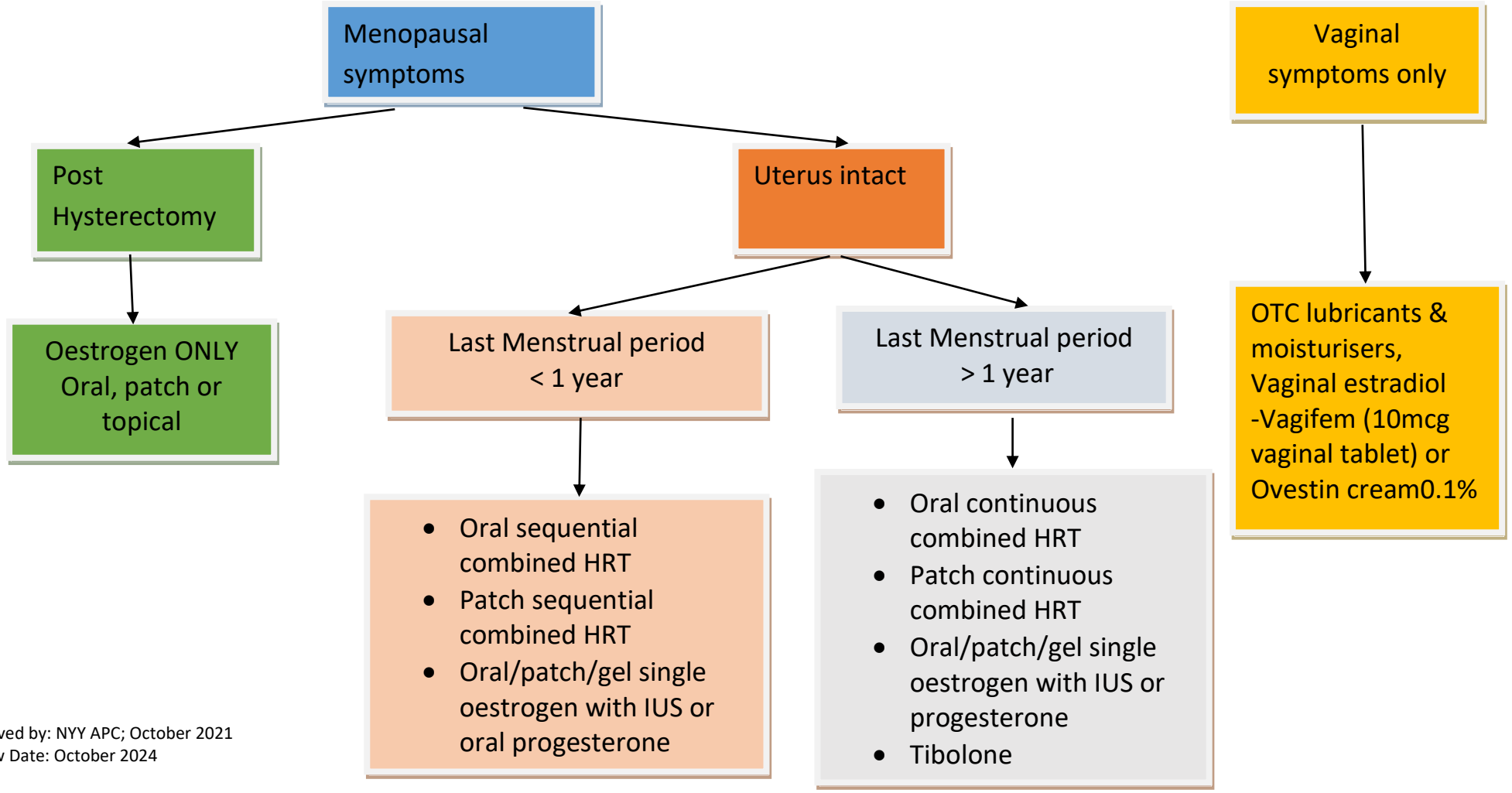
NHS North Yorkshire Clinical Commissioning Group

NHS Vale of York Clinical Commissioning Group

North Yorkshire and York Menopause Guidance – HRT

(refer to table overleaf for formulary choices)



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HRT Formulary

	Type of HRT	Oestrogen ONLY	Sequential combined HRT	Continuous combined HRT	Adjunctive Progestogen
	Criteria for Use	➢ Post hysterectomy	➢ Intact uterus ➢ Perimenopausal – under 1 yr or amenorrhoea	➢ Intact uterus - amenorrhoeic >1yr ➢ >54 yrs old ➢ >3 yrs on sequential HRT	**As adjunct to oral/ transdermal/topical oestrogen** if not had a hysterectomy to provide endometrial protection.
Transdermal treatment options	1st Line	Evorel patch 25, 50, 75, 100mcg estradiol Change TWICE a week	Evorel Sequi patch 50micrograms estradiol & 170micrograms norethisterone Change patch TWICE a week	Evorel Conti patch 50micrograms estradiol & 170micrograms norethisterone Change patch TWICE a week	Levonorgestrel (Mirena) device In an HRT regime, it has a 4-year license. FSRH state it can be used for 5 years for endometrial protection (note offlabel)
	2nd Line	Estraderm MX patches. 25, 50, 75, 100mcg estradiol Change TWICE per week	FemSeven Sequi 50micrograms estradiol & 10micrograms levonorgestrel Change patch ONCE a week	FemSeven Conti patches 50micrograms estradiol & 7micrograms levonorgestrel Change patch ONCE a week	
Oral treatment options	1st Line	Elleste Solo 1mg or 2mg estradiol	Elleste Duet 1mg or 2mg estradiol & 1mg norethisterone	Kliovance (1mg estradiol and 0.5mg norethisterone) Kliofem (2mg estradiol and 1mg norethisterone)	Medroxyprogesterone acetate (Provera) 10mg on Days 14-28 (licensed) or 2.5mg - 5mg daily(unlicensed)
	2nd Line	Premarin 0.3mg, 0.625, 1.25mg.	Femoston 1/10 or 2/10 tablets 1mg or 2mg estradiol & 10mg dydrogesterone	Femoston Conti 0.5/2.5 = 0.5mg estradiol & 2.5mg dydrogesterone OR 1/5 = 1mg estradiol & 5mg dydrogesterone	Progesterone 200 mg nocte day 15-26 of 28 day cycle 100 mg/d nocte 1-25 of 28 day cycle or, preferably, 100mg nocte continuously (unlicensed).
	3rd line			Tibolone 2.5mg tablets	
Other		Oestrogel 0.06% oestradiol gel 2 measures (2.5g) oestradiol daily			

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Diagnosis

- The following can be diagnosed without laboratory tests in otherwise healthy women aged over 45 years with appropriate menopausal symptoms:
    - Peri-menopause — if the woman has vasomotor symptoms.
    - Menopause in women who have:
        - not had a period for at least 12 months and are not using hormonal contraception

      OR

        - symptoms without a uterus

    The mean age for the menopause is 52.

- Follicular Stimulating Hormone (FSH) test to diagnose menopause should only be done in women:
    - Aged <40 years where menopause is suspected
    - Aged 40-45 years with menopausal symptoms, including a change in their menstrual cycle
    - Aged >45 years exhibiting atypical symptoms (include anything other than classic menopausal symptoms)

    Level greater than 30 mIU/mL indicates post menopause, should be taken on day 2-5 of cycle

    Note This test is often not required as treatment is generally guided by symptoms rather than a blood level.

    In women taking hormonal contraception causing amenorrhoea (IUS, POP, nexplanon) take two levels 6 weeks apart to determine whether menopausal, in which case contraception can be stopped after 1 year if over 50y.

    Some women may have normal levels of FSH during the menopausal transition, so this should not exclude peri-menopause as a cause of their symptoms.

- A pelvic examination should be performed only if clinically indicated and to exclude other possible causes of symptoms.

- Consider HRT to manage menopause symptoms including vasomotor symptoms, psychological symptoms (including low mood that arises as result of menopause) and altered sexual function. Urogenital atrophy alone only requires topical estradiol and can be used before the menopause but can also be used in some women in addition to systemic HRT.

- The benefits of HRT are likely to outweigh the risks for women with disruptive symptoms below the age of 60 years or with-in 10 years of menopause.

- In women with premature ovarian insufficiency (premature menopause), systemic HRT is recommended, if not contraindicated, until at least the average age of natural menopause (51-52 years) to prevent the early onset of osteoporosis.

- HRT may be appropriate for prevention of osteoporosis related fractures in women below the age of 60 years or within 10 years of menopause in symptomatic women or if other bone protection medication is contraindicated.

Initiating and managing HRT

- Managing symptoms: Address modifiable lifestyle factors to reduce menopausal symptoms:
    - healthy balanced diet, to maintain an appropriate weight
    - consume adequate calcium intake (700mg/day)
    - undertaking regular weight bearing exercise
    - Advise and support women in smoking cessation and reducing alcohol intake
    - Ensure other long-term conditions are managed appropriately and any treatment is optimised
    - Avoiding triggers for hot flushes if experiencing them (spicy foods, alcohol etc.)
    - Good sleep hygiene
- The option of taking HRT is an individual decision made after a consultation with the woman that addresses quality of life, health priorities, risks (including age and time since menopause), benefits and her personal preference.
    - Consider HRT, if not contraindicated, for treatment of vasomotor symptoms, low mood arising as a result of the menopause (other causes should be ruled out), uro-genital atrophy (either topical alone or alongside systemic).
    - Discuss effectiveness of HRT, risks, benefits, bleeding patterns, side effects.

- Check have up to date Blood pressure, BMI and family history of risk factors (osteoporosis, breast cancer and coronary heart disease)

- 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.

- **Choice of route**

  Offer patient choice of oral or transdermal. Note that there is lower risk of DVT with transdermal HRT compared to oral route, this may be the case as well for stroke especially when comparing to a low does patch preparation.

  Avoid oral if

  - VTE risks or personal history of VTE (both provoked and unprovoked consider referring to haematologist for advice before initiating any type of HRT.
  - Poor symptom control with oral
  - Bowel disorder /absorption problems /gastric banding,
  - Lactose intolerance
  - History of migraines
  - Stroke risks e.g., BMI>30/smoker/sedentary
  - History of or concerns of gall stones
  - On hepatic enzyme inducing agent including OTC preparations

- **Treatment regimens**

Non-hysterectomised		Hysterectomised	Urogenital atrophy only
Perimenopausal	Postmenopausal	Oestrogen only	Low dose topical vaginal oestradiol or oestriol
Combined cyclical (sequential) regime (Note includes Oral/patch/gel single oestrogen with IUS or oral progesterone)	Cycle free HRT, continuous oestrogen and progestogen /progesterone		
Continuous oestrogen/ cyclical progestogen for 10-14 days in 28 day cycle, giving cyclical progestogen withdrawal bleed. Consider changing to continuous combined HRT when postmenopausal or 54 years.	(Note includes Oral/patch/gel single oestrogen with IUS or oral progesterone)	Prescribe continuous combined (both oestrogen & progestogen) • If history of severe endometriosis • Subtotal hysterectomy • TCRE (transcervical resection of endometrium)	Start early before irreversible changes have occurred. Can be taken whilst on systemic HRT (note latter is not required to specifically treat urogenital atrophy

- The dose and duration should be consistent with safety issues and treatment goals. Generally the lowest effective dose is advised for symptom control.
- Review after 3 months as symptom control and side effects (including bleeding) can take time to be effective and/or settle, then annually or earlier if concerns.
- Encourage women to maintain healthy diet and lifestyle, invite them to seek information at www.menopausematters.co.uk and www.nos.org.uk .
- Tibolone: It is a synthetic steroid with oestrogenic, progestogenic and androgenic activity so is a type of continuous combined HRT and so this is a no bleed preparation. Because of its androgenic activity, it has been shown to have a positive effect on libido. There is an increased risk of breast cancer and venous thromboembolism, broadly similar to combined HRT. Its use in women over 65 years needs to be cautious because of increased stroke risk.

- **Follow-up/Annual Review/Duration of treatment**
  - Follow up after 3/12 of treatment to assess effect, enquire about side effects & bleeding pattern.
  - Unscheduled vaginal bleeding is a common side-effect of HRT within the first 3 months of treatment but should be reported promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NICE guideline on suspected cancer.
  - Managing side effects: Encourage women to persist with treatment for 3 months (as adverse effects may resolve)

	Side effects	Management strategies
Oestrogen related	Breast tenderness, GI side effects, Migraine, Leg cramps Above side effects may occur continuously or randomly throughout the cycle	• Reduce dose • Change route • GI side effects: take with or after food • Leg cramps may improve with lifestyle changes e.g. exercise, stretching calf muscles. • Breast tenderness may be alleviated by a low-fat, high-carbohydrate diet. • Migraine – switch to transdermal
Progestogen related	PMS type symptoms, Breast tenderness, Lower abdominal pain, Headache Above side effects tend to occur in a cyclical pattern during the	• Change type of progestogen • Change route e.g. oral to transdermal • Change regime - consider long cycle HRT or continuous combined HRT, perhaps with IUS to provide progestogen

	progestogen phase of cyclical hormone replacement therapy (HRT).	

- **At annual review** check efficacy, side-effects, ensure correct dose, optimal route of delivery and compliance. Also check:
  - Pros & cons of continuing HRT, increased risk of breast cancer with long-term use, do benefits outweigh risks?
  - Check blood pressure, encourage breast awareness/attendance of screening mammography
  - Ensure cervical screening is up to date
  - Assess osteoporosis risk & consider the need for investigation/monitoring Enquire about symptoms of urogenital atrophy
- **Duration of treatment**:
  - Most guidelines recommend that HRT for around 5 years in women as they enter menopause (i.e. in late 40's/early 50's) is likely to confer benefit and not harm
  - There are no reasons to place mandatory limitations on duration of HRT

  Guidance from the Committee on Safety of Medicine says:
    - use the lowest effective dose of HRT to control menopausal symptoms
    - use HRT for the shortest length of time
  - Therefore it is important that the benefits and risks should be reassessed with each woman on an annual basis
  - Withdrawing HRT slowly may reduce the chance of recurrent symptoms. It should be noted that 5% of women will have hot flushes for life
- **Contraception and HRT**: please see FSRH guidance(Contraception for Women Aged over 40 Years)
- Topical oestrogen for urogenital atrophy
    - Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms.
    - Vagifem (10mcg vaginal tablet) or Ovestin cream0.1% are preferred options (NOTE Estriol 0.01% cream is 12 times more costly than estriol 0.1%

(Ovestin®) cream but delivers an identical amount of estriol per application and therefore not on formulary).

- If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider other diagnosis such as Lichen Sclerosus or get further advice from a healthcare professional with expertise in menopause.

Contraindications and risks of HRT

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Contraindications (see SPC for full details: http://www.medicines.org.uk/emc)

- Current, past, or suspected breast cancer.
- Known or suspected oestrogen-sensitive cancer.
- Undiagnosed abnormal vaginal bleeding.
- Untreated endometrial hyperplasia.
- Current venous thromboembolism (deep vein thrombosis or pulmonary embolism), unless the woman continues on anticoagulant treatment.
- Active or recent arterial thromboembolic disease (for example angina or myocardial infarction).
- Untreated hypertension.
- Active liver disease with abnormal liver function tests.
- Porphyria cutanea tarda.
- Pregnancy.
- Dubin-Johnson and Rotor syndromes

Risks of HRT Summary

Summary of risks during current use from age of menopause and up to age 69, per 1000 women with 5 years or 10 years use of HRT

Age range (years)	Time (years)	Background incidence per 1000 women years in Europe	Oestrogen only HRT – additional cases per 1000 HRT users	Oestrogen-progestogen HRT – additional cases per 1000 HRT users
Cancer risk				
Breast				
Current use from age 50	5	13	+3	+8
	10	27	+7	+20
Total risk from age 50 to age 69 (HRT use + past use)	5	63	+5	+17
	10	63	+11	+34
Endometrial				
50-59	5	2	+4	NS
	10	4	+32	NS
60-69	5	3	+6	NS
	10	6	+48	NS
Ovarian				
50-59	5	2	+<1	+<1
	10	4	+1	+1
60-69	5	3	+<1	+<1
	10	6	+2	+2
Cardiovascular risk				
Venous thromboembolism (VTE)				
50-59	5	5	+2	+7
60-69	5	8	+2	+10
Stroke				
50-59	5	4	+1	+1
60-69	5	9	+3	+3
Coronary heart disease (CHD)				
50-59	5	14	NS	NS
60-69	5	31	NS	NS

The NICE clinical guideline on menopause from 2015 is the best source to look at the risks of long-term HRT use, in order to explain such risks to your patient. See section 1.5 (p11) and tables 1 to 4: https://www.nice.org.uk/guidance/ng23

Further reference
MHRA safety alert: Summary of the HRT risks and benefits
MHRA safety alert: Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping

When to refer to specialist service

- Premature ovarian insufficiency/menopause. It is likely that most women <40 years will need referral to specialist clinic.
- Complex medical history
- Concerns about the safety of HRT in a particular patient
- Persistent treatment problems e.g. side effects, lack of efficacy
- There is a sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding — assess appropriately and arrange an urgent 2-week referral if a gynaecological cancer is suspected.
- History of hormone dependent cancer

Patient resources

Rock My Menopause website (www.rockmymenopause.com) has a variety of factsheets and podcasts on various aspects of menopause.

Menopause Matters (www.menopausematters.co.uk) provides information on the menopause, menopausal symptoms, and treatment options.

Women's Health Concern (the patient arm of the British Menopause Society, website available at www.womens-health-concern.org) has a range of factsheets and an email advice service.

The Royal College of Obstetricians and Gynaecologists menopause Hub: www.rcog.org.uk/en/patients/menopause

The Daisy Network (www.daisynetwork.org) is a nationwide support group for women diagnosed with premature ovarian insufficiency or premature menopause.

The NHS leaflet Menopause.

https://patient.info/womens-health/menopause/hormone-replacement-therapy-hrt

References

NICE guidelines [NG23] Menopause: diagnosis and management, November 2015 (last updated 05 December 2019) https://www.nice.org.uk/guidance/ng23

NICE Clinical Knowledge Summaries Menopause last revised November 2020 http://cks.nice.org.uk/menopause

The British Menopause Society: http://www.thebms.org.uk/

Menopause. NICE Quality standard [QS143] Published date: February 2017 https://www.nice.org.uk/guidance/qs143

Menopause. NICE Pathway. Last updated: May 2021 https://pathways.nice.org.uk/pathways/menopause

FSRH Clinical Guideline: Contraception for Women Aged over 40 Years (August 2017, amended September 2019) https://www.fsrh.org/documents/fsrh-guidance-contraception-for-women-aged-over-40-years-2017/

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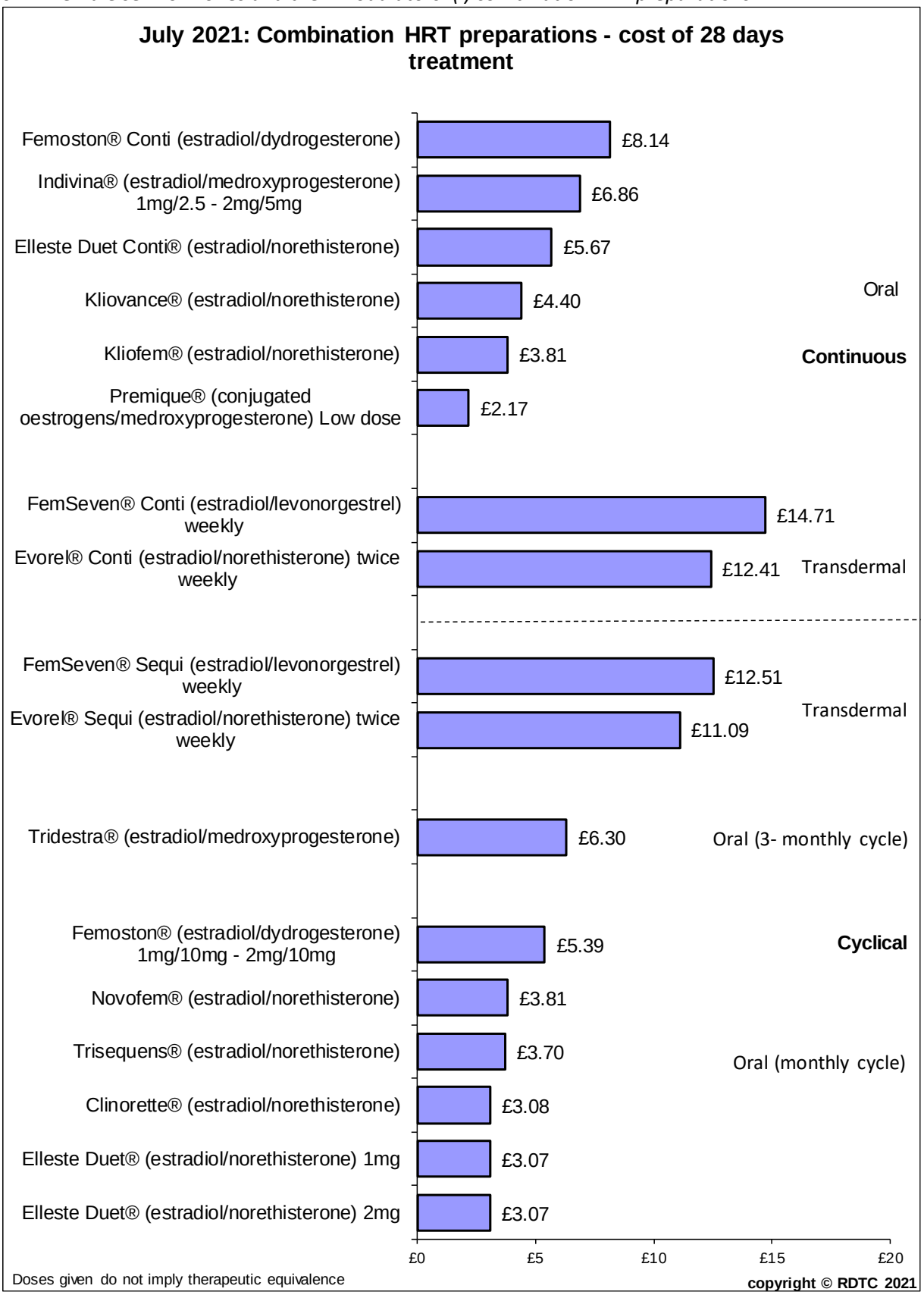
Appendix 1: HRT cost comparison charts (RDTC July 2021)

6.4.1 Female sex hormones and their modulators: (i) combination HRT preparations



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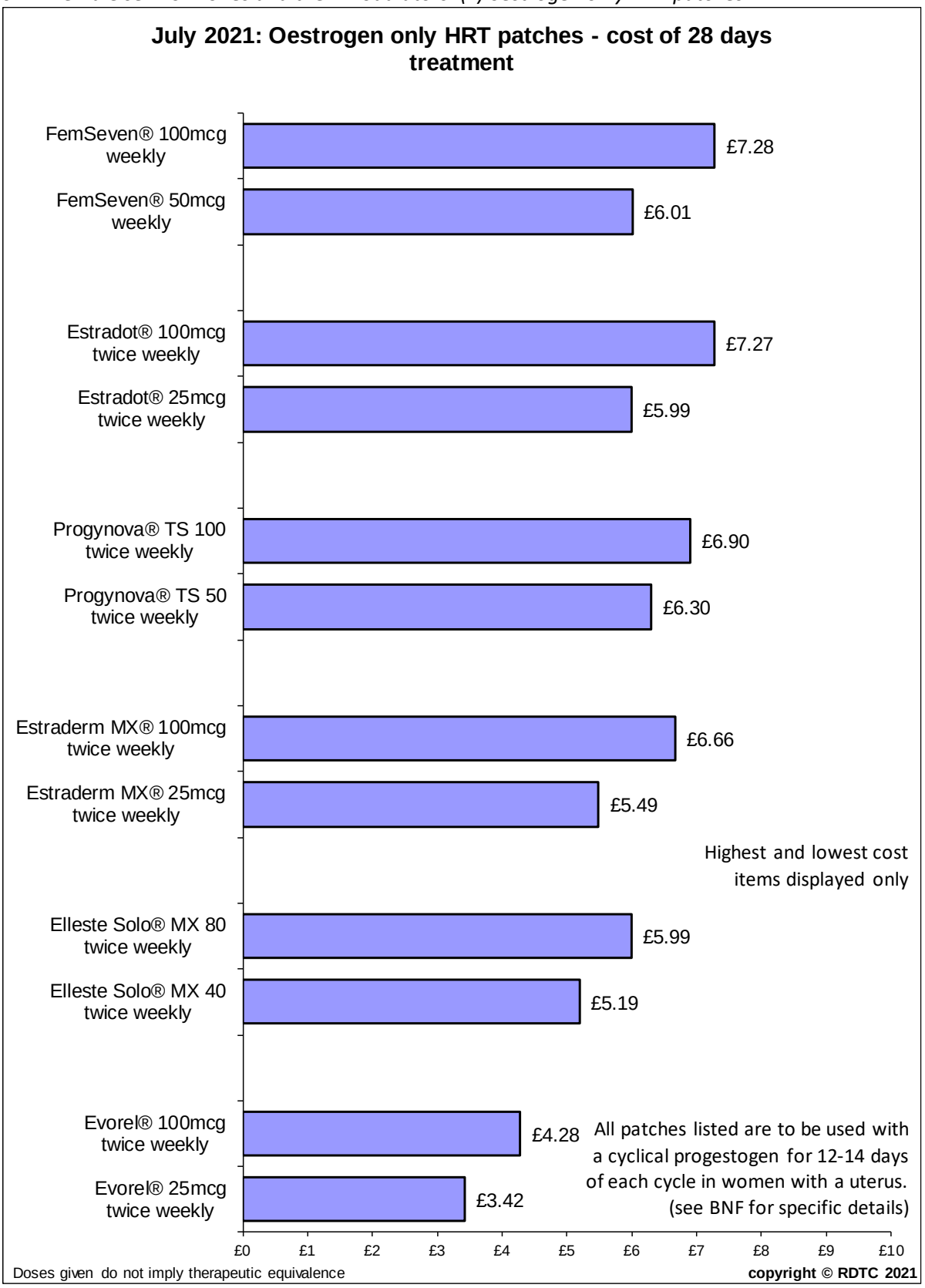
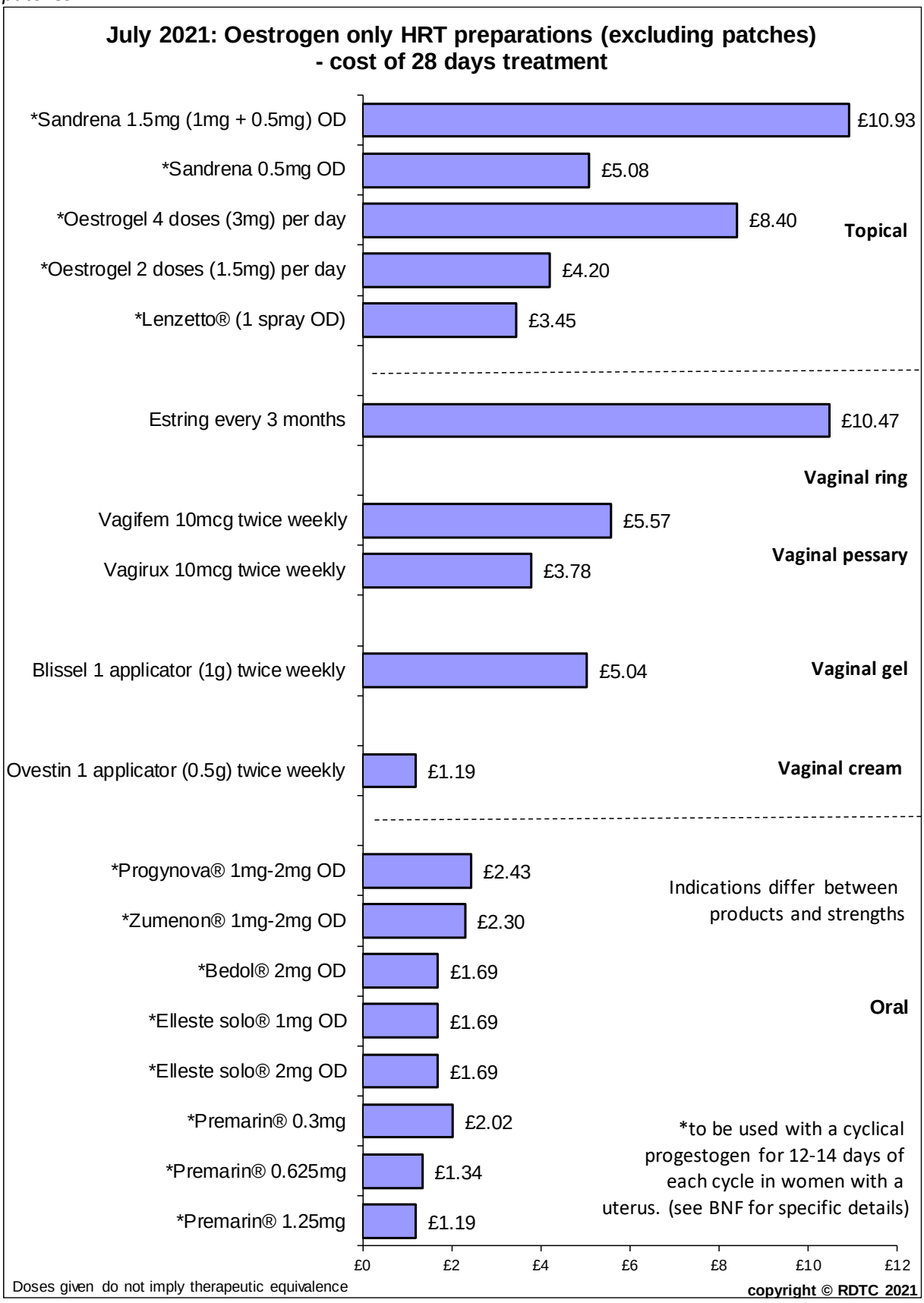

July 2021: Oestrogen only HRT patches - cost of 28 days treatment
FemSeven® 100mcg weekly
£7.28
FemSeven® 50mcg weekly
£6.01
Estradot® 100mcg twice weekly
£7.27
Estradot® 25mcg twice weekly
£5.99
Progynova® TS 100 twice weekly
£6.90
Progynova® TS 50 twice weekly
£6.30
Estraderm MX® 100mcg twice weekly
£6.66
Estraderm MX® 25mcg twice weekly
£5.49
Highest and lowest cost items displayed only
Elleste Solo® MX 80 twice weekly
£5.99
Elleste Solo® MX 40 twice weekly
£5.19
Evorel® 100mcg twice weekly
£4.28
Evorel® 25mcg twice weekly
£3.42
All patches listed are to be used with a cyclical progestogen for 12-14 days of each cycle in women with a uterus. (see BNF for specific details)
£0 £1 £2 £3 £4 £5 £6 £7 £8 £9 £10
Doses given do not imply therapeutic equivalence
copyright © RDTC 2021

6.4.1 Female sex hormones and their modulators: (iii) oestrogen only HRT preparations except patches



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