New Medicine Assessment

Ospemifene 60mg tablets (Senshio®▼)

For The Treatment Of Moderate To Severe Symptomatic Vulvar And Vaginal Atrophy (VVA) In Post-Menopausal Women Who Are Not Candidates For Local Vaginal Oestrogen Therapy

Recommendation:

Black. Ospemifene is considerably more expensive than other products available to treat vulvar and vaginal atrophy. No direct evidence is available to make comparison with currently available products.

Summary of supporting evidence:

- Ospemifene is the first oral treatment for VVA and provides an alternative treatment for patients unsuitable for vaginal oestrogens (including where treatment is deemed inconvenient, messy or exposing a partner to an acceptable risk of vaginal oestrogen).
- No active comparators were included in the pivotal trials for ospemifene, although an indirect comparison of ospemifene with vaginal oestrogens demonstrated similar magnitudes of effects relative to placebo.
- Statistical superiority of ospemifene to placebo for improvement in the most bothersome symptom "vaginal dryness" was only demonstrated in one of the two pivotal trials. However, both studies permitted the use of non-hormonal lubricants in all patient groups making superiority for vaginal dryness symptoms more difficult to demonstrate.
- Increased risk of venous thromboembolism (VTE) cannot be excluded due to the wide confidence intervals of the VTE safety data submitted to the EMA and observed increases in VTEs across the SERMs drug class.
- Assuming that no active switching occurs of the approximately 14,000 patients already receiving treatment for VVA and 5-30% of the 7,350 remaining eligible patients were treated with ospemifene for a full year (annual cost of ospemifene 60mg tablets = £514.68), the total annual acquisition cost of ospemifene for the Lancashire and South Cumbria CCGs would be:

368 patients to 2,205 patients X £514.68 = **£189,000 to £1,135,000**

Date: March 2019

Details of Review

Name of medicine (generic & brand name)**:** Ospemifene (Senshio®)

Strength(s) and form(s): 60mg tablets

Dose and administration: 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. [1]

BNF therapeutic class / mode of action: Selective oestrogen receptor modulator (SERM)

Licensed indication(s): The treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy

Proposed use (if different from, or in addition to, licensed indication above):

Course and cost:

A box of 28 tablets = £39.50; annual cost of treatment = £514.91

Current standard of care/comparator therapies:

- Vagifem® 10µg vaginal tablets – cost of 24 tablets = £16.72
  Annual cost (assuming one tablet daily for two weeks then one tablet twice weekly thereafter) = £79.42
- Ovestin® cream 15g = £4.45
  Annual cost assuming wastage and one applicator dose daily for 2 weeks, then decrease to twice weekly thereafter) = £17.80
- Estring® vaginal ring – cost = £31.42
  Annual cost (inserted every 3 months) = £125.68

Relevant NICE guidance:

NICE guideline NG23 - Menopause: diagnosis and management [2]

Urogenital atrophy

1.4.9 Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms.

1.4.10 Consider vaginal oestrogen for women with urogenital atrophy in whom systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause.

1.4.11 If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause.

1.4.12 Explain to women with urogenital atrophy that:

symptoms often come back when treatment is stopped adverse effects from vaginal oestrogen are very rare they should report unscheduled vaginal bleeding to their GP.

1.4.13 Advise women with vaginal dryness that moisturisers and lubricants can be used alone or

in addition to vaginal oestrogen.

1.4.14 Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy.

Background and context

Vulvovaginal atrophy (VVA) is a common and underreported condition associated with decreased oestrogenisation of the vaginal tissue. Symptoms include dryness, irritation, soreness, and dyspareunia with urinary frequency, urgency, and urge incontinence. It can occur at any time in a woman's life cycle, although more commonly in the postmenopausal phase, during which the prevalence is close to 50%. [3] During menopause, the ratio of the three vaginal epithelial cell types (parabasal, intermediate, and superficial) changes. The proportion of these vaginal cell types is categorised by the vaginal maturation index (VMI). The VMI provides an objective assessment of vaginal hormone response as well as overall hormonal environment. [4] Increasing progression from parabasal to superficial epithelial cells is a characteristic of increasing oestrogenisation of the vaginal tissue.

Treatment goals for VVA include alleviating symptoms, reversing or minimising the physiologic changes, and improving quality of life for the patient. There are:

- Non-hormonal treatments: A number of over-the-counter (OTC) vaginal moisturiser and lubricant products are considered first-line non-hormonal treatments for vaginal dryness. This option can be appropriate for women concerned about hormone use, those with minimal physiologic changes or symptoms, or those who are not candidates for oestrogen treatment.
- Hormonal treatments: Local, low-dose oestrogen preparations to be applied vaginally are considered first-line pharmacologic treatment (Royal College of Obstetricians and Gynaecologists Guideline Menopause and Hormone Replacement). The guideline further states: “There is no evidence that local vaginal oestrogen treatment is associated with significant risks”. These preparations include: Vagifem® 10 mg (estradiol tablets for vaginal application), Estring® (estradiol in vaginal ring) and Ovestin® (estriol cream for vaginal application). [5]

Summary of evidence

Summary of efficacy data in proposed use:

Four double-blind, placebo-controlled clinical studies were submitted in support of the efficacy of Ospemifene for the treatment of VVA, one Phase 2 and three Phase 3 studies. [6] [7] [8]

From the three main studies, two 12-week studies [6] [7] were considered the most important for efficacy. Long-term efficacy data were collected from the double-blind long-term (52 weeks) safety study. [8] Participants of the studies were post-menopausal women aged 40-80 years with a vaginal pH of greater than 5.0%; and 5% or fewer superficial cells in the vaginal maturation index (VMI). The use of non-hormonal lubricants was permitted in all patient groups in the 12-week studies. No active comparator groups were included in any of the phase 2/3 studies submitted to the EMA. Consequently, an indirect comparison between ospemifene and local oestrogens (Vagifem® 10mg) was provided to the EMEA.

Pivotal studies

Bachmann et al study [6]

This was a randomised, double-blind phase 3 study in which 826 postmenopausal women were randomised 1:1:1 to receive treatment with ospemifene 30 or 60 mg/day or placebo orally for 12

weeks. Analysis of efficacy included change from baseline to week 12 (primary efficacy) and to week 4 (secondary efficacy) in the following four coprimary endpoints: percentage of superficial cells on the vaginal smear, percentage of parabasal cells on the vaginal smear, vaginal pH, and self-assessed most bothersome moderate to severe symptoms (MBS) of vaginal dryness or dyspareunia (more specifically, vaginal pain associated with sexual activity).

After 12 weeks the percentage of superficial cells significantly increased in ospemifene 60mg group compared to placebo (10.8% versus 2.2%; P < 0.001). Similarly, the percentage of parabasal cells was significantly decreased in ospemifene 60mg group (30.1%) compared with an increase in the placebo group (3.98%; P <0.001).

After 12 weeks of treatment, the decrease in vaginal pH was 1.01 in the ospemifene 60 mg groups, compared with 0.10 in the placebo group (P < 0.001). In addition, a significant decrease in vaginal pH was observed after 4 weeks of treatment. Also, at 12 weeks the symptom score for participants reporting an MBS of vaginal dryness was significantly decreased in the ospemifene 60 mg groups (1.26) compared with the placebo group (0.84; P = 0.021 for the ospemifene 60 mg groups). The symptom score for participants reporting an MBS of dyspareunia was significantly decreased in the ospemifene 60 mg group (1.19) compared with the placebo group (0.89; P = 0.023). No significant differences between study groups were found at week 4 in the MBS of vaginal dryness or dyspareunia.

All women were provided with a nonhormonal lubricant for use as needed throughout the 12-week treatment period. During the first week of treatment, 33% of the placebo group and 36% of the ospemifene group participants used the lubricant. Towards the end of the treatment, the percentage of women using the lubricant was somewhat decreased in all study groups, but the decrease was more pronounced in the ospemifene 60 mg group. During the last week of treatment 22% and 29% of participants in the ospemifene 60 mg and placebo groups, respectively, were using the lubricant.

Portman et al study [7]

This multicentre phase 3 study used a randomised, double-blind, parallel-group design to compare the efficacy, safety, and tolerability of oral ospemifene 60 mg/day versus placebo. A total of 605 women aged 40 to 80 years who self-reported a most bothersome symptom of dyspareunia and had a diagnosis of VVA were randomised to take a once-daily dose of 60mg ospemifene (n = 303) or placebo (n = 302) for 12 weeks. The coprimary endpoints mirrored those assessed in the study by **Bachmann et al** [6].

After 12 weeks of treatment, the percentage of parabasal cells significantly decreased by 40.2% in the ospemifene group compared with no reduction in the placebo group (P < 0.0001). Similarly, the percentage of superficial cells significantly increased by 12.3% in the ospemifene group compared with 1.7% in the placebo group (P < 0.0001). During the same period, the mean reduction in vaginal pH in the ospemifene group (-0.94) was significantly greater than that in the placebo group (-0.07; P < 0.0001). The reduction in MBS severity score was also significantly different between the ospemifene group (-1.5) and the placebo group (-1.2; P = 0.0001), demonstrating efficacy in the treatment of VVA among the participants reporting dyspareunia as their MBS. Notably, the percentage of participants reporting no vaginal pain or mild vaginal pain with sexual activity on week 12 was greater in the ospemifene group (38.0% or 25.1%, respectively) than in the placebo group (28.1% or 19.2%, respectively). Also, the severity of vaginal pain on week 12 in the intention-to-treat population improved by two to three levels in 52.8% of participants in the ospemifene group compared with 38.8% of participants in the placebo group (a three-level improvement being a change from “severe” to “none”; a two-level improvement being either a change from “severe” to “mild” or from “moderate to none”).

During the first week of treatment, similar proportions of participants used lubricants (41.7% and 43.1% in the ospemifene and placebo groups, respectively). On week 12, the percentage of

women using lubricants somewhat decreased for both groups, but more so in the ospemifene group (35.1%) compared with the placebo group (39.3%). In contrast, the frequency of sexual activity remained consistent across the study groups from week 1 to week 12.

Other efficacy data:

Goldstein et al study [8]

In this 52-week, randomised, double-blind, placebo-controlled, parallel-group study, 426 women aged 40 – 80 years with VVA and an intact uterus were randomised 6:1 to ospemifene 60 mg/day or placebo. The primary objective was 12-month safety, particularly endometrial; however, 12-week efficacy was assessed. The primary efficacy assessments were changes from baseline to week 12 in the percentages of superficial cells and parabasal cells (VMI) and in vaginal pH in the vaginal smear sample.

For ospemifene, the median percentage of superficial cells was increased (5%, [CI95% 5.0, 7.0] versus 0% for placebo [CI95% 0, 0]) and the median percentage of parabasal cells was decreased (40% [CI95% 55.0, 30.0] versus 0% [CI95% 0, 5.0]) at week 12 ($p < 0.0001$ for both). Similarly, greater decreases in vaginal pH were seen with ospemifene 60 mg/day over placebo (-1.21 versus -0.16, $p < 0.0001$).

Bruyniks et al indirect comparison of ospemifene versus local oestrogens [9]

A literature search was carried out of clinical efficacy/safety trials of local vaginal oestrogens in VVA approved in Europe. For efficacy comparison, studies had to be placebo-controlled and of 12 weeks' duration. For safety comparison, studies had to be > 40 weeks' duration. Efficacy endpoints were the difference between active and placebo in change from baseline to week 12 for symptoms, vaginal pH, and maturation value (MV). Seven studies were identified and used for the comparison of efficacy.

The study authors concluded that the magnitudes of changes relative to placebo in both subjective and objective efficacy measures were similar to or greater with 60mg ospemifene than those observed with 10µg estradiol or estriol. The improvements in placebo-subtracted composite symptom scores at week 12 were similar for ospemifene vs. 10µg estradiol (MBS) and for ospemifene vs. estriol gel 0.005%. The percentages of women achieving a pH <5 or <5.5 with 60mg ospemifene relative to placebo were greater than that observed with 10µg estradiol relative to placebo. In the two estriol studies, the placebo-subtracted mean changes from baseline pH with an estriol pessary or estriol gel were comparable to those observed with ospemifene. The Maturation value for vaginal epithelial cells demonstrated improvements relative to placebo were similar or greater after 12 weeks for 60mg ospemifene vs.10µg estradiol and vs. estriol pessary/gel.

Summary of safety data:

According to the EPAR, 2471 study participants received at least one dose of Ospemifene. Treatment ranged from six weeks to 64 weeks in duration and evaluated doses of Ospemifene varying from 5 mg/day to 90 mg/day. 1242 subjects received 60 mg/day Ospemifene with a median duration of exposure to Ospemifene 60 mg of 86 days. Only 384 subjects were given Ospemifene 60 mg for more than 6 months and 191 subjects for more than 12 months.

Adverse Events

The most common treatment-related adverse events (TEAEs) reported by patients that participated in all of the double-blind placebo-controlled Phase 2/3 studies and who received Ospemifene were: hot flushes (7.5% for Ospemifene and 2.6% for placebo); vaginal discharge (3.7% for Ospemifene and 0.3% for placebo); and headache (3.1% for Ospemifene and 2.4% for

placebo).

Thirty-nine (2.3%) patients experienced a serious adverse event (SAE) compared to 17 (1.8%) in the placebo group, representing an exposure corrected rate of 57 SAEs/1000 women years exposure on Ospemifene and 62.3 SAEs/1000 women years exposure on placebo.

Thirty-two subjects (2.6%) experienced 41 SAEs of them 7 were considered by the manufacturer as drug related. In the placebo group, 17 subjects (1.8%) experienced 33 SAEs, from which 1 was considered drug related. SEAs reported in the Ospemifene group were cardiovascular accident, endometrial hyperplasia, ovarian cyst, deep vein thrombosis (two subjects), global amnesia and nausea.

The SPC for Senshio lists the following adverse events [1]:

Tabulated list of adverse reactions

Adverse 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).

Adverse reactions observed in pooled Phase 2 and 3 studies		
MedDRA system organ class	**Common**	**Uncommon**
Infections and infestations	Vulvovaginal candidiasis / mycotic infections	-
Vascular disorders	Hot flush	-
Musculoskeletal and connective tissue disorders	Muscle spasms	-
Reproductive system and breast disorders	Vaginal discharge, genital discharge	Endometrial hypertrophy[a] (sonographic endometrial thickness)
Post-marketing experience with ospemifene		
MedDRA system organ class	**Common**	**Uncommon**
Immune system disorders		Drug hypersensitivity[b], Hypersensitivity[b], swollen tongue
Nervous system disorders	Headache[c]	
Skin and subcutaneous tissue disorders	Rash (includes rash erythematous, rash generalised)	Pruritus Urticaria

[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.

Contraindications, precautions and interactions

Ospemifene is contraindicated in patients with current or past history of thromboembolic events including deep vein thrombosis, pulmonary embolism or retinal vein thrombosis; unexplained vaginal bleeding or signs and symptoms of endometrial hyperplasia; patients with suspected/active breast cancer or sex-hormone dependent malignancy (e.g. endometrial cancer) including patients undergoing active treatment (including adjuvant therapy for breast cancer);

patients with a hypersensitivity to the active substance or any of the ingredients in ospemifene.

As for other hormone-based treatments for VVA, ospemifene should only be initiated for symptoms that adversely affect the patient's quality of life e.g. dyspareunia and vaginal dryness. As endometrial thickening was noted in the clinical studies for ospemifene the SPC advises that if spotting or bleeding occurs or any additional gynaecological pathology is identified before, during or following treatment, this should be investigated to exclude endometrial malignancy. The incidences of venous thromboembolic events and cerebro-vascular events in the clinical studies were not higher than the expected background incidence, however the SPC warns that an increased risk of thromboembolic/cerebro-vascular events cannot be excluded as this is a class effect of selective oestrogen receptor modulators (SERMs).

Caution is recommended when co-administering ospemifene with fluconazole. If necessary, because of impaired tolerance, ospemifene should be stopped as long as treatment with fluconazole lasts. 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. 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. Inhibition of UGT1A3, UGT2B7, UGT1A1, or UGT1A8 may potentially affect the glucuronidation of ospemifene and/or 4-hydroxyospemifene.

Ospemifene may increase concentrations of medicinal products which are substrates of OCT1 (e.g. metformin, acyclovir, ganciclovir and oxaliplatin). The pharmacokinetics of drugs that are mainly metabolised by UGT1A3 and UGT1A9 could be affected when administered concomitantly with ospemifene and co-administration should be made with caution. Due to its lipophilic nature and absorption characteristics, caution is recommended when ospemifene is combined with orlistat. A clinical monitoring of a decrease in the efficacy of ospemifene should be made.

Strengths and limitations of the evidence:

Strengths

- Ospemifene is the first oral treatment for VVA and provides an alternative treatment for patients unsuitable for vaginal oestrogens (including where treatment is deemed inconvenient, messy or exposing a partner to an acceptable risk of vaginal oestrogen).
- Ospemifene demonstrated statistically significant improvements in the VMI, vaginal pH and the most bothersome symptom of "pain during sexual activity". This effect was maintained over 12 months.
- The safety profile of ospemifene was considered to be acceptable by the EMA. The upper limit of incidence of endometrial changes for ospemifene at 12 months was 1.7% (below the 2% level of incidence outlined by the EMA as acceptable).

Limitations

- No active comparators were included in the pivotal trials for ospemifene, although an indirect comparison of ospemifene with vaginal oestrogens demonstrated similar magnitudes of effects relative to placebo.
- Statistical superiority of ospemifene to placebo for improvement in the most bothersome symptom "vaginal dryness" was only demonstrated in one of the two pivotal trials. However, both studies permitted the use of non-hormonal lubricants in all patient groups making superiority for vaginal dryness symptoms more difficult to demonstrate.
- Increased risk of venous thromboembolism (VTE) cannot be excluded due to the wide confidence intervals of the VTE safety data submitted to the EMA and observed increases

in VTEs across the SERMs drug class.
- Uncertainty exists about ospemifene's action on the ovaries and whether there is an increased risk of ovarian cancer with ospemifene use.
- VVA is a chronic condition and the clinical studies for ospemifene only provide data for up to 15 months of treatment. There is uncertainty relating to the safety of ospemifene use beyond 15 months.

Summary of evidence on cost effectiveness:

No cost-effectiveness data is available for the use of ospemifene.

Prescribing and risk management issues:

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.

Commissioning considerations:

Comparative unit costs:

Drug	**Example regimen**	**Pack cost**	**Cost per patient per year (ex VAT)**
Senshio® (ospemifene) 60mg tablets	**One tablet daily**	**£39.50**	**£514.68**
Vagifem® 10µg vaginal tablets	Use one tablet daily for two weeks then one tablet twice weekly thereafter	£16.72	£79.42
Ovestin® cream 15g	one applicator dose daily for 2 weeks, then decrease to twice weekly thereafter	£4.45	£17.80 (assuming wastage)
Estring® vaginal ring	Insert every 3 months	£31.42	£125.68

Costs based on MIMS list prices January 2019.
This table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

None identified.

Productivity, service delivery, implementation:

N/A

Anticipated patient numbers and net budget impact:

Vaginal atrophy occurs in the majority of postmenopausal women, but not all will be symptomatic.

Large cohort studies have reported the prevalence of vaginal dryness in women from 27% to 55% and dyspareunia from 32% to 41%. Using data from ePACT2, it is estimated that approximately 14,000 patients are already being treated with existing vaginal hormonal products (Vagifem®, Ovestin® and Estring®). NICE estimates a total of 4.3 million post-menopausal women aged >50 in England but the manufacturer of ospemifene suggests up to 5% (210,000 women = 420/100,000 population approx.) may be eligible for the drug once available. [10]

Based on a population estimate of 1.75 million patients for Lancashire and South Cumbria, the number of patients eligible for ospemifene is **7,350**. Assuming that no active switching occurred of the approximately 14,000 patients already receiving treatment for VVA and 5-30% of the 7,350 remaining eligible patients were treated with ospemifene for a full year (annual cost of ospemifene 60mg tablets = £514.68), the total annual acquisition cost to the Lancashire and South Cumbria CCGs would be:

368 patients to 2,205 patients X £514.68 = **£189,000 to £1,135,000**

Innovation, need, equity:

Ospemifene is the first oral treatment for VVA and provides an alternative treatment for patients unsuitable for vaginal products or for who oestrogen is unsuitable.

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Senshio 60mg film-coated tablets," Shionogi, 23 July 2018. [Online]. Available: https://www.medicines.org.uk/emc/product/9417. [Accessed 15 January 2019].

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[4] R Hess et al, "Vaginal maturation index self-sample collection in mid-life women: acceptability and correlation with physician collected samples," *Menopause,* vol. 4, no. 1, pp. 726-729, 2008.

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[6] GA Bachmann et al, "Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study," *Menopause: The Journal of The North American Menopause Society,* vol. 17, no. 3, pp. 480-486, 2010.

[7] DJ Portman et al, "Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy," *Menopause: The Journal of The North American Menopause Society,* vol. 20, no. 6, pp. 623-630, 2013.

[8] SR Goldstein et al, "Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy," *Climacteric,* vol. 17, no. 2, pp. 173-182, 2014.

[9] N Bruyniks et al, “Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy,” *Climacteric,* vol. 20, no. 3, pp. 195-204, 2017.

[10] Specialist Pharmacy Service, “Ospemifene,” 17 January 2019. [Online]. Available: https://www.sps.nhs.uk/medicines/ospemifene/. [Accessed 21 January 2019].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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