Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-111-z (Prasteron)

Stand: Juli 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Prasteron **Behandlung der symptomatischen vulvovaginalen Atrophie** **Kriterien gemäß 5. Kapitel § 6 VerfO20**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verfahren nach § 35a SGB V: - Ospemifen (Beschluss vom 20.10.2016)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Prasteron ATC-Code <Noch nicht zugewiesen> Intrarosa®	Anwendungsgebiet laut Zulassung: Intrarosa wird angewendet zur Behandlung vulvärer und vaginaler Atrophie bei postmenopausalen Frauen mit mittelschweren bis schweren Symptomen.
G03C	**Estrogene**
G03CA	**Natürliche oder halbsynthetische Estrogene, rein**
Estradiol G03CA03 z.B. Estradiol 2 – 1A Pharma®	• Hormonsubstitutionstherapie (HRT) bei Estrogenmangelsymptomen nach der Menopause. HRT bei Estrogenmangelsymptomen bei Frauen, deren letzte Monatsblutung mindestens 12 Monate zurückliegt. • Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahre vor.
Estriol G03CA04 z.B. Ovestin®	Hormonsubstitutionstherapie (HRT) bei Estrogenmangelsymptomen nach der Menopause. Hinweise zu den Anwendungsgebieten - Das Arzneimittel ist nur zur Anwendung bei hysterektomierten Frauen bestimmt. - Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor. - Eine HRT sollte nur zur Behandlung solcher postmenopausaler Beschwerden begonnen werden, welche die Lebensqualität beeinträchtigen. - Nutzen und Risiken sollten in jedem Einzelfall mindestens jährlich sorgfältig gegeneinander abgewogen werden. - Eine HRT sollte nur so lange fortgeführt werden, wie der Nutzen die Risiken überwiegt. - Es liegen nur begrenzte Daten zur Bewertung der Risiken einer HRT bei vorzeitiger Menopause vor. Da jedoch das absolute Risiko bei jüngeren Frauen niedriger ist, könnte das Nutzen-Risiko-Verhältnis bei jüngeren Frauen günstiger sein als bei älteren.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Estradiol, Kombinationen G03CA53 Climen®	1. Hormonsubstitutionstherapie (HRT) bei peri- und postmenopausalen Estrogenmangelsymptomen. 2. Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen. Hinweise zu den Anwendungsgebieten - Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor. - Eine HRT sollte nur zur Behandlung solcher postmenopausaler Beschwerden begonnen werden, welche die Lebensqualität beeinträchtigen. - Nutzen und Risiken sollten in jedem Einzelfall mindestens jährlich sorgfältig gegeneinander abgewogen werden. - Eine HRT sollte nur so lange fortgeführt werden, wie der Nutzen die Risiken überwiegt. - Das Arzneimittel ist nicht zur Schwangerschaftsverhütung bestimmt. Zur Kontrazeption sind gegebenenfalls nichthormonale Methoden (mit Ausnahme der Kalendermethode nach Knaus-Ogino und der Temperaturmethode) anzuwenden.
Konjugierte Estrogene G03CA57 Presomen® 28/06mg	Hormonsubstitutionstherapie (HRT) bei Estrogenmangelsymptomen nach der Menopause. Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen.
G03CD	**Estrogene, vaginale Zubereitungen**
Estriol G03CD01 z.B. Ovestin® 1 mg Creme	Therapie (bei Estrogenmangel): – Entzündliche Veränderungen der Scheidenhaut mit Gewebeschwund (während und nach den Wechseljahren); – Schmerzen beim Geschlechtsverkehr wegen trockener Scheide; – Ausfluss bei Estrogenmangel; – Juckreiz an den Schamlippen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Estradiol G03CD03 z.B. Gynokadin® Gel; Estring® Vaginalinsert	Gynokadin® - Zur Behandlung von durch Beschwerden bei nachlassender Estradiolproduktion der Eierstöcke in und nach den Wechseljahren bzw. nach Ovarektomie (klimakterisches Syndrom), - zur Behandlung von durch Estrogenmangel bedingten Rückbildungserscheinungen an den Harn- und Geschlechtsorganen. Die alleinige Anwendung dieses Arzneimittels (ohne regelmäßigen Zusatz von Gestagenen) zur Behandlung in den Wechseljahren und auch danach darf jedoch nur bei hysterektomierten Frauen erfolgen. Estring® Lokale Behandlung von durch Estrogenmangel verursachten postmenopausalen Beschwerden des Genitaltrakts, wie z. B. trockene Scheide, verursacht durch atrophische Vaginitis mit oder ohne Pruritus vulvae. Estring ist nur zur Behandlung örtlicher Beschwerden vorgesehen. Bei sonstigen körperlichen Beschwerden der Wechseljahre (Hitzewallungen) oder zur Verhütung der Verminderung von Knochengewebe (Osteoporoseprophylaxe) ist Estring nicht geeignet.
Estradiol, Kombinationen G03CD51 z.B. Gynoflor®	1. Atrophische Vaginitis bei post-menopausalen Frauen. 2. Anschlussbehandlung nach anti-infektiver Therapie von Vaginalinfektionen (von z.B. bakterieller Vaginose, Trichomoniasis, Candidose), wenn nach Infektsanierung Symptome (z.B. Fluor) persistieren.
G03CX	**Andere Estrogene**
Tibolon G03CX01 Liviella®	Behandlung von Estrogenmangelsymptomen bei postmenopausalen Frauen, bei denen die Menopause mehr als ein Jahrzurückliegt. Bei allen Frauen sollte einer Entscheidung, Liviella zu verschreiben, eine Bewertung der Gesamtrisiken der individuellen Patientin zugrunde gelegt werden. Insbesondere bei Frauen über 60 Jahre sollte auch das Schlaganfallrisiko berücksichtigt werden
G03FA	**Gestagene und Estrogene, fixe Kombinationen**
Estradiol + Dienogest G03FA Climodien®	Hormonsubstitutionstherapie (HRT) zur Behandlung von Estrogenmangelsymptomen bei postmenopausalen nicht hysterektomierten Frauen, deren Menopause länger als ein Jahr zurückliegt. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor.
Estradiol + Norethisteron G03FA01 Estramon®	Hormonsubstitutionstherapie (HRT) zur Behandlung von Estrogenmangelsymptomen bei postmenopausalen Frauen, deren Menopause länger als ein Jahr zurückliegt. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor. Stand Dezember 2018

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Drospirenon und Drospirenon G03FA17 Angeliq®	Hormonsubstitutionstherapie (HRT) bei Estrogenmangelsymptomen bei postmenopausalen Frauen, deren Menopause mehr als 1 Jahr zurückliegt. Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor
G03FB	**Gestagene und Estrogene, Sequentialpräparate**
Estradiol + Estriol + Levonorgestrel G03 FB Cycloöstrogynal®	Hormonsubstitutionstherapie (HRT) bei Estrogenmangelsymptomen bei Frauen, deren letzte Monatsblutung mindestens 6 Monate zurückliegt. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor.
Estradiolvalerat + Levonorgestrel G03 FB09 Cyclo-Progynova®	Hormonsubstitutionstherapie bei Estrogenmangelsymptomen nach der Menopause. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-111-z (Prasteron)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
VVA	vulvovaginale Atrophie

Indikation

Intrarosa wird angewendet zur Behandlung vulvärer und vaignaler Atrophie bei postmenopausalen Frauen mit mittelschweren bis schweren Symptomen.

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation: *vulvovaginale Atrophie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 107 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 3 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Ergebnisse

G-BA Beschlüsse/IQWiG Berichte

G-BA, 2016 [1].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ospemifen vom 20. Oktober 2016

Anwendungsgebiet:

„Senshio® ist angezeigt zur Behandlung der mittelschweren bis schweren symptomatischen vulvovaginalen Atrophie (VVA) bei postmenopausalen Frauen, bei denen eine lokale vaginale Estrogentherapie nicht in Frage kommt (siehe Abschnitt 5.1 der Fachinformation).“

Zweckmäßige Vergleichstherapie

Für jede Patientin ist eine patientenindividuelle Nutzen-/Schadenabwägung unter Berücksichtigung weiterer Symptome vorzunehmen.

Die zweckmäßige Vergleichstherapie für Ospemifen zur Behandlung der mittelschweren bis schweren symptomatischen vulvovaginalen Atrophie (VVA) bei postmenopausalen Frauen, bei denen eine lokale vaginale Östrogentherapie nicht in Frage kommt, ist:

Best-Supportive-Care

oder

eine systemische Hormontherapie (bei Frauen mit intaktem Uterus (Estrogen/Gestagen Kombination) bzw. bei Frauen ohne Uterus (nur Estrogen))

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

Cochrane Reviews

Lethaby, A. et al., 2016 [2].

Local oestrogen for vaginal atrophy in postmenopausal women (Review)

Fragestellung

The objective of this review was to compare the efficacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women.

Methodik

Population:

Postmenopausal women, who had not menstruated for more than 12 months or who had a serum follicle stimulating hormone (FSH) level >= 40 IU/L were eligible for inclusion. Women who had undergone bilateral oophorectomy (removal of both ovaries) were also eligible for inclusion.Women with intercurrent major disease or who had had previous hormone therapy (HT) within three months of commencement of the study were excluded.

Intervention/Komparator:

Trials comparing oestrogen supplementation administered intravaginally versus any other active intervention or placebo were eligible for inclusion. These included creams or gels, tablets, vagitories, ovules, pessaries, and an oestradiol-releasing ring. Duration of treatment must have been at least three months, as this treatment duration should be sufficient to improve vaginal symptoms. For the purpose of the review vagitories, ovules and pessaries were termed as vaginal tablets.

Endpunkte:

Improvement in symptoms as assessed by participants

Endometrial thickness

Improvement in symptoms as assessed visually by clinicians

Improvement in symptoms as assessed by clinicians using laboratory parameters

Other adverse events

Adherence to treatment

Recherche/Suchzeitraum:

all published and unpublished RCTs of studies comparing intra-vaginal oestrogen supplementation with any other active intervention or placebo, without language restriction and in consultation with the Gynaecology and Fertility Group Information Specialist

several databases, trial registers and websites

handsearch reference list of retrieved articles

date of last search: 12 April 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

30 studies (31 references) studying 6235 postmenopausal women

24 studies included in quantitative meta-analysis

Charakteristika der Population:

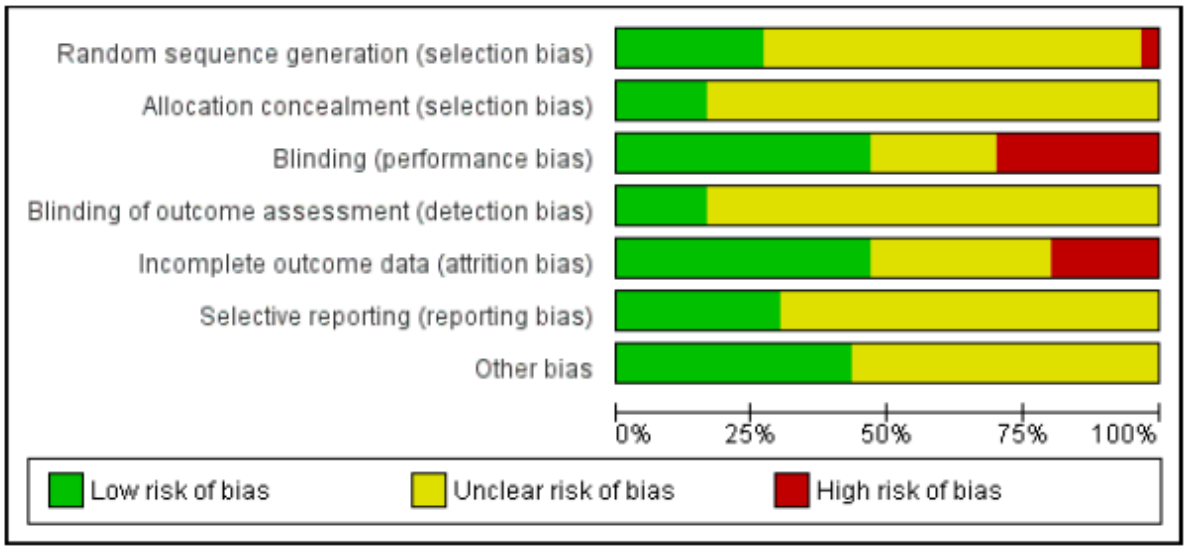
mean age across studies ranged from 45 to 66 years.

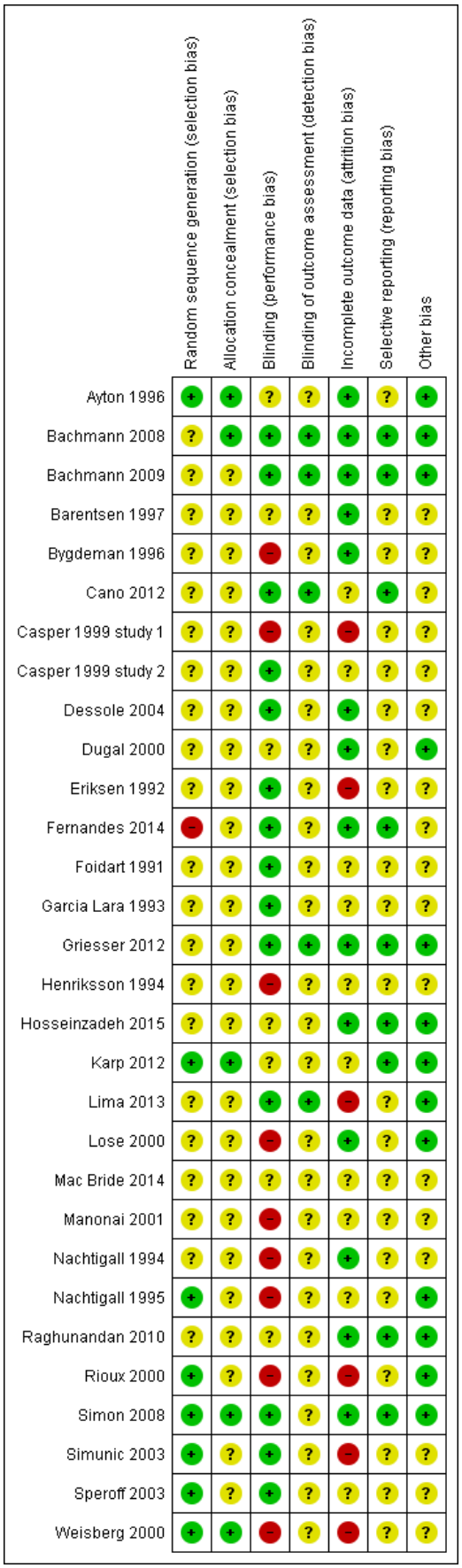
Most of the included trials required that women had any, or all symptoms of urogenital atrophy: vaginal dryness with or without dyspareunia, pruritus, dysuria and or urgency; and signs of atrophic vaginitis, including: pallor (pale appearance to skin), petechiae, friability (fragile and delicate skin) and dryness.

Other inclusion criteria included being naturally menopausal for at least one year, or surgically menopausal (bilateral oophorectomy) for at least one year.

Qualität der Studien:

The main limitations of the evidence were poor reporting (a majority of the included studies had most risk of bias domains assessed as unclear due to insufficient information).



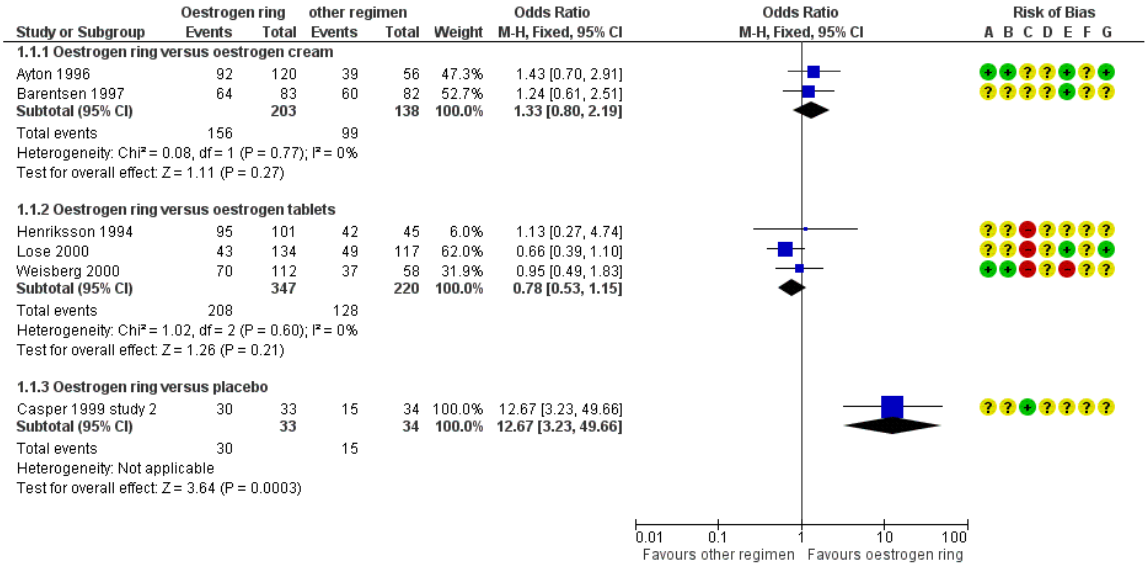

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Ayton 1996
Bachmann 2008
Bachmann 2009
Barentsen 1997
Bygdeman 1996
Cano 2012
Casper 1999 study 1
Casper 1999 study 2
Dessole 2004
Dugal 2000
Eriksen 1992
Fernandes 2014
Foidart 1991
Garcia Lara 1993
Griesser 2012
Henriksson 1994
Hosseinzadeh 2015
Karp 2012
Lima 2013
Lose 2000
Mac Bride 2014
Manonai 2001
Nachtigall 1994
Nachtigall 1995
Raghunandan 2010
Rioux 2000
Simon 2008
Simunic 2003
Speroff 2003
Weisberg 2000

Studienergebnisse:

Oestrogen ring versus other regimens

Improvement in symptoms (participant-assessed at end point)

Figure 4. Forest plot of comparison: 1 Oestrogen ring versus placebo or other regimens, outcome: 1.1 Improvement in symptoms (participant-assessed at end point).



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Endometrial thickness

A higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs, n = 273; I_2 = 0%, low-quality evidence).

Improvement in symptoms (clinician-assessed at end point)

There was no difference in improvement in symptoms for the following comparisons:

- Oestrogen ring versus oestrogen cream
- Oestrogen ring versus oestrogen tablets
- Oestrogen ring versus placebo

Improvement in symptoms (decrease in vaginal pH at end point)

There was no difference in improvement in symptoms for the following comparisons:

- Oestrogen ring versus oestrogen cream
- Oestrogen ring versus oestrogen tablets
- Oestrogen ring versus placebo

Improvement in symptoms (increase in maturation indices at end point)

- Oestrogen ring versus oestrogen cream: no difference in improvement

- Oestrogen ring versus oestrogen tablets and Oestrogen ring versus placebo: not estimable (no usable data)

Adverse events (breast disorders)

There was no evidence of a difference in the proportions for following comparisons:

- Oestrogen ring versus oestrogen cream
- Oestrogen ring versus tablets

Adverse events (total adverse events)

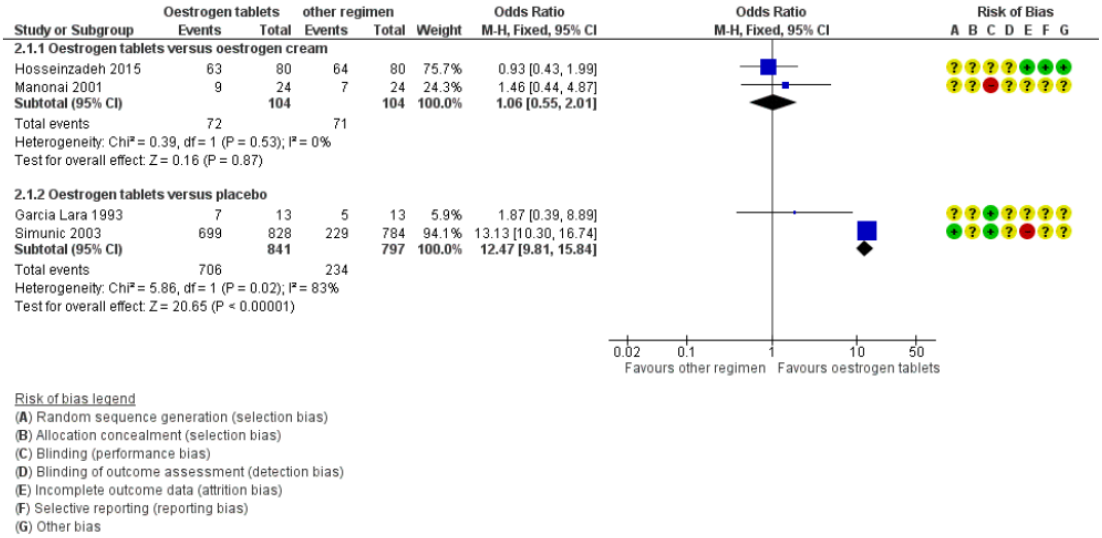
There was no evidence of a difference in the proportions for following comparisons

- Oestrogen ring versus oestrogen cream
- Oestrogen ring versus placebo

Oestrogen tablets versus other regimens

Improvement in symptoms (participant-assessed at end point)

Figure 5. Forest plot of comparison: 2 Oestrogen tablets versus placebo or other regimens, outcome: 2.1 Improvement in symptoms (participant-assessed at end point).



Endometrial thickness

- Oestrogen tablets versus oestrogen cream: there was no evidence of a difference in the proportions

Improvement in symptoms (clinician-assessed at end point)

- Oestrogen tablets versus oestrogen cream: There was no evidence of a difference in the proportions
- Oestrogen tablets versus placebo: A higher proportion of women who were treated with oestrogen tablets showed evidence of improvement in symptoms when compared to those who received placebo (OR 12.85, 95% CI 10.39 to 15.89, four RCTs, n = 2078, I2 = 93%, low-quality evidence).

Improvement in symptoms (decrease in vaginal pH at end point)

- Oestrogen tablets versus oestrogen cream: There was no evidence of a difference in improvement in symptoms

- Oestrogen tablets versus placebo: Women who were treated with oestrogen tablets demonstrated evidence of improvement in symptoms with a lowermean difference (MD) in vaginal pH (better outcome) compared with those who received placebo (MD -0.95, 95% CI -1.10 to -0.80, three RCTs, n = 524, I2 = 40%).

Improvement in symptoms (increase in maturation indices at end point)

- Oestrogen tablets versus oestrogen cream: There was no evidence of a difference in improvement
- Oestrogen tablets versus placebo: Women who were treated with oestrogen tablets demonstrated evidence of improvement in symptoms with a higher mean difference in maturation indices (better outcome) compared with those who received placebo (MD 18.63, 95% CI 14.57 to 22.69, two RCTs, n = 436, I2 = 72%)

Adverse events (breast disorders)

- Oestradiol tablets versus oestriol tablets: There was no evidence of a difference in the proportions of women with breast disorders between the two treatment groups

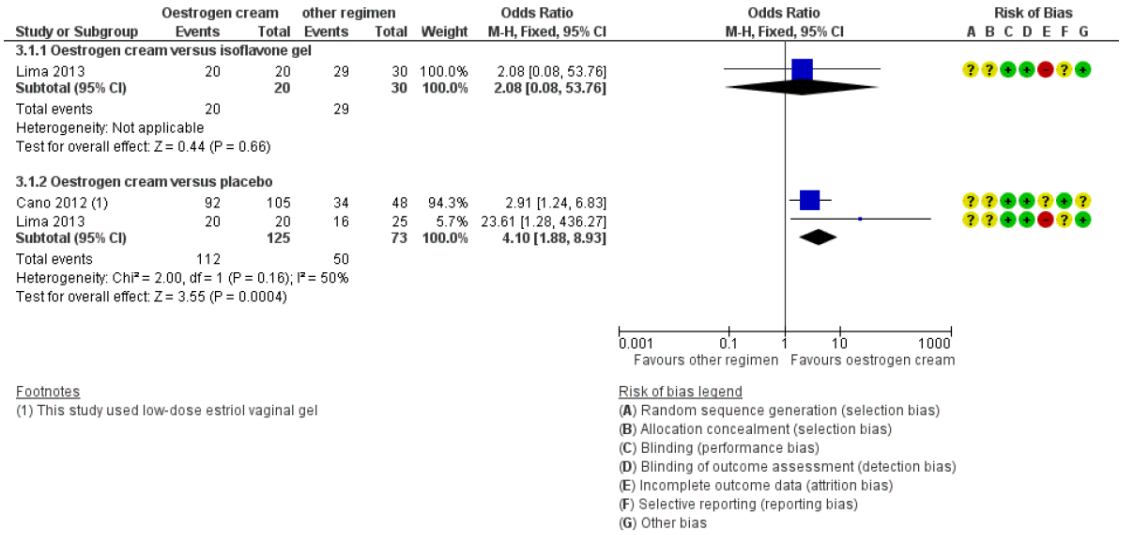
Adverse events (total adverse events)

- Oestrogen tablets versus placebo: There was no evidence of a difference in the proportions of women with total adverse events between the two treatment groups

Oestrogen cream versus other regimens

Improvement in symptoms (participant-assessed at end point)

Figure 6. Forest plot of comparison: 3 Oestrogen cream versus placebo or other regimens, outcome: 3.1 Improvement in symptoms (participant-assessed at end point).



Endometrial thickness

- This outcome was not reported by any of the included studies.

Improvement in symptoms (clinician-assessed at end point)

- Oestrogen cream versus placebo: A higher proportion of women who were treated with oestrogen cream demonstrated improvement in symptoms as assessed by the clinicians, compared to those who received placebo (OR 3.29, 95% CI 1.47 to 7.36, one RCT, n = 153, low-quality evidence)

Improvement in symptoms (decrease in vaginal pH at end point)

- Oestrogen cream versus non-hormonal local bio adhesive vaginal moisturising gel: There was evidence of a lower mean difference value (better outcome) in women who received oestrogen cream compared with those who were treated with non-hormonal local bio adhesive vaginal moisturising gel
- Oestrogen cream (21 days) versus placebo (21 days): Women who were treated with oestrogen cream daily for 21 days demonstrated evidence of improvement in symptoms with a lower mean difference in vaginal pH (better outcome) compared with those who received placebo for the same number of days (MD -1.20, 95% CI -1.47 to -0.93, one RCT, n = 215).
- Oestrogen cream (twice weekly) versus placebo (twice weekly): There was evidence of a lower mean difference value (better outcome) in women who received oestrogen creamtwice weekly compared with those who were treated with placebo twice weekly (MD -1.30, 95% CI -1.58 to -1.02, one RCT, n = 208).
- Oestriol gel (50 ug) versus placebo: Women who were treated with oestriol gel (50 ug) demonstrated evidence of improvement in symptoms with a lower mean difference in vaginal pH (better outcome) compared with those who received an equivalent dose of placebo (MD -0.80, 95% CI -1.23 to -0.37, one RCT, n = 153).

Improvement in symptoms (increase in maturation indices at end point)

- Oestrogen cream versus placebo: Women who were treated with oestrogen cream demonstrated evidence of improvement in symptoms with a higher mean difference in maturation indices (better outcome) compared to those who received placebo (MD 23.70, 95% CI 17.25 to 30.15, one RCT, n = 153).

Adverse events (breast disorders)

- None of the included studies reported this outcome

Adverse events (total adverse events)

- Oestrogen cream versus non-hormonal lubricant gel: There was no evidence of a difference in the proportions

Anmerkung/Fazit der Autoren

There was no evidence of a difference in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there was low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There was low-quality evidence that oestrogen cream may be associated with an increase in endometrial thickness compared to oestrogen ring; this may have been due to the higher doses of cream used. However there was no evidence of a difference in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo.

Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

Leitlinien

NICE, 2015 [3].

National Institute for Health and Care Excellence

Menopause, Version 1.5

Leitlinienorganisation/Fragestellung

Verschiedene Fragen wurden formuliert

Relevante Fragestellung: What is the clinical effectiveness of local oestrogens and ospemifene compared with placebo for menopause-related vaginal/urogenital atrophy?

Methodik

Grundlage der Leitlinie

Gremium: A multidisciplinary Guideline Development Group comprising healthcare professionals and researchers as well as lay members developed this guideline

The group met every 4 to 6 weeks during the development of the guideline. At the start of the guideline development process all group members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent group meetings, members declared arising conflicts of interest.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed

Critical appraisal of the evidence using the appropriate checklist

Summaries of evidence were generated by outcome and were presented in Guideline Development Group meetings

Of all data extracted, 80% was quality assured by a second reviewer and 50% of the GRADE quality assessment was quality assured by a second reviewer to minimise any potential risk of reviewer bias or error

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally, in an economic model, or informally.

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document.

Recherche/Suchzeitraum:

Where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in MEDLINE, Embase and The Cochrane Library. All searches were updated on 22 January 2015

LoE

Table 4: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 5: Levels of quality elements in GRADE level

Levels of quality elements in GRADE level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 6: Overall quality of outcome evidence in GRADE Level

Overall quality of outcome evidence in GRADE level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GoR

There are three levels of certainty:

recommendations for interventions that must (or must not) be used

recommendations for interventions that should (or should not) be used

recommendations for interventions that could be used.

NICE reflects the strength of the recommendation in the wording (see section 9.2). NICE uses 'offer' (or words such as 'measure', 'advise', or 'refer') to reflect a strong recommendation,

usually where there is clear evidence of benefit. NICE uses 'consider' to reflect a recommendation for which the evidence of benefit is less certain.

Sonstige methodische Hinweise

The majority of evidence was of moderate to very low quality. Different dosages of local oestrogens were used but data were too limited to allow further subgroup analyses. There was a paucity of information for any long-term follow-up data longer than 1 year of treatment, therefore the results of the included studies should be interpreted with caution given the unknown long-term efficacy and safety of this treatment. Selection bias, mainly due to no reporting of details on allocation concealment, inconsistency and imprecision, were the main domains downgraded in GRADE quality assessment.

8.3.7.6 Key conclusions

The Guideline Development Group concluded that vaginal local oestrogens were found effective in relieving symptoms in the short term and long term for women in menopause with urogenital atrophy without risking the safety outcomes for this population.

Empfehlung 1 (Empfehlungsgrad)

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

Empfehlung 2 (Empfehlungsgrad)

27. 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.

Empfehlung 3 (Empfehlungsgrad)

28. 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.

Empfehlung 4 (Empfehlungsgrad)

30. Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.

Evidenzbasis

Nine studies in total were included in this review comparing local oestrogens with placebo; three were RCTs (Dessole 2004, Casper 2009, Eriksen 1992) included in the systematic review by Suckling (2010) and 6 additional RCTs (Bachmann 2008, Bachmann 2009, Cano 2012, Griesser 2012, Karp 2012, Simon 2008) were identified for inclusion in this review.

Two placebo-controlled RCTs were of long-term treatment (52 weeks) (Simunic 2003, Simon 2008) and were included in this section.

A total of 7 RCTs comparing ospemifene with placebo were included in this review (Bachmann 2010, Portman 2014, Portman 2013, Rutanen 2003, Voipio 2002, Goldstein 2014, Simon 2013). Five of these studies (Bachmann 2010, Portman 2014, Portman 2013, Rutanen 2003, Voipio 2002) assessed short-term (less than 52 weeks) outcomes of ospemifene treatment; 1 (Simon

2013) assessed long-term outcomes (52 weeks or more); and 1 assessed both short- and long-term outcomes (Goldstein 2014).

Consideration of clinical benefits and harms

The evidence showed that local vaginal oestrogen was beneficial for improving short-term outcomes (vaginal pH, maturation index, patients' symptomatic improvement) for menopausal women when compared with placebo. Furthermore, no difference in the experience of adverse events was found between those women treated with local vaginal oestrogen and those on placebo. In terms of long-term outcomes, although a significant improvement was found for women who used local vaginal oestrogens compared with placebo groups in relieving vaginal dryness symptoms, dyspareunia and itching or discomfort, there was also a case of endometrial hyperplasia (although the difference in this outcome was not significant) among those who used local oestrogen treatment compared with placebo. Endometrial hyperplasia is an abnormal proliferation of endometrium and is considered as a risk factor for endometrial cancer.

The Guideline Development Group concluded that given the effectiveness of vaginal local oestrogen in relieving symptoms of urogenital atrophy and the reasonable safety profile, it should be considered as a treatment for this condition for women in menopause (including those who take systemic HRT but experience persistent urogenital symptoms).

[…] With regard to adverse events, the group wished to inform women who may opt for this local treatment that adverse events are considered rare, but, as is the case with systemic HRT, unscheduled vaginal bleeding should be reported to a healthcare professional.

[…] The group discussed the role of local oestrogens for women in whom systemic HRT is contradicted, for example women with a history of breast cancer, and concluded that local oestrogen should still be considered for relieving symptoms of urogenital atrophy in these women, as there is minimal systemic absorption of local preparations, although this decision should be discussed with a healthcare professional with expertise in the field as even very small amounts of oestradiol may decrease the effect of aromatase inhibitors which are used in the treatment of breast cancer.

While the group did not review the clinical effectiveness and safety of the various moisturisers and lubricants, they discussed that these are widely used and generally considered to be a safe option for the relief of symptoms of urogenital atrophy.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 22.05.2019

#	Suchfrage
1	MeSH descriptor: [Atrophic Vaginitis] explode all trees
2	MeSH descriptor: [Atrophy] explode all trees
3	MeSH descriptor: [Vagina] explode all trees
4	MeSH descriptor: [Vulva] explode all trees
5	#2 and (#3 or #4)
6	MeSH descriptor: [Vaginitis] this term only
7	MeSH descriptor: [Vaginal Diseases] this term only
8	MeSH descriptor: [Vulvar Diseases] this term only
9	#6 or #7 or #8
10	(vaginitis or vaginosis or vagina* or uro-genital or vulva* or vulvo or vulvo-vaginal or genitourinary*):ti,ab,kw
11	atroph*:ti,ab,kw
12	#10 and #11
13	#9 or #12
14	MeSH descriptor: [Climacteric] this term only
15	MeSH descriptor: [Menopause] this term only
16	MeSH descriptor: [Postmenopause] explode all trees
17	#14 or #15 or #16
18	(menopaus* or postmenopaus* or climacteri*):ti,ab,kw
19	#17 or #18
20	#1 or #5 or #13 or #19
21	(genitourinary syndrome*):ti,ab,kw
22	#20 or #21
23	#2 or #11
24	#22 AND #23

Systematic Reviews in Medline (PubMed) am 22.05.2019

#	Suchfrage
1	atrophic vaginitis[mh]
2	atrophy[mh]
3	vagina[mh]
4	vulva[mh]
5	#2 AND (#3 OR #4)
6	vaginitis[mh:noexp]

#	Suchfrage
7	vaginal diseases[mh:noexp]
8	vulvar diseases[mh:noexp]
9	#6 OR #7 OR #8
10	vaginitis[tiab] OR vaginosis[tiab] OR vagina*[tiab] OR uro-genital[tiab] OR urogenital OR vulva*[tiab] OR vulvo[tiab] OR vulvo-vaginal[tiab] OR genitourinary*[tiab]
11	atroph*[tiab]
12	#10 AND #11
13	#9 OR #12
14	climacteric[mh:noexp]
15	menopause[mh:noexp]
16	postmenopause[mh]
17	#14 OR #15 OR #16
18	menopaus*[tiab] OR postmenopaus*[tiab] OR climacteri*[tiab]
19	#17 OR #18
20	#1 OR #5 OR #13 OR #19
21	"genitourinary syndrome"[tiab] OR "genitourinary syndromes"[tiab]
22	#20 OR #21
23	#2 OR #11
24	#22 AND #23
25	(#24) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR

#	Suchfrage
	(systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
26	((#25) AND ("2014/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
27	(#26) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 22.05.2019

#	Suchfrage
1	atrophic vaginitis[mh]
2	atrophy[mh]
3	vagina[mh]
4	vulva[mh]
5	#2 AND (#3 OR #4)
6	vaginitis[mh:noexp]
7	vaginal diseases[mh:noexp]
8	vulvar diseases[mh:noexp]
9	#6 OR #7 OR #8
10	vaginitis[tiab] OR vaginosis[tiab] OR vagina*[tiab] OR uro-genital[tiab] OR vulva*[tiab] OR vulvo[tiab] OR vulvo-vaginal[tiab] OR genitourinary*[tiab]
11	atroph*[tiab]
12	#10 AND #11
13	#9 OR #12
14	climacteric[mh:noexp]
15	menopause[mh:noexp]
16	postmenopause[mh]
17	#14 OR #15 OR #16
18	menopaus*[tiab] OR postmenopaus*[tiab] OR climacteri*[tiab]
19	#17 OR #18
20	#1 OR #5 OR #13 OR #19
21	"genitourinary syndrome"[tiab] OR "genitourinary syndromes"[tiab]
22	#20 OR #21
23	#2 OR #11
24	#22 AND #23
25	(#24) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])

26	(((#25) AND ("2014/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
27	(#26) NOT retracted publication[ptyp]

Referenzen

1. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ospemifen vom 20. Oktober 2016 [online]. Berlin (GER): G-BA; 2016. [Zugriff: 04.06.2019]. URL: https://www.g-ba.de/downloads/39-261-2734/2016-10-20_AM-RL-XII_Ospemifen_D-223_BAnz.pdf.

2. **Lethaby A, Ayeleke RO, Roberts H.** Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews [online]. 2016(8):CD001500. URL: http://dx.doi.org/10.1002/14651858.CD001500.pub3.

3. **National Institute for Health and Care Excellence (NICE).** Menopause: Version 1.5 [online]. London (GBR): NICE; 2015. [Zugriff: 22.05.2019]. (NICE guideline; Band 23). URL: https://www.nice.org.uk/guidance/ng23/evidence/full-guideline-pdf-559549261.