# New Medicine Recommendation

# 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene (Duavive®) modified release tablets for treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate

**Recommendation: Black**

Conjugated oestrogens and bazedoxifene tablets are not recommended for prescribing for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin containing therapy is not appropriate.

There is a lack of evidence demonstrating increased efficacy to mitigate the increased cost of the product.

There are concerns about the adverse event profile of the product which introduces those of a new drug in addition to those already present due to the presence of oestrogen in the product.

**Summary of Supporting Evidence**

- The drug's manufacturer submitted data from 4 pivotal Phase 3 studies: studies 303, 305, 306, and 3307 to support the licensing application of bazedoxifene acetate 20mg/conjugated oestrogens 0.45 mg
- Study 303 demonstrated relatively low levels of endometrial hypoplasia after 24 months of treatment with bazedoxifene/conjugated oestrogens.
- Study 305 showed a reduction in number of hot flushes at week 4 with a further reduction at week 12 versus placebo for bazedoxifene/conjugated oestrogens
- Study 306 studies markers for vulvular/vaginal atrophy. It showed bazedoxifene/ conjugated oestrogens significantly ($P < 0.01$) increased superficial cells and decreased parabasal cells compared with placebo. Vaginal pH and 'most bothersome symptom' significantly improved with and improvements in vaginal dryness were also observed.
- Study 3307 evaluated biopsies in patients treated with bazedoxifene 20 mg / conjugated oestrogens 0.45 mg and bazedoxifene 20 mg / conjugated oestrogens 0.625 mg. Respectively, the incidence of endometrial hyperplasia / malignancy at month 12 was 0.32% (95% CI 0.01%; 1.76%) and 0.30% (2-sided 95% CI 0.01; 01.66%). The combined drugs also demonstrated significant increases in mean percent change from baseline in BMD of lumbar spine at Month 12 and Month 6 compared to placebo as well as well as in total hip BMD at Month 12.
- In the clinical study programme, 3,322 women were exposed to conjugated oestrogens/ bazedoxifene for at least 1 year, and 1,999 women were exposed for 2 years

**Details of Review**

| |
|---|
| Name of medicine (generic & brand name): 0.45 mg conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene (Duavive®) |
| Strengths and forms:<br>0.45 mg conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene[1] |
| Dose and administration:<br>For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.<br>The recommended dose for Duavive® is 0.45 mg conjugated oestrogens and 20 mg bazedoxifene taken as a single oral tablet, once daily.<br>If a tablet is forgotten, it should be taken as soon as the patient remembers. Therapy should then be continued as before. If more than one tablet has been forgotten, only the most recent tablet should be taken, the patient should not take double the usual dose to make up for missed tablets.[1] |
| BNF therapeutic class / mode of action: Section: Obstetrics and Gynaecology<br>Sub Section: Menopausal disorders. A combination of the third generation selective oestrogen receptor modulator (SERM), bazedoxifene, and conjugated oestrogens<br>Drug Class: HRT, other[2] |
| Licensed indication(s): Treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.<br>The experience treating women older than 65 years is limited.[1] |
| Proposed use: Within licensed indication |
| Course and cost:<br>28 tablets cost £15.00[2] |
| Current standard of care/comparator therapies: HRT products and raloxifene |
| **Relevant NICE guidance:**<br>NICE Guideline 23 'Menopause: diagnosis and management'[3] provides guidance on the management of short-term menopausal symptoms as follows:<br>**Vasomotor symptoms**<br>1.4.2 Offer women HRT for vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of preparations as follows:<br>o oestrogen and progestogen to women with a uterus<br>o oestrogen alone to women without a uterus. |

1.4.3 Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone.

**Altered sexual function**

1.4.8 Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.

**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.

The guideline then goes on to explain HRT's association with venous thromboembolism, cardiovascular events, cancers and stroke.

**Background**

Conjugated oestrogens have been available as 'hormone replacement therapy' for the treatment of menopausal symptoms and prophylaxis of osteoporosis for several years. The drug is usually prescribed with cyclical progestogen in women with a uterus to reduce the risk of endometrial cancer associated with treatment containing only oestrogens.[4] Progestogens, being an additional drug, will expose the patient to potential additional side effects such as vaginal bleeding, breast tenderness and altered mood which may not be tolerated by some patients.[5]

Due to the established risks, HRT should be administered in the lowest effective dose for the shortest duration and should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risks of HRT.[6]

Oestrogens reduce the risk of fragility fracture however, oestrogens are only used for this purpose in patients who are intolerant of or contraindicated to other medicinal products approved for the prevention of osteoporosis.[6]

Bazedoxifene is a third generation selective oestrogen-receptor modulator. It was approved by the EMEA for the treatment of postmenopausal osteoporosis in women at increased risk of fracture in 2009[7] although it is not marketed in the UK.[8] Bazedoxifene has both tissue selective oestrogen receptor agonist and antagonist activity, with agonist activity on the skeletal system and antagonist activity in breast and uterine tissues.[7]

Duavive® is a combination of conjugated oestrogens and bazedoxifene licensed for treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.[1]

The developmental rationale for the combination was based on the assumption that bazedoxifene acetate would inhibit proliferative effects of conjugated oestrogens on the endometrium reducing the incidence of irregular uterine bleeding and prevent oestrogenic stimulatory effects of conjugated oestrogens in breast tissue. Established benefits of oestrogen therapy for the treatment of postmenopausal oestrogen deficiency symptoms are maintained with the fixed combination therapy. The effects of the combination are theoretically the result of a synergy rather than those of the individual components combined.[6]

Combined bazedoxifene acetate/conjugated oestrogens are potentially an alternative to current HRT (i.e. oestrogen plus progestin) offering some of the benefits of replacing oestrogen, while

reducing side effects and risks associated with oestrogen plus progestin use.[6]

**Summary of efficacy data in proposed use:**

Pivotal studies

The drug's manufacturer submitted data from 4 pivotal Phase 3 studies: studies 303, 305, 306, and 3307 to support the licensing application of bazedoxifene acetate 20 mg/conjugated oestrogens 0.45 mg.[6]

Study 303

It is important to note that study 303 was classified as being GCP non-compliant and was therefore not be taken into account by the European Medicines Agency when assessing the efficacy of bazedoxifene/conjugated oestrogens.

Study 303: 'A double-blind, randomised, placebo- and active-controlled safety and efficacy study of bazedoxifene / conjugated oestrogens combinations in postmenopausal women' was a Phase 3 multi centre, double-blind, randomised, outpatient, 8-parallel-group placebo- and active-controlled dose-ranging study evaluating efficacy and safety of 6 combinations of bazedoxifene / conjugated oestrogens (bazedoxifene 10 mg, 20 mg, 40 mg; conjugated oestrogens 0.45 mg, 0.625 mg) over 2 years of therapy. [9,7]

The primary endpoint of this study was the incidence of endometrial hyperplasia after 1 year of therapy. The main secondary endpoint was the mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy.

Incidence of Endometrial Hyperplasia / malignancy at Months 12 and 24 (Efficacy Evaluable Population)

| | | | | | Confidence interval | |
|---|---|---|---|---|---|---|
| Treatment | Timepoint | N evaluable biopsies | N endometrial hyperplasia / malignancy | Incidence of hyperplasia/ malignancy (%) | Lower limit | Upper limit |
| BZA 20 mg / CE 0.45 mg | Month 12 | 294 | 0 | 0.00 | 0.00 | 1.25 |
| | Month 24 | 229 | 2 | 0.87 | 0.11 | 3.12 |
| BZA 20 mg / CE 0.625 mg | Month 12 | 271 | 1 | 0.37 | 0.01 | 2.04 |
| | Month 24 | 195 | 2 | 1.03 | 0.12 | 3.66 |

The modified-intent-to-treat population[a] analysis of the main secondary endpoint mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy showed significant increases in lumbar spine BMD from baseline to month 24 in both substudies for all groups except placebo were BMD values decreased. Increases in BMD were most pronounced with the lowest dose of bazedoxifene of 10 mg attenuating with increasing doses of bazedoxifene. In the elder group of women >5 years postmenopausal effects were more pronounced with bazedoxifene/ conjugated oestrogens containing either 10 or 20 mg bazedoxifene, but not 40 mg, compared to raloxifene 60 mg. In the younger women ≤5 years postmenopausal BMD increases were pronounced with all doses of bazedoxifene/conjugated oestrogens.

Study 305

Study 305 was a 12 week, Phase 3, multi-centre, double-blind, randomised, 3-parallel-group placebo-controlled study designed to evaluate the safety and efficacy of bazedoxifene 20 mg / conjugated oestrogens 0.45 mg and bazedoxifene 20 mg / conjugated oestrogens 0.625 mg for the treatment of vasomotor symptoms (VMS).[10,6]

[a] Defined as all subjects who were randomised, took at least 1 dose of test article, had a baseline value, and had at least 1 on-therapy value for the parameter being analysed

The study enrolled generally healthy women with an intact uterus, aged 40 to 65 years, with at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea, and who had a serum follicle-stimulating hormone level > 40 mIU/mL. In addition, the women had to be seeking treatment for hot flushes and report at screening a minimum of 7 moderate to severe hot flushes per day or 50 per week. 310 patients were included in the final analysis.

The primary efficacy variables were the change from baseline at week 4 and week 12 in the average daily number of moderate and severe hot flushes and the severity of hot flushes. Secondary endpoints included further parameters related to VMS, self-administered questionnaires, sleep scale, Menopause-Specific Quality of Life, and Menopause Symptoms – Treatment Satisfaction Questionnaire as well as the presence of breast pain.

Mean change from baseline in the average daily number of moderate and severe hot flushes at week 4 and week 12

| | | | --Adjusted Change-- | | |
|---|---|---|---|---|---|
| **Treatment** | **Time Slot** | **No. of Pairs** | **Mean** | **SE** | **p-Value vs Placebo** |
| **LOCF** | | | | | |
| **BZA 20 mg/CE 0.45 mg** | **Week 4** | 122 | -5.90 | 0.42 | < 0.001 |
| | **Week 12** | 122 | -7.63 | 0.36 | < 0.001 |
| **BZA 20 mg/CE 0.625 mg** | **Week 4** | 125 | -6.60 | 0.41 | < 0.001 |
| | **Week 12** | 125 | -8.05 | 0.35 | < 0.001 |
| **Placebo** | **Week 4** | 63 | -2.84 | 0.56 | -- |
| | **Week 12** | 63 | -4.92 | 0.48 | -- |

With regard to all secondary endpoints related to VMS and most items of the sleep scale, statistically significant differences favouring the 2 active groups vs. placebo were observed.

Study 306

Study 306 was a 12 week, 652 patient, Phase 3, multi-centre, double-blind, randomised, outpatient, 4-parallel-group placebo- and active-controlled study designed to assess the efficacy of bazedoxifene 20 mg/conjugated oestrogens 0.45 mg and bazedoxifene 20 mg/ conjugated oestrogens 0.625 mg compared with placebo and bazedoxifene 20 mg for the treatment of vulvar/vaginal atrophy.[11,6]

Generally healthy women, 40 to 65 years of age, who had an intact uterus and were postmenopausal, were enrolled.

The co-primary endpoints for vulvar / vaginal atrophy were the increase in superficial cells, decrease in parabasal cells, lowering of vaginal pH, and improvement in the most bothersome symptom at week 12.

Bazedoxifene 20 mg/conjugated oestrogens 0.625mg or 0.45 mg significantly ($P < 0.01$) increased superficial cells and decreased parabasal cells compared with placebo. Vaginal pH and most bothersome symptom significantly improved with bazedoxifene 20 mg/conjugated oestrogens 0.625 mg compared with placebo ($P < 0.05$). Improvements in vaginal dryness were also observed with both bazedoxifene/conjugated oestrogens doses ($P < 0.05$).

With regard to vaginal maturation statistically significant differences favouring both bazedoxifene / conjugated oestrogens groups vs. placebo were found in the nonparametric analysis in the MITT population using the LOCF approach which had been prespecified as the primary analysis in the study protocol in case data were not normally distributed. With regard to vaginal pH, the difference vs. placebo was statistically significantly improved only in the bazedoxifene 20 mg / conjugated oestrogens 0.625 mg group.

For most bothersome symptom, a statistically significant difference favouring bazedoxifene 20mg / conjugated oestrogens 0.625mg vs. placebo was found in the parametric analysis in the MITT population using the LOCF approach which had been prespecified as the primary analysis in the study protocol. For bazedoxifene 20mg / conjugated oestrogens 0.625mg and bazedoxifene

20mg monotherapy, the differences vs. placebo were not statistically significant.

Study 3307

Study 3307 'A double-blind, randomised, placebo-and active-controlled efficacy and safety study of the effects of bazedoxifene / conjugated oestrogens combinations on endometrial hyperplasia and prevention of osteoporosis in postmenopausal women' was a Phase 3 outpatient, multi-centre, double-blind, randomised, placebo- and active-controlled study.[12,7] It included generally healthy postmenopausal women with an intact uterus aged between 40 to 65 years, n= 1,886. The trial consisted of a main study and 3 substudies: osteoporosis, sleep and breast density.

Participants received either bazedoxifene 20 mg / conjugated oestrogens 0.45 mg, bazedoxifene 20 mg / conjugated oestrogens 0.625 mg, bazedoxifene 20 mg, conjugated oestrogens 0.45 mg /medroxyprogesterone acetate 1.5 mg, or placebo. The primary objectives of this study were to investigate the endometrial safety of both bazedoxifene 20 mg / conjugated oestrogens doses and the effect in preventing postmenopausal osteoporosis after 1 year of therapy.

Based on 314 and 333 evaluable biopsies in the bazedoxifene 20 mg / conjugated oestrogens 0.45 mg group and the bazedoxifene 20 mg / conjugated oestrogens 0.625 mg group, respectively, the incidence of endometrial hyperplasia / malignancy at month 12 was 0.32% (95% CI 0.01%; 1.76%) and 0.30% (2-sided 95% CI 0.01; 01.66%), respectively. The EPAR however stresses that, due to the low number of patients in the study, endometrial safety can currently not be concluded based on study 3307.

For both bazedoxifene / conjugated oestrogens doses there were significant increases in mean percent change from baseline in BMD of lumbar spine at Month 12 and Month 6 (secondary) compared to placebo as well as well as in total hip BMD at Month 12. Changes in BMD were not statistically significant between bazedoxifene monotherapy, bazedoxifene / conjugated oestrogens, and conjugated oestrogens / medroxyprogesterone acetate groups, but effects were most pronounced with conjugated oestrogens / medroxyprogesterone acetate.

The analyses of the BMD of the lumbar spine at Month 12 in the MITT population observed cases and in the per protocol population were consistent with the results from the primary analyses. In the BMD responder analysis the lumbar spine responder rates were significantly greater for both bazedoxifene / conjugated oestrogens and the conjugated oestrogens / medroxyprogesterone acetate group compared to placebo at Month 12 ($p \leq 0.001$). Differences for bazedoxifene 20 mg / conjugated oestrogens compared to bazedoxifene 20 mg at Month 12 were not statistically significant ($p=0.323$ and 0.101, respectively). The total hip responder rates were significantly greater for all treatment groups compared with placebo at Month 12, but total hip responder rates were not statistically significant different between bazedoxifene 20 mg / conjugated oestrogens and bazedoxifene 20 mg at Month 12 ($p=0.740$ and 0.127, respectively).

**Summary of safety data:**

In the five phase 3 studies reviewed by the EMEA, 1585 women received bazedoxifene 20mg / conjugated oestrogens 0.45mg and 1583 received bazedoxifene 20 mg / conjugated oestrogens 0.625 mg for a 3 month period. Overall, more than 1,000 women have been exposed to the fixed dose combinations of bazedoxifene / conjugated oestrogens with 20 mg bazedoxifene for more than 1 year.[6] 3,322 women were exposed to conjugated oestrogens /bazedoxifene for at least 1 year, and 1,999 women were exposed for 2 years.[1]

The most commonly reported adverse event is abdominal pain, occurring in more than 10% of patients in clinical trials.

The SPC for conjugated oestrogens and bazedoxifene acetate (Duavive®) lists the following adverse events:[1]

| Incidence of Event | Adverse Event |
|---|---|
| **Very Common (≥1/10)** | Abdominal pain |
| **Common (≥1/100 to <1/10)** | Vulvovaginal candidiasis, constipation, diarrhoea, nausea, muscle spasms, blood triglycerides increased |
| **Uncommon (≥1/1,000 to <1/100)** | Cholecystitis |
| **Rare (≥1/10,000 to <1/1,000)** | Venous thromboembolic events (including, pulmonary embolism, retinal vein thrombosis, deep vein thrombosis and thrombophlebitis) |

As conjugated oestrogens have been used for several years, their adverse event profile is well known and will apply to the drug in combination with bazedoxifene.

The SPC for bazedoxifene / conjugated oestrogens provides details of the known risks relating to oestrogen containing therapies i.e. risks of endometrial cancer, ovarian cancer, breast cancer and ischaemic stroke. This information is sourced from large scale studies such as the Women's Health Initiative and the Million Women study and do not relate to the dataset for conjugated oestrogens / bazedoxifene. Bazedoxifene reduces the risk of endometrial hyperplasia that can occur with oestrogen-only use; endometrial hyperplasia may be a precursor to endometrial cancer.

In the bazedoxifene osteoporosis treatment trial (mean age = 66.5 years), the VTE rate per 1,000 women-years through the 3-year study period was 2.86 in the bazedoxifene (20 mg) group and 1.76 in the placebo group and through the 5-year study period was 2.34 in the bazedoxifene 20 mg group and 1.56 in the placebo group. After 7 years, the VTE rate per 1,000 women-years was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group.

The EMEA concluded in its public assessment report:

> The known selective oestrogen receptor modulator and conjugated oestrogens class effects include venous thromboembolic events, cardiovascular events, cerebrovascular accidents, and malignancies. Considering the number of women exposed, the lack of data in elderly women, and the duration of treatment the available safety data for bazedoxifene/conjugated oestrogens do not allow to assess whether the incidence of these rare adverse events is increased in women treated with bazedoxifene 20 mg / conjugated oestrogens compared to placebo or to historical data for conjugated oestrogens/medroxyprogesterone acetate.

It was agreed to address these issues in a risk management plan.[6]

**Strengths and limitations of the evidence:**

Strengths:

- New combination is based on an existing drug, combined with a selective oestrogen receptor modulator which should counteract negative effects of conjugated oestrogens on the endometrium.
- Strong safety dataset developing: 3,322 women were exposed to conjugated oestrogens /bazedoxifene for at least 1 year, and 1,999 women were exposed for 2 years.[1]
- Combination's licence is based on four large pivotal studies which have identified the most appropriate dose.
- Offers a new type of therapy where oestrogens can be given without progesterone and hence side effects associated with progesterones avoided.

Limitations

- Study 303 was classified as being GCP non-compliant and was therefore not be taken into account by the European Medicines Agency when assessing the efficacy of bazedoxifene/conjugated oestrogens.
- Combination failed to gain a licence for prevention of osteoporosis because of deficiencies in the clinical trials programme – this differs from the position in the US where this aspect of the indication was granted.[13]
- In the clinical trials investigating the combination product the duration of exposure was too short and the number of women exposed was too small to draw any conclusions regarding a possible risk of cancer, including breast cancer or ovarian cancer.
- The combination product contains 0.45mg of conjugated oestrogens which is not available in any of the products currently available in the UK that contain conjugated oestrogens.

**Prescribing and risk management issues:**

Bazedoxifene is a new drug hence prescribers will have no experience in its use. There could therefore be a need for targeted education about the combination product.

**Commissioning considerations:**

**Cost of combined HRT comparators**

| Drug | Example regimen | Pack cost | Cost per patient per course/ per year (ex VAT) |
|---|---|---|---|
| Bazedoxifene 20mg/conjugated oestrogens 0.45mg tabs | 1 each day | 28 tabs £15.00 | £195.00 |
| Conjugated oestrogens 0.625mg/norgestrel 0.15mg tabs | 1 conjugated oestrogen each day, 1 norgestrel daily from day 17 to 28 | 120 tabs £6.25 | £25.00 |
| Estradiol 2mg/norethisterone 1mg tabs | 1 white tablet daily for 16 days, 1 pink tablet daily 12 days | 84 tabs £9.20 | £36.80 |
| Estradiol 3.2mg patch, estradiol 3.2mg plus norethisterone 11.2mg patch | 1 estradiol only patch for 14 days then 1 estradiol/norethisterone for 14 days Patches changed twice a week | 8 patches £11.09 | £144.17 |
| Costs based on MIMS list prices October 2016. Table does not imply therapeutic equivalence of drugs or doses. | | | |

**Prescribing of combined HRT across Lancashire September 2015 to August 2016**

| Drug | Items | Cost |
|---|---|---|
| Estradiol and Estriol with Progestogen | 129 | £1,387 |
| Estradiol with Progestogen | 19,299 | £359,499 |
| Oestrogens Conjugated with Progestogen | 5,574 | £44,998 |
| TOTAL | 25,002 | £405,885 |

**Anticipated patient numbers and net budget impact**

Calculating the budget impact of introducing the new product is complex as any uptake will be either newly prescribed HRT in place of currently available products or switches from established HRT when the alternative would likely be discontinuation of HRT. The magnitude of any change is dificult to assess with any accuracy as prescribers may be slow to accept such a new type of therapy, especially for HRT products where there have been well documented safety issues previously.

Bazedoxifene/conjugated oestrogens are at least four times the price of alternative oral HRT preparations and around 25% more expensive than patch preparations. Introduction of the new product could expand the market for combined HRT and, if this occurs, the current spend of £405,885 per year in Lancashire is likely to increase above normal growth. Added to this the new product is more expensive than alternatives; if accepted by prescribers, the new product's introduction could place a disproportionately large cost on CCG budgets in Lancashire.

**Associated additional costs or available discounts:**

None identified

**Productivity, service delivery, implementation:**

N/A

**Innovation, need, equity:**

Conjugated oestrogens and bazedoxifene acetate offers an alternative product for patients who cannot tolerate the progesterone component of combined therapy.

Grading of evidence (based on SORT criteria):

| Levels | Criteria | Notes |
|---|---|---|
| Level 1 | Patient-oriented evidence from:<br>high quality randomised controlled trials (RCTs) with low risk of bias<br>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:<br>clinical trials at moderate or high risk of bias<br>systematic reviews or meta-analyses of such clinical trials or with inconsistent findings<br>cohort studies<br>case-control studies | |
| Level 3 | Disease-oriented evidence, or evidence from:<br>consensus guidelines<br>expert opinion<br>case series | Any trial with disease-oriented evidence is Level 3, irrespective of quality |

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