patient group has not been studied.

4.4 Special warnings and precautions for use

For the treatment of vulvar and vaginal atrophy, ospemifene 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. Ospemifene should only be continued as long as the benefit outweighs the risk.

Endometrial findings

In clinical studies, a mean increase of 0.8 mm in endometrial thickness after 12 months (as assessed by protocol-specified ultrasonography) was observed and there was no increase in vaginal bleeding or spotting in the ospemifene-treated group compared to the placebo-treated group. If bleeding or spotting occurs on therapy, or continues after treatment has been discontinued, this should always be investigated, which may include an endometrial biopsy to exclude endometrial malignancy. The incidence of endometrial hyperplasia was 0.3% (1 case out of 317 biopsies) after 1 year of treatment with an upper 95% confidence limit of 1.74% (see section 5.1). In post-menopausal women who received ospemifene treatment up to 1 year, benign endometrial polyps were reported in 0.4% compared to 0.2% in women who received placebo treatment.

Venous thromboembolic events (VTEs)

The risk of VTE (deep vein thrombosis and pulmonary embolism) is increased with other selective oestrogen receptor modulators (SERMs). The risk of VTE associated with ospemifene cannot be excluded. Generally recognised risk factors for VTE include advanced age, a family history, severe obesity (BMI>30 kg/m^2) and systemic lupus erythematosus (SLE). The risk of VTE is temporarily increased with prolonged immobilisation, major trauma or major surgery. Ospemifene should be discontinued at least 4 to 6 weeks prior to and during prolonged immobilisation (e.g., post-surgical recovery, prolonged bed rest). Treatment should be resumed only after the patient is mobilised.
If VTE develops after initiating therapy, the treatment should be discontinued. Patients should be advised to contact their doctors immediately when they experience a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Cerebro-vascular events

The risk of cerebrovascular events is possibly increased with other SERMs. The risk of cerebrovascular events associated with ospemifene cannot be excluded. This should be considered when prescribing ospemifene for post-menopausal women with a history of stroke or other significant stroke risk factors.

Pre-existing gynaecological pathology other than signs of vaginal atrophy

There are limited clinical trial data on the use of ospemifene in patients with other gynaecological conditions. It is recommended that any additional pathology be investigated and treated appropriately before starting ospemifene.

Breast cancer

Ospemifene has not been formally studied in women with a prior history of breast cancer. No data are available on its concomitant use with medicinal products used in the treatment of early or advanced breast cancer. Therefore ospemifene should be used for the treatment of VVA only after the treatment of breast cancer, including adjuvant therapy, has been completed.

Hot flushes

Ospemifene may increase the incidence of hot flushes and is not effective in reducing hot flushes associated with oestrogen deficiency. In some asymptomatic patients, hot flushes may occur upon beginning therapy. About 1% of subjects discontinued in the phase 2/3 clinical programme due to hot flushes.

Co-administration with fluconazole

Caution is recommended when co-administering ospemifene with fluconazole (see section 4.5). If necessary, because of impaired tolerance, ospemifene should be stopped as long as treatment with fluconazole lasts.

Lactose content
Senshio contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content

Senshio contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ospemifene

Fluconazole, a moderate CYP3A / moderate CYP2C9 / strong CYP2C19 inhibitor, increased the area under the curve (AUC) of ospemifene by 2.7-fold. These results suggest that co-administration of ospemifene with any medicinal product that inhibits both CYP3A4 and CYP2C9 activity (e.g. fluconazole) would be expected to increase the exposure of ospemifene in a similar way. Therefore, caution is recommended when co-administering ospemifene with fluconazole. In case of impaired tolerance of ospemifene, the latter should be stopped as long as treatment with fluconazole lasts.

Ketoconazole, a strong CYP3A4 inhibitor and moderate P-glycoprotein inhibitor, increased the AUC of ospemifene by 1.4-fold. This increase is not considered to be clinically significant given the inherent pharmacokinetic variability of ospemifene. There is therefore no reason to expect that strong CYP3A4 inhibitors would cause a clinically meaningful change in ospemifene exposure. Co-administration of ospemifene with strong/moderate CYP3A4 inhibitors should be avoided in patients who are known or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates.

Rifampicin, a strong CYP3A / CYP2C9 enzyme inducer, decreased the AUC of ospemifene by 58%. Therefore, co-administration of ospemifene with strong enzyme inducers like carbamazepine, phenytoin, St John's wort and rifabutin would be expected to decrease the exposure of ospemifene, which may decrease the clinical effect.

Inhibition of UGT1A3, UGT2B7, UGT1A1, or UGT1A8 may potentially affect the glucuronidation of ospemifene and/or 4-hydroxyospemifene.

In healthy subjects, the absorption of ospemifene is not affected by co-administration of oral omeprazole, a medicinal product that increases gastric pH.

Effects of ospemifene on other medicinal products

Interaction studies were performed with probe substrates for CYP2C9 (warfarin), CYP3A4 (midazolam), CYP2C19, and CYP3A4 (omeprazole) and CYP2B6 (bupropion). Ospemifene did not cause a clinically meaningful change in the exposure to the substrates, indicating that ospemifene does not affect those enzyme activities *in vivo* to a clinically significant extent.
Ospemifene and its major metabolite, 4-hydroxyospemifene, inhibited organic cation transporter (OCT)1 *in vitro* at clinically relevant concentrations. Therefore, ospemifene may increase concentrations of medicinal products which are substrates of OCT1 (e.g. metformin, acyclovir, ganciclovir and oxaliplatin).

In vitro, ospemifene and 4-hydroxyospemifene inhibited glucuronidation mainly via UGT1A3 and UGT1A9 at clinically relevant concentrations. The pharmacokinetics of medicinal products that are mainly metabolised by UGT1A3 and UGT1A9 could be affected when administered concomitantly with ospemifene and co-administration should be made with caution.

The safety of using ospemifene concomitantly with oestrogens or other SERMS, such as tamoxifen, toremifene, bazedoxifene and raloxifene, has not been studied and its concurrent use is not recommended.

Due to its lipophilic nature and absorption characteristics, an interaction between ospemifene and medicinal products like orlistat, cannot be ruled out. Therefore, caution is recommended when ospemifene is combined with orlistat. A clinical monitoring of a decrease in the efficacy of ospemifene should be made.

4.6 Fertility, pregnancy and lactation

Pregnancy

Senshio is only for use in post-menopausal women and should not be used in women of child-bearing potential. If pregnancy occurs during treatment with ospemifene, ospemifene should be withdrawn immediately.

There are no data from the use of ospemifene in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk in humans is unknown.

Breast-feeding

Senshio should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Senshio has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are hot flushes (7.5%).

Tabulated list of adverse reactions

Averse reactions are listed below by MedDRA preferred term system organ class and by frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 1Adverse reactions

MedDRA system organ class	**Common**	**Uncommon**
Infections and infestations	Vulvovaginal candidiasis / mycotic infections	-
Immune system disorders	-	Drug hypersensitivity[b], Hypersensitivity[b], Swollen tongue
Nervous system disorders	Headache[c]	
Vascular disorders	Hot flush[d]	-
Skin and subcutaneous tissue disorders	Rash (includes rash erythematous, rash generalised)	Pruritus Urticaria
Musculoskeletal and connective tissue disorders	Muscle spasms	-
Reproductive system and breast disorders	Vaginal discharge, Genital discharge, Vaginal haemorrhage	Endometrial hypertrophy[a] (sonographic endometrial thickness)

[a] Endometrial hypertrophy is a MedDRA dictionary term that represents sonographic endometrial thickness findings.
[b] Hypersensitivity reactions including adverse reactions listed under skin and subcutaneous tissue disorders, swollen tongue, pharyngeal oedema and throat tightening were reported.
[c] The frequency of headache reported in the table is that calculated from the Phase 2/3 clinical trials, where the frequency was comparable between 60 mg ospemifene (5.4%) and placebo (5.9%) groups.
[d] Hot flushes including hyperhidrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ospemifene has been administered to subjects in single doses for up to 800 mg day and repeat doses up to 240 mg/day for 7 days and up to 200 mg/day for 12 weeks. There is no specific antidote for ospemifene. In the event of overdose, general supportive measures should be initiated based on the patient's signs and symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, selective oestrogen receptor modulators, ATC code: G03XC05.

Pharmacodynamic effects

Ospemifene is a nonsteroidal selective oestrogen receptor modulator.

Decreases in oestrogen levels that occur after the menopause lead to VVA, characterised by decreased maturation of vaginal epithelial cells, a progressive decrease in the vascularity of the vaginal tissues, and decreased lubrication. The glycogen content of vaginal epithelial cells also decreases, resulting in reduced colonisation by lactobacilli and increased vaginal pH. These changes result in clinical signs which include vaginal dryness, redness, petechiae, pallor, and friability in the mucosa. In addition, these changes can result in chronic symptoms associated with VVA, the most common of which are vaginal dryness and dyspareunia.

The biological actions of ospemifene are mediated through the binding of ospemifene and its major metabolite to oestrogen receptors. The relative contribution of the metabolite to the pharmacological effect is estimated to be approximately 40%. This binding results in activation of some oestrogenic pathways (agonism) and blockade of other oestrogenic pathways (antagonism). The biological activity profile in humans is predominantly due to the parent compound.

Non-clinical findings show that ospemifene and its major metabolite have an oestrogen like effect in the vagina increasing the cellular maturation and mucification of the vaginal epithelium. In the mammary gland, they have a predominantly oestrogen antagonist effect. In bone, ospemifene has agonist-like activity. In the uterus ospemifene and its major metabolite have weak partial agonist/antagonist effects. These non-clinical findings are consistent with findings from clinical trials, in which ospemifene demonstrated benefits on vaginal physiology without apparent oestrogen-like effects on breast tissue (see subheading 'Clinical efficacy and safety').

Clinical efficacy and safety

The clinical efficacy and safety of ospemifene was determined primarily from two multi-centre, placebo-controlled trials of 12 weeks duration (trials 15-50310 and 15-50821) and a third long-term safety trial of 52 weeks duration (trial 15-50718) in post-menopausal patients with VVA. In those trials, a total of 1,102 subjects received 60 mg of ospemifene and 787 subjects received placebo.

In the two 12 weeks studies (trials 15-50310 and 15-50821), 739 patients received ospemifene and 724 patients received placebo. All patients received non-hormonal vaginal lubricant for use as needed; therefore, the effects on efficacy endpoints in the ospemifene treatment group were in addition to those achieved with lubricant use alone. The study population consisted of generally healthy post-menopausal women between 41 to 80 years of age (mean age = 59 years), who at baseline had ≤ 5.0% superficial cells in the vaginal smear, a vaginal pH >5.0 and were required to have at least one moderate or severe VVA symptom, where patients had to choose the symptom that was the most bothersome (MBS). There were four co-primary endpoints for which change from baseline was assessed: percentage parabasal cells and superficial cells in the vaginal smear, vaginal pH, and MBS of VVA (dryness or dyspareunia).

The long-term study (trial 15-50718) was a 52-week, randomised, double-blind, placebo-controlled safety and efficacy study in 426 post-menopausal women with an intact uterus. Of the 426 subjects enrolled in the study, 363 (85.2%) subjects were randomised to once-daily oral doses of ospemifene 60 mg and 63 (14.8%) subjects were randomised to placebo. The mean age of participants was 61.7 years in the ospemifene 60 mg group and 62.9 years in the placebo group.

Clinical efficacy

Physiological responses (objective measures)
Ospemifene (OSP) improved post-menopausal physiologic changes. In two separate 12 week pivotal trials (trials 15-50310 and 15-50821), ospemifene was associated with a statistically significant mean decrease from baseline in the percentage of parabasal cells and vaginal pH and a statistically significant mean increase from baseline in the percentage of superficial cells, compared with placebo (P<0.001 for each parameter) at weeks 4 and 12. This improvement in objective measures (superficial and parabasal cells and pH) were sustained in ospemifene treated women in a long-term study of up to 52 weeks. The magnitude of effect was similar in all three trials (trials 15-50310 and 15-50821 and 15-50718).

Symptoms (subjective measures)
The most bothersome symptom (MBS) was assessed at baseline, 4 and 12 weeks with the severity scored as follows: None=0, Mild=1, Moderate=2, Severe=3. Table 2 shows the mean change in severity score in MBS after 12 weeks with the associated statistical testing for the difference vs. placebo for trials 15-50310 and 15-50821.

Table 2: Primary efficacy analysis - change from baseline to week 12 in most bothersome symptom (ITT, LOCF)

Study	Dryness			Dyspareunia		
	60 mg OSP	Placebo	p-value (P)	60 mg OSP	Placebo	p-value (P)

Trial 15-50310	-1.26	-0.84	0.021	-1.19	-0.89	0.023
Trial 15-50821	-1.3	-1.1	0.0803	-1.5	-1.2	0.0001

Table 3 shows the percentage of subjects who reported a change in their MBS at week 12.
"Improvement" was defined as a reduction in the severity score of 1 or more.
"Relief" was defined as no or only mild symptoms at week 12.
"Substantial improvement" was restricted to patients who had moderate or severe MBS at baseline and changed from severe to mild or severe or moderate to none.

Table 3. Percentage of patients with improvement, relief or substantial improvement of MBS after 12 weeks on ospemifene vs. placebo (ITT, LOCF)

	Improvement		**Relief**		**Substantial improvement**	
	60 mg OSP	**Placebo**	**60 mg OSP**	**Placebo**	**60 mg OSP**	**Placebo**
Trial 15-50310 Dryness	74.6%	57.7%	66.1%	49.0%	42.4%	26.9%
	P=0.0101		P=0.0140		P=0.0172	
Trial 15-50821 Dryness	70.6%	68.2%	61.9%	53.2%	46.3%	34.3%
	P=0.7134		P=0.1380		P=0.0385	
Trial 15-50310 Dyspareunia	68.3%	54.1%	57.5%	41.8%	40.8%	29.5%
	P=0.0255		P=0.0205		P=0.0799	
Trial 15-50821 Dyspareunia	79.9%	63.9%	63.0%	47.4%	52.8%	38.7%
	P=0.0000		P=0.0001		P=0.0006	

A trend was observed in both trials in the improvement of MBS from baseline to week 4 in favour of ospemifene compared to placebo, although the difference was not statistically significant.

Clinical safety

Across all placebo-controlled clinical trials of ospemifene, deep vein thrombosis occurred at a frequency of approximately 3.65 cases per 1000 patient years on 60 mg ospemifene (95% confidence interval of 0.44 to 13.19) versus 3.66 cases per 1000 patient years for placebo (95% confidence interval of 0.09 to 20.41; relative risk is 1.0).

Endometrial safety in women was assessed at baseline and 12 weeks in the two 12-week phase 3 studies (trials 15-50310 and 15-50821: ospemifene, n=302; placebo, n=301). For subjects completing the trial 15-50310 extension study (ospemifene, n=41; placebo, n=18) and for subjects in the long-term 52-week safety study (trial 15-50718: ospemifene, n=276; placebo, n=46), endometrial safety was assessed by endometrial biopsy at baseline and at 12 months. In total, there were 317 subjects on ospemifene and 64 subjects on placebo who had a baseline as well as a week 52 biopsy. No cases of endometrial hyperplasia were reported at either time point.

There was a single subject (0.3%) who developed endometrial hyperplasia in the ospemifene group (simple hyperplasia without atypia) 88 days after the last dose of study drug. No subjects in either group developed endometrial cancer or breast cancer during the trials. Across all placebo-controlled clinical trials, there was no significant difference in breast related adverse events between ospemifene and placebo. The incidence of abnormal, but not clinically significant, findings on breast palpation and mammography decreased in the ospemifene 60 mg population during the 1-year study (trial 15-50718) from 1.6% to 0.6% and from 11.8% to 8.1% respectively. In contrast, abnormal, not clinically significant, findings on mammography increased in the placebo population from 6.5% to 8.3%. There were no abnormal breast palpation findings in the placebo group at baseline or at study end.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ospemifene in all subsets of the paediatric population in VVA (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ospemifene is absorbed rapidly after oral administration, with a T_{max} of approximately 3 - 4 hours post-dose in the fed state. The absolute bioavailability of ospemifene has not been established. Mean ospemifene C_{max} and AUC_{0-24hr} were 785 ng/mL and 5448 ng•hr/mL, respectively, after repeat doses of 60 mg ospemifene once daily in the fed state.

When ospemifene is administered with a high fat meal, the C_{max} and AUC are 2.5-fold and 1.9-fold higher, respectively, with lower variability relative to the fasting state. A low fat meal resulted in approximately a two-fold increase in exposure of ospemifene and a high fat meal resulted in approximately a three-fold increase in exposure of ospemifene in two food effect studies with tablet formulations different from the commercial formulation. It is recommended that ospemifene should be taken with food at the same time each day.

Distribution

Ospemifene and 4-hydroxyospemifene are highly (both >99%) bound to serum proteins. Plasma/blood cell partitioning of [^{14}C]-Ospemifene (< 3%) and [^{14}C]-4-hydroxyospemifene (< 2%) is low. The apparent volume of distribution is 448 l.

Biotransformation

Ospemifene and its major metabolite, 4-hydroxyospemifene, are metabolised by multiple metabolic pathways, the main enzymes involved are UGT1A3, UGT2B7, UGT1A1 and UGT1A8, and CYP2C9, CYP3A4 and CYP2C19. The major metabolite, 4-hydroxyospemifene, was seen to undergo formation rate-limited elimination (with $t_{1/2}$ similar to the parent compound) in a human mass balance study. The principal radioactive component in both plasma and faeces was ospemifene and the main metabolite 4-hydroxyospemifene. Ospemifene and 4-hydroxyospemifene accounted for approximately 20% and 14% of the total radioactivity in serum,

respectively. The apparent total body clearance is 9.16 l/hr using a population approach.
In vitro, ospemifene and 4-hydroxyospemifene did not inhibit or induce the activity of CYP450 enzymes at clinically relevant concentrations. *In vitro*, ospemifene and 4-hydroxyospemifene inhibited glucuronidation via UGT1A3 and UGT1A9 at clinically relevant concentrations. In *in vitro* studies ospemifene is a weak inhibitor for CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6. Furthermore *in vitro* studies have shown that ospemifene is a weak inducer for CYP2B6 and CYP3A4. In *in vitro* studies, ospemifene and 4-hydroxyospemifene did not inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT2, organic anion transporter (OAT)1, OAT3, or bile salt export pump (BSEP) transporters at clinically relevant concentrations. It is unknown if ospemifene is a substrate for BCRP in the intestine. Therefore care should be taken if ospemifene is administered with a BCRP inhibitor.

Elimination

The apparent terminal half-life of ospemifene in post-menopausal women is approximately 25 hours. Following oral administration of [^{3}-H]-ospemifene in the fasted state, approximately 75% and 7% of the dose was excreted in faeces and urine respectively. Less than 0.2% of the ospemifene dose was excreted unchanged in urine. Following a single oral administration of 60 mg ospemifene in the fed state, 17.9%, 10.0% and 1.4% of the administered dose was excreted in faeces as ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene, respectively. The fate of remaining fraction is unknown but can probably be explained by formation of glucuronide metabolites.

Linearity/non-linearity

Ospemifene exhibits linear pharmacokinetics in the fed state within the dose range of 60 mg to 240 mg.

Special populations

Age
No clinically meaningful differences in ospemifene pharmacokinetics have been observed over the age range studied (40-80) years of age. No dose adjustment is necessary in elderly patients.

Paediatric population
Pharmacokinetic studies have not been performed with ospemifene in the paediatric population.

Renal impairment
Renal clearance of unchanged active substance is a minor pathway of elimination, less than 0.2% of the ospemifene dose is excreted unchanged in urine. In patients with severe renal impairment the ospemifene exposure was increased by approximately 20%, when compared to healthy matched subjects. No clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects were observed. This difference is not considered clinically relevant and no dose adjustment is necessary in patients with renal impairment.

Hepatic impairment
Ospemifene is primarily metabolised by the liver. The pharmacokinetics of ospemifene is only mildly affected by mild and moderate hepatic impairment (Child

Pugh scores 5-9) when compared to healthy matched controls. In patients with moderate hepatic impairment the exposure of ospemifene and 4-hydroxyospemifene was approximately 30% and 70% higher. These changes in pharmacokinetics of ospemifene by moderate hepatic impairment are not considered to be clinically significant in consideration of inherent pharmacokinetic variability of ospemifene. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of ospemifene has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class score >9).

Gender
Senshio is indicated for use only in post-menopausal women.

Race
Pharmacokinetic differences due to race have been studied in 1,091 post-menopausal women, including 93.1% White, 3.9% Black, 1.8% Asian and 1.1% other in VVA trials. There were no discernible differences in ospemifene plasma concentrations among these groups; however, the influence of race cannot be conclusively determined.

CYP2C9 poor metabolisers
Both CYP2C9 and CYP3A4 are involved in the metabolism of ospemifene. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the AUC of ospemifene by 1.4-fold. In CYP2C9 poor metabolizers, co-administration of CYP3A4 inhibitors may increase systemic concentration of ospemifene to a larger extent. Therefore, co-administration of ospemifene with strong/moderate CYP3A4 inhibitors should be avoided in patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates.

5.3 Preclinical safety data

In repeated dose toxicity studies in mice, rats, dogs and cynomolgus monkeys the main target organs of toxicity were the ovary, uterus and the liver. Ospemifene-related changes included ovarian follicular cysts, endometrial stromal atrophy and endometrial hypertrophy/hyperplasia which are consistent with the pharmacologic activity of ospemifene in the intact, normally cycling animal. In the liver hepatocyte hypertrophy or increased glycogen storage, increase in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were observed. Overall, these findings are characteristic for an induction of CYP isoenzymes and are regarded as adaptive responses without any histopathological signs of liver injury. No changes in blood biochemical parameters such as ALT or ALP were determined in post-menopausal women treated with ospemifene in clinical studies. Taken together, the liver changes observed in experimental animals in repeated dose toxicity studies are regarded as adaptive changes due to enzyme induction and given the lack of any clinical signs are unlikely to represent a safety concern for humans.

Ospemifene was not mutagenic or clastogenic when evaluated in a standard battery of *in vitro* and *in vivo* tests.

In a 2-year carcinogenicity study in female mice, ospemifene caused treatment related increases in neoplastic findings in the adrenal gland and ovary. Systemic exposure (AUC) at these doses was 2.1-, 4.0- and 4.7-times the AUC in post-menopausal woman administered 60 mg/day. In the adrenal gland, there was an increased

incidence of adrenal subcapsular cell and adrenal cortical tumours in animals dosed at high dose. In the ovary, there was an increase in sex-cord stromal tumours, tubulostromal tumours, granulosa cell tumours and luteomas in all treatment groups.

In a 2-year carcinogenicity study in rats, a clear increase in mostly benign thymic tumours was recorded at all ospemifene dose levels. This effect was likely due to the anti-oestrogenic effect of ospemifene in this target tissue, which was attenuating the physiological thymic involution (atrophy) process induced by oestrogens starting during puberty. In the liver, an increase in hepatocellular tumours were recorded at all ospemifene dose levels. Systemic exposure (AUC) at the administered doses was 0.3-, 1.0- and 1.2-times the AUC in post-menopausal women administered 60 mg/day.

Overall, tumour development in these studies is believed to be the result of rodent specific hormonal mechanisms when treated during their reproductive lives; these findings are unlikely to have any clinical relevance in post-menopausal women.

Ospemifene was not teratogenic in rats or rabbits. In a two-generation reproductive study on pre-and post-natal development ospemifene induced an increased post-implantation loss, an increased number of dead pups at birth as well as an increased incidence of postnatal loss of pups in the F1 generation. In the F0 maternal generation, a significant prolonged gestation was observed. However, all exposures were far below the intended human exposure. The reproductive effects observed are considered to be related to oestrogen receptor activity of ospemifene. Fertility studies were not conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Colloidal silicon dioxide (E 551)
Magnesium stearate (E 578)
Mannitol (E 421)
Microcrystalline cellulose (E 460)
Povidone (E 1201)
Pregelatinised starch (maize)
Sodium starch glycolate (type A)

Film coating
Hypromellose (E 464)
Lactose monohydrate
Titanium dioxide (E 171)
Triacetin (E 1518)
Macrogols (E 1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 Years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC-Aluminium blister. Pack sizes of 7, 28 or 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Herengracht 464
1017 CA Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 50999/0001

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