Chapter 6: Endocrine System

6.1 Drugs used in diabetes

6.1.1 Insulins

Consult BNF for full details.
Refer to Sheffield Guidelines on Diabetes:
https://www.intranet.sheffieldccg.nhs.uk/medicines-prescribing/prescribing-guidelines.htm

- Type 1 Diabetes: Insulin is usually initiated in secondary care following admission or urgent referral from primary care.
- Type 2 Diabetes: Insulin can be initiated in primary care with support from the community diabetes team.
- When prescriptions of insulin are prescribed, dispensed or administered, healthcare professionals should cross-reference available information to confirm the correct identity of insulin products.
- Brand prescribing of all insulins is recommended.
- In line with the NHS greener agenda, opting for prescribing insulin cartridges and reusable pens, where available, is preferred to the pre-filled pens to reduce the adverse environmental impact.

6.1.1.1 Short-acting insulins

Insulin aspart (analogue)
NovoRapid®: 3ml cartridge (for NovoPen® devices), 10ml vial (for pump and syringes users)

Insulin lispro (analogue)
Humalog®: 100units/ml 3ml cartridge (for Autopen® Classic or HumaPen®), 200units/ml KwikPen® 3ml disposable pen, 100units/ml 10ml vial (for pump and syringes users)

6.1.1.2 Intermediate and long-acting insulins

Isophane Insulin
Humulin I®: 3ml cartridge (for Autopen® Classic or HumaPen®), 10ml vial (for patients still using syringes)
Insulatard®: 10ml vial (for patients still using syringes)

Long-acting Insulin Analogues
Levemir® (Insulin detemir): 3ml Cartridge (for NovoPen® devices)
Tresiba® (Insulin degludec): 100units/ml solution for injection 3ml Cartridge (for Novo Nordisk® devices), 200units/ml FlexTouch® 3ml disposable pen
Toujeo® (Insulin glargine): 300units/ml solution for injection 1.5ml pre-filled SoloStar® pen and 3ml pre-filled DoubleStar® pen

- NICE guidance should be followed when prescribing long-acting insulin analogues. When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies
- Type 1 Diabetes in adults: diagnosis and management: https://www.nice.org.uk/guidance/ng17
- Type 2 Diabetes: The management of type 2 diabetes: https://www.nice.org.uk/guidance/ng28
- It is advisable where insulins are available in two strengths e.g., Tresiba® (insulin degludec) 100units/ml solution for injection or 200units/ml solution for injection 3ml Cartridge please take care in selecting the right strength
- Remove dose labelling and replace with “As directed” except at the prescriber’s discretion where there are processes in place to ensure the doses are always updated.

Biphasic Isophane Insulin
Humulin M3®: 10ml vial, 3ml cartridge (for most Autopen® Classic or HumaPen®)
Biphasic Analogue Insulin

Humalog® mix 25: 10ml vial, 3ml cartridge (for Autopen® Classic or HumaPen®)
Humalog® mix 50: 3ml cartridge (for Autopen® Classic or HumaPen®)
NovoMix® 30: 3ml cartridge (for NovoPen® devices)

6.1.1.3 Hypodermic equipment

Needles
Insupen Original needles 4mm, 5mm, 6mm
BD Viva needles 4mm, 5mm, 6mm

Syringes
U100 Insulin Syringe (with needle) 0.3ml (8mm), 0.5ml (8mm,12.7mm), 1ml (8mm, 12.7mm)

Accessories
B-D Safe-Clip® needle chopping device
Sharpsguard®, 1L, 5L

Sharpsafe 1.8L is specifically designed for the disposal of GLP-1 pens as the pens can be stacked on top of each other

6.1.2 Antidiabetic drugs
For place in therapy see Type 2 diabetes in adults: choosing medicines NICE guidance visual summary

6.1.2.1 Sulfonylureas
Gliclazide 80mg tabs – **not m/r preparation, tablet can be halved if 40mg is required**

Glibenclamide should be avoided in the elderly due to the risk of hypoglycaemia.

6.1.2.2 Biguanides
Metformin 500mg, 850mg tabs
Metformin m/r 500mg, 750mg, 1g tabs

Metformin
A slow increase of dose may improve gastrointestinal (GI) tolerability. **Avoid metformin in patients if eGFR falls below 30ml/min/1.73m^2; severe heart failure or severe liver disease because of increased risk of lactic acidosis.** Note maximum dose of the m/r preparation is 2g/day. Above this dose only standard release metformin should be used, although the usual maximum dose of standard release metformin is also 2g daily in divided doses.

The MHRA warned that reduced vitamin B12 levels is now considered to be a common side effect on patients on metformin, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. See MHRA alert for more information.
See Chaper 20: Common blood monitoring schedules for local recommendations on when to check serum vitamin B12 levels in patients on metformin treatment.

6.1.2.3 Other antidiabetic drugs

Sodium-glucose co-transporter-2 (SGLT2) inhibitors
Canagliflozin 100mg, 300mg tabs
Dapagliflozin 5mg, 10mg tabs
Empagliflozin 10mg, 25mg tabs
Ertugliflozin ▼ 5mg, 15mg tabs (currently there is no published CVD evidence)

The MHRA has issued safety alerts regarding the use of SGLT-2 inhibitors:

MHRA warning on ketoacidosis advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal. See MHRA alert for more information.

MHRA warning on increased risk of lower-limb amputation: canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect. Preventive foot care is important for all patients with diabetes. See MHRA alert for more information.

MHRA have warned that there have been reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perinium). If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and start treatment urgently. See MHRA alert for more information.

Dipeptidylpeptidase-4 (DPP-4) inhibitors
Sitagliptin 25mg, 50mg, 100mg tabs
Linagliptin 5mg tabs (only to be used only after sitagliptin tried or if eGFR <45mL/min/1.73m^2)

The MHRA have warned that there has been reports of acute pancreatitis associated with drugs in the DPP-4 inhibitor class of antidiabetic agents ('gliptins'). Gliptins should also not be prescribed in conjunction with Glucagon-Like Peptide-1 receptor agonists (GLP-1 RAs) as they both work on the same pathway increasing risk of associated acute pancreatitis.

Thiazolidinediones
Pioglitazone 15mg, 30mg, 45mg tabs

The MHRA have warned about a small increased risk of bladder cancer with pioglitazone. Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone. See MHRA alert for more information.

Glucagon-like peptide-1 (GLP-1) agonists
Dulaglutide (Trulicity®) 0.75mg/0.5ml,1.5mg/0.5ml injection-WEEKLY
Liraglutide (Victoza®) 6mg/ml (0.6mg, 1.2mg and 1.8mg doses only) injection-DAILY
Semaglutide (Ozempic®) 0.25mg/0.19ml, 0.5mg/0.37ml, 1mg/0.74ml injection – WEEKLY

Glucagon-like peptide-1 (GLP-1) agonists are classified as **amber** on the traffic light drug list.

Information for healthcare professionals and patients on NovoNordisk PenCycle recycling scheme.

Treatment of hypoglycaemia
Glucose (Glucogel®) 10g per 25g tube
Glucagon 1mg injection

6.1.6 Blood Glucose Monitoring
Accu-Chek® **Instant Testing Strips**

The Accu-Chek Instant system fully conforms to the requirements of EN ISO 15197:2015 & ISO 15197:2013.
Refer to the following documents for further guidance on self-monitoring of blood glucose:

Prescribing guidance in the self-monitoring of blood glucose (SMBG)
BGTS formulary choice

The SY ICB Guidance for Continuous Glucose Monitoring (CGM) in Adults and Children with Type 1 and Type 2 Diabetes can be found here.

6.2.1 Thyroid hormones

Levothyroxine sodium 25 microgram, 50 microgram and 100 microgram tabs

Levothyroxine (TEVA) brand is suitable for patients who have lactose intolerance, as well as the less common but more serious galactose intolerance. Further information can be found here.
Liothyronine is currently black on the traffic light drug list and requires an Individual Funding Request (IFR) if prescribing is required. Further information can also be found on the Liothyronine Q&A Guidance.

6.3.2 Glucocorticoid therapy

Prednisolone 1mg, 5mg tabs
Dexamethasone 500 micrograms, 2mg tabs; 2mg SF soluble tablets, 4mg SF soluble tablets

Patients who require a soluble formulation of prednisolone should be prescribed prednisolone tablets which can be crushed and mixed with cordial and sugar free jam(off-label). Without crushing they disperse in two to five minutes. See BMJ article for further information.
There is no conclusive evidence that enteric coated formulations reduce the risk of peptic ulcers.

An NHS Steroid Emergency Card should be issued to all patients with (or likely to develop) adrenal insufficiency or steroid dependence as they are at risk of an adrenal crisis during intercurrent illness or an invasive procedure/surgery if not managed appropriately. Please see additional guidance which contains detailed information to support identifying which patients require a Steroid Emergency Card and additional 'sick day rules'.

The following advice should be offered to patients:

- Glucocorticoids should preferably be taken in the morning (if the condition being treated will allow it) to minimise adverse effects
- Those without a history of chickenpox or measles should avoid close contact with people who have chickenpox, shingles, or measles and to seek urgent medical advice if they are exposed
- To seek medical advice if any mood or behavioural changes are experienced
- That regular monitoring is required

6.4.1 Female Sex Hormones

6.4.1.1 Oestrogens and Hormone Replacement Therapy (HRT)

Hormonal Replacement Therapy (HRT):

- See Appendix 1 "Deciding about HRT for managing menopausal symptoms" for prescribing guidance.
- See Appendix 2 for product information

Choice of HRT treatment should be individualised following informed discussion with the woman - see table for patient resources. Factors to consider include:

- Preference for 'body identical' products (e.g. estradiol and micronised progesterone). Use of transdermal estradiol with oral micronised progesterone, or with Mirena® intrauterine system, is a suitable first choice option.
- Venous thromboembolism (VTE) risk is reduced with transdermal compared with oral products. Transdermal administration is recommended in national guidelines for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2.[1,2]
- Age: for women over 60 years transdermal products are recommended as they have a reduced risk of stroke compared with oral administration.[2]
- Ease of use and potentially improved compliance with oral products.
- Transdermal products are suitable for women who cannot tolerate oral therapy or with liver dysfunction.
- Formulary first line oral choices are cost effective.

[1] NICE NG23 Menopause: diagnosis and management
[2] BMS/WHS Consensus statement HRT in menopausal women

Oestrogens for HRT

Brand prescribing is recommended

Estradiol only*****

Transdermal	**Evorel®** patches Estradot® patches **Oestrogel®** gel pump Lenzetto® spray Sandrena® gel sachets
Oral	**Elleste Solo®** tablets

*****If prescribing estradiol only products in women with a uterus additional progestogen for endometrial protection must be prescribed. See section 6.4.1.2 for progestogens.

See Chapter 7 (section 7.2.1) for topical oestrogen preparations for the treatment of urogenital atrophy.

See Trans Women Medication collaborative care guidelines for further information on prescribing of estradiol products for patients undergoing or having undergone gender dysphoria treatments.

Estradiol with progestogen

Sequential combined

Transdermal	Evorel® Sequi patches
Oral	**Elleste Duet®** tablets Femoston® tablets

Continuous combined

Transdermal	Evorel® Conti patches
Oral	**Elleste Duet® Conti** tablets **Kliovance®** tablets Bijuve® capsules Femoston® conti tablets

Tibolone

Tibolone 2.5mg tablets

Tibolone has oestrogenic, progestogenic and weak androgenic activity. It is given continuously without cyclical progestogen; unsuitable for use in perimenopause or within 12 months of the last period.

Raloxifene is not included in the formulary. It does not reduce menopausal vasomotor symptoms and is licensed only for the treatment and prevention of postmenopausal osteoporosis. It should normally be initiated by specialists in bone metabolism.
NICE does not recommend raloxifene as a treatment option for primary prevention of osteoporotic fragility fractures in postmenopausal women. It may be considered as an alternative option to the bisphosphonates for secondary prevention.
www.nice.org.uk/TA160 (Primary prevention)
www.nice.org.uk/TA161 (Secondary prevention)

6.4.1.2 Progestogens

Generic prescribing is recommended

Medroxyprogesterone acetate 2.5mg, 5mg, 10mg tabs *

Progesterone micronised (Utrogestan®, Gepretix®) 100mg oral capsules

* No medroxyprogesterone acetate (MPA) preparation is licensed for the progestogenic opposition of oestrogen only HRT in individuals with an intact uterus. However, this is an evidence-based treatment and 'off label' prescribing is recommended where MPA is the progestogen of choice.

Norethisterone 5mg tabs is not included as a formulary choice due to its thromboembolic risk and adverse effects on lipids. It is, however, the only progestogen licensed for the postponement of menstruation; off-label medroxyprogesterone is advised as an alternative (see Primary Care Woman's Health Forum top tips). Norethisterone is not licensed for progestogenic opposition of oestrogen only HRT in individuals with an intact uterus other than in combination products where a lower dose is used (see 6.4.1.1 and Appendix 2); 'off label' prescribing is not routinely recommended due to the lack of suitable strength (See Women's' Health Concern Statement regarding progestogens).

Mirena® levonorgestrel 20 micrograms/24 hours intrauterine delivery system (see chapter 7 section 7.3.2.3) is licensed for protection from endometrial hyperplasia during oestrogen replacement therapy for 4 years. However the FSRH recommends it can be used for up to 5 years. Off label use of other 52mg levonorgestrel intrauterine delivery system (LNG-IUS) e.g. Levosert®, but not those with a lower strength of levonorgestrel, is supported by the FSRH and the BMS. LNG-IUS provides contraception in the perimenopausal period.

For further information on use of progestogens to reduce the risk of endometrial hyperplasia with unopposed oestrogen replacement in individuals with an intact uterus, see BMS Tools for Clinicians Progestogens and endometrial protection.

BMS has also produced guidance on Management of unscheduled bleeding on hormone replacement therapy

6.4.2 Male sex hormones and antagonists

Nebido® (Testosterone undecanoate oily injection 250mg/ml)
Sustanon 250® (Testosterone esters oily injection 250mg/ml)
Testogel® 40.5mg gel (Testosterone 40.5mg/2.5mg gel unit dose sachets)
Tostran® 2% gel pump (Testosterone10mg per pump actuation)

Androgens should not be a treatment for impotence or impaired spermatogensis unless there is associated hypogonadism, which should be properly investigated. Refer to low testosterone pathway.

See Trans Men Medication collaborative care guidelines for further information on prescribing of testosterone products for patients undergoing or having undergone gender dysphoria treatments.

Refer to shared care protocol for the use of topical testosterone in the management of loss of libido in menopausal women. Testosterone products are not licensed for this indication but Testogel® sachets are preferred due to ease of administering the appropriate dose and less risk of high testosterone levels.

MHRA Drug Safety Update Jan 23: topical testosterone can accidentally be transferred to another adult or child through skin to skin contact. If repeated, this can lead to an increase in their blood testosterone levels with adverse effects. The alert provides further details and precautions to be taken.

Anti-androgens

Cyproterone acetate 50mg tabs
- Prescribing for prostate cancer (BNF 8.3.4.2) - see SC Guideline for Hormonal Management of Prostate Cancer for more information.
- Prescribing for male hypersexuality: specialist use only.
- Used at low dose in co-cyprindiol for acne and hirsutism see Chapter 13 (section 13.6.2) for more information

Finasteride 5mg tabs
- For benign prostatic hyperplasia – see Chapter 7 (section 7.4.1) for more information
- Note - Finasteride 1mg is not prescribable under the NHS for the treatment of androgenetic alopecia in men
- See MHRA safety warnings on rare reports of depression and suicidal thoughts associated with finasteride and reminder of the risk of psychiatric and sexual side effects. Healthcare professionals are reminded to monitor patients for both psychiatric and sexual side-effects.

See Trans Women Medication collaborative care guidelines for further information on prescribing of cyproterone or finasteride products for patients undergoing or having undergone gender dysphoria treatments.

6.5.2 Posterior pituitary hormones and antagonists

Prescribing desmopressin for diabetes insipidus: specialist initiation.
See Chapter 7 (Section 7.4.2) for information on prescribing for nocturnal enuresis.

6.6 Drugs affecting bone metabolism

Calcium and Vitamin D - Refer to chapter 9 section 9.6.4 and see advice below:

The daily recommended intake for calcium in elderly patients is 1000 – 1200mg. For all institutionalised or housebound elderly and those with a prior hip fracture, consider dietary intake of calcium and if the recommended daily amount is not being achieved then supplementation of Calcium and Vitamin D should be considered. Note supplementation at these doses does not require routine monitoring.

From 9.6.4

Calci-D® chewable tablets (1000mg calcium +1000 units vitamin D) (gelatine free)
NB. usual recommended daily dose – ONE daily

Adcal-D_3® Caplets (300mg calcium + 200 units vitamin D per caplet) (gelatine free)
NB. usual recommended daily dose – TWO twice daily providing daily dose of 1200mg calcium and 800 units vitamin D

For patients requiring a dissolvable calcium / vitamin D preparation, Adcal-D_3 Dissolve Effervescent Tablets is an appropriate alternative. The usual recommended daily dose is ONE twice daily providing a daily dose of 1200mg calcium and 800 units vitamin D.
For patients who require administration via enteral tube feeding, Cacit D_3 effervescent granules sachets are a suitable option as per NEWT guidelines recommendation.

Vitamin D

In July 2016, SACN and Public Health England updated their advice on the supplementation of Vitamin D. It is now recommended those patients at risk take a supplement all year round and those not at risk take a supplement containing 10 micrograms of Vitamin D during the autumn and winter months to help prevent Vitamin D deficiency. This should be alongside safe sun exposure and dietary intake.

In Sheffield, we encourage self-care and recommend patients to purchase low cost supplements from their local supermarkets or pharmacy, or if they are eligible via the national scheme. We discourage the prescribing of maintenance dose Vitamin D. However, certain eligible groups of patients will be able to have access to free Healthy Start Vitamins available from their local Family Hub . Please see 'The Sheffield Extended Healthy Start Scheme'

Risk groups:

Key recommendations for Healthcare Professionals are;

Promote vitamin D supplementation in at risk groups; consider; adding prompts to clinical records, recommend and record vitamin D supplementation whenever possible, e.g. flu clinics, newly registered patient template, medication review, falls follow up appointments.
Risk groups are;

- Infants and children aged under 4
- all pregnant and breastfeeding women, especially teenagers and young women
- older people aged 65 years and over
- people who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods
- people who have darker skin, for example people of African, African-Caribbean and South Asian origin, because their bodies are not able to make as much vitamin D
- those with particular dietary needs (for example, those who avoid nuts, are vegan or have a halal or kosher diet

Only check vitamin D status if patient has symptoms of deficiency or at very high risk

See Prescribing Guidelines under 'Vitamin D' for patient information leaflets to support self-care with vitamin D

Deficiency - Refer to local Adults, Pregnancy/Breastfeeding and Children's guidance.

Adults
InVita® D_3 50,000 IU soft capsules – weekly dose for 6 weeks

NB: For those patients with a low BMI (<20kg/m^2) a lower dose is indicated in this cohort of patients. This is in line with local guidance.
InVita® D_3 25,000 IU soft capsules – weekly dose for 6 weeks

If liquid preparation required:
InVita® D_3 25,000 or 50,000 IU oral solution – see above for appropriate dosing.

Please note InVita® D_3 25,000 and 50,000 IU capsules contain gelatine, however, this is Halal and Kosher certified, therefore, this formulary choice is suitable for those who follow a Halal or Kosher diet. However, they are not suitable for those who follow a vegetarian or vegan diet. Plenachol® 20,000 or 40,000 IU capsules are a suitable first line alternative for vegetarians. Please note, the InVita® oral solutions are also suitable for vegetarians, however this is not as cost effective. For further information on preparations suitable for vegetarians / vegans see here.

Pregnant / Breastfeeding Women
Fultium® - D_3 3,200 IU capsules – daily dose for 10 weeks

Children
Thorens 10,000 IU/ml oral drops solution – see guidelines for dosing

Insufficiency / post correction of deficiency – Refer to local Adults, Pregnancy/Breastfeeding and Children's guidance.

Patients who are identified as being insufficient or who have previously had vitamin D deficiency corrected should be advised first line to purchase a suitable supplement over the counter to prevent them from becoming deficient. Also refer to local guidelines (Links above and the self-care guidance)

Adults (including pregnant women) - Advise taking a daily supplement containing between 800IU – 1,000IU (20-25 micrograms) vitamin D.
Preparations can be obtained from community pharmacies, supermarkets or health food stores.
Children – Advise taking a supplement that provides 340 - 400 units / day (8.5 – 10 micrograms). Dose dependant on age.

Consider prescribing supplementation in the following groups;

- Calcium and vitamin D for Osteoporosis
- Has other active bone diseases and there are concerns about compliance i.e. Osteopenia
- Renal Disease
- If poor compliance and repeated episodes of deficiency
- In patients who may have a lifelong or chronic condition or have undergone surgery that results in malabsorption

Continuing need should however be reviewed on a regular basis

Adults
InVita® D_3 800 IU soft capsules – daily dose
InVita® D_3 25,000 IU soft capsules – monthly dose*
InVita® D_3 25,000 IU oral solution - monthly dose*

*Please note monthly dose can be an option in patients with compliance issues

Please note InVita® D_3 800 unit capsules contain gelatine; however this is Halal and Kosher certified, therefore this formulary option is suitable for those who follow a Halal / Kosher diet. However, they are not suitable for those who follow a vegetarian or vegan diet. Stexerol® 1000 IU tablets are a suitable alternative for vegetarians. For further information on preparations suitable for vegans see here

Pregnant / Breastfeeding women
Fultium® - D_3 800 IU capsules – daily dose

Children
Healthy Start Vitamins for Children – if eligible on extended scheme these are available from Family Hubs
InVita® D_3 2,400 IU/ml liquid drops – daily dose
Abidec® multivitamin drops (contains arachis oil) – daily dose
Dalivit® oral drops (only prescribe these if child has an allergy to peanuts) – daily dose

While children are taking multivitamin drops no other vitamin supplement containing vitamins A and D should be taken unless under medical supervision. Patients should not exceed the stated dose

6.6.2 Bisphosphonates and other drugs affecting bone metabolism

Risedronate 35mg tablets – weekly dose
Alendronic acid 70mg tablets – weekly dose

Risedronate once weekly should be the first line agent for all osteoporosis patients. All patients receiving a bisphosphonate should have an adequate calcium intake and be vitamin D replete. If these criteria are not met, then calcium and vitamin D supplementation should be considered. (Refer to chapter 9.6.4).

For patients who experience swallowing difficulties or for those who experience intolerable side effects despite following recommendations for administration could try Alendronic Acid 70mg effervescent tablets (Binosto®) as an alternative. Further information on bisphosphonates can be found here.

Additional information can also be accessed from NICE TA160 (primary prevention) and NICE TA161 (secondary prevention). Note NICE TA160 / 161 apply only to post menopausal women with osteoporosis.

Atypical femoral fractures have been reported rarely with bisphosphonate therapy. MHRA advises that the need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use. See NOGG guidance section 7 for more comprehensive information.

Fracture risk assessment requesting (FRAS / DEXA / bone density) is now on ICE – look under Radiology Specials. The Metabolic Bone Centre will no longer accept paper referrals. However, referrals for IV bisphosphonates and other metabolic bone disease referrals should still be sent on paper.

For younger postmenopausal women who are at an increased risk of fracture and are aged over 50 years, HRT should be used to prevent osteoporosis only in those who are intolerant of, or contraindicated for, other osteoporosis therapies. For further information please refer to NOGG guidance.

Denosumab can be prescribed under the SCP for the prevention of osteoporotic fractures in men and post-menopausal women in patients that are unable to take bisphosphonates (because of compliances problems, intolerance or contraindications, see NICE guidance). Due to risk of hypocalcaemia, calcium levels should be monitored and results reviewed prior to each injection.

Dental hygiene – patients on denosumab and bisphosphonates need to maintain good oral health to minimise the risk of osteonecrosis of the jaw. A dental examination with appropriate preventative dentistry should be considered prior to treatment. The Metabolic Bone Centre will assess dental hygiene prior to initiating denosumab.

Advise all patients on bisphosphonates and denosumab: to maintain good oral hygiene, receive routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain or swelling to a doctor and dentist. Whilst on treatment patients should avoid invasive dental procedures, if possible.

Version control: 9th edition April 2023

Section 6.1.1 to 6.1.2 – reviewed and updated Mar 23; 6.1.1.1 minor amendment May 24 6.1.1.2 minor amendment Sept 23 and May 24; 6.1.1.3 minor amendment Oct 23 and May 24. Section 6.1.6 minor amendment May 2024. Review date Mar 2026.
Section 6.2.1, 6.3.2, 6.6, 6.6.2 – reviewed and updated Feb 22; 6.6 minor amendment Mar 23 and Dec 23; 6.6.2 minor amendment June 23. Review date Feb 2025
Sections 6.4.1 and 6.4.2 – reviewed and updated April 22; minor amendment 6.4.1.2, appendix 2 April 23 and May 24; 6.4.2 minor amendment May 24. Review date April 2025. Section 6.1.1.2 reviewed and updated 16/01/2025. Review date Feb 2026.

Appendix 1: Deciding about HRT for management of menopausal symptoms

Women should be advised about lifestyle modifications to reduce menopausal symptoms.

- See NICE guidance NG23 for full details of benefits and risks of HRT, including risk tables (section 1.5). Note: This guideline covers the diagnosis and management of menopause. When evaluating data about the long term effects of HRT, the age that HRT treatment is commenced should be considered. Current advice to offer HRT for menopausal symptoms means that it is likely to be initiated in women aged 45 to 55 years (average age of menopause in the UK is 51 years).The absolute risk of conditions such as VTE, stroke, heart disease and breast cancer is low in this age group but increases with age.

- When considering HRT, the balance of risks and benefits should be carefully weighed on an individual basis and discussed with the woman to allow informed decision making. Treatment should be reviewed at three months to assess efficacy and tolerability. A review of therapy and discussion of an individual's risk:benefit ratio for continuing HRT should occur at least annually.

    - HRT effectively treats menopausal vasomotor symptoms and menopausal low mood.
        - Urogenital atrophy - offer vaginal oestrogen (including to those on systemic HRT) and continue for as long as needed to relieve symptoms. See Chapter 7 (section 7.2.1) for more information.
        - Note that there is no clear evidence that SSRIs/SNRIs ease low mood in menopausal women without a diagnosis of depression. Consider HRT or CBT.
    - The lowest effective dose of HRT should be used for the shortest possible time.
        - Older women may be less tolerant of oestrogen and need to start (and are usually maintained) on a lower dose (for example 1 mg of oral estradiol or 25–50 micrograms of transdermal estradiol).
        - Younger women may require higher doses (for example 2mg of oral estradiol or 100 micrograms of transdermal estradiol) to remain symptom-free.
    - Refer to prescribing information in the NICE Clinical Knowledge Summary on Menopause or individual product SPCs for a full list of contraindications

    - The risks of HRT include an increase in VTE, CVD, breast and ovarian cancer; see NICE NG23 tables (section 1.5)
        - **Venous thromboembolism (VTE) -** risk of VTE associated with HRT is greater for oral than transdermal preparations. Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis compared with that noted with other progestogens (BMS Mar 2021).
        - **Coronary heart disease (CHD) and stroke –**
            - HRT with oestrogen alone is associated with no, or reduced, risk of CHD;
            - HRT with oestrogen and progestogen is associated with little or no increase in the risk of CHD;
            - Oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke.
        - **Breast cancer –** the risks of breast cancer with HRT was updated by the MHRA (Drug Safety Update Aug 2019**):** HRT with oestrogen alone and in combination with a progestogen is associated with an increase in the risk of breast cancer. The risk is greater for oestrogen combined with progestogen than for oestrogen alone and increases with duration of use. After stopping HRT, the risk reduces compared with current users, but remains increased for more than 10 years in ex-users compared with non-users. The risk is not affected by the route of administration (oral v transdermal), although there is no evidence of an increased risk with topical oestrogen applied directly via the vagina to treat local symptoms.
          Whilst the MHRA reported that the risk was irrespective of the type of oestrogen or progestogen, micronised progesterone and dydrogesterone may have a lower risk than other oral progestogens (BMS Mar 2021)
        - **Ovarian cancer** - Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer (MHRA Drug Safety Update Dec 2014)

- Tibolone increases risk of stroke but limited data do not suggest an increased risk of VTE. The increase in breast cancer risk is less than with combined HRT. See MHRA Drug Safety Update (Dec 2014). There is insufficient data on the risk of CHD with tibolone.
- Experience of treating women over 65 years with HRT is limited.
- See NICE guidance NG23 for management of premature ovarian insufficiency.

Sources of further information

For Healthcare Professionals	For Patients
NICE NG23 – Menopause: diagnosis & management https://www.nice.org.uk/guidance/ng23 Nov 2015, updated Dec 2019 (under review – due August 2023)	Womens Health Concern – Factsheets for patients https://www.womens-health-concern.org/help-and-advice/factsheets/menopause/
NICE CKS clinical topic: Menopause http://cks.nice.org.uk/menopause	NHS Choices clinical topic: Menopause http://www.nhs.uk/Conditions/Menopause/Pages/Introduction.aspx
PrescQIPP bulletin – Menopause https://www.prescqipp.info/resources/category/365-menopause May 2017 - under review	Menopause Matters www.menopausematters.co.uk
MHRA Drug Safety Update Hormone-replacement therapy: updated advice (Article date Sept 2007; published Dec 2014) https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-updated-advice	The Menopause Exchange www.menopause-exchange.co.uk
MHRA Drug Safety Update Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping. (Aug 2019) https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-hrt-further-information-on-the-known-increased-risk-of-breast-cancer-with-hrt-and-its-persistence-after-stopping	The Daisy Network – Premature menopause support www.daisynetwork.org.uk
MHRA Drug Safety Update Tibolone: benefit-risk balance (Article date Sept 2007; published Dec 2014) http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON079163	Rock My Menopause https://rockmymenopause.com/
British Menopause society – tools for clinicians https://thebms.org.uk/publications/tools-for-clinicians/	
Electronic Medicines compendium - for individual drug SPCs https://www.medicines.org.uk/emc/	
BNF https://bnf.nice.org.uk/	

Please note: The sources of information listed for patients include those from NICE NG23 - Information for the Public. NICE and Sheffield place, SY ICB are not responsible for the quality or accuracy of any information or advice provided by these organisations.

Appendix 2: Product Information: HORMONE REPLACEMENT THERAPY

Note - First choice preparation of each type indicated in **bold**. Abbreviations - Bleed: N/A = Not applicable M = Monthly X = No bleed

Preparation	Formulation	Oestrogen	Progestogen	Dose	Bleed	No. of Rx charges[#]
Women without uterus (or with uterus if prescribed with a licensed progestogen)						
Unopposed oestrogen preparations (NB in endometriosis foci may remain despite hysterectomy and addition of progestogen should be considered)						
Elleste Solo®	Tablet	Estradiol 1mg, 2mg	N/A	One tablet daily	N/A	1
Evorel®	Patch	Estradiol 25 / 50 / 75 / 100microgram over 24 hrs	N/A	One patch twice weekly	N/A	1
Estradot®	Patch	Estradiol 25 / 37.5 / 50 / 75 / 100microgram over 24 hrs	N/A	One patch twice weekly	N/A	1
Oestrogel®	Gel	Estradiol 0.75 mg/metered dose (one pump actuation)	N/A	Two pumps once daily increasing to a maximum of four pumps once daily	N/A	1
Lenzetto®	Spray	Estradiol 1.53 mg/spray	N/A	One spray once daily increasing to a maximum of three sprays once daily	N/A	1
Sandrena®	Gel	Estradiol 0.5mg/0.5g, 1mg/1g (one sachet)	N/A	Apply 1 mg once daily. Dose may be adjusted after two to three cycles to lowest effective dose; usual dose 0.5–1.5 mg daily.	N/A	1
Women with uterus						
Sequential combined						
Elleste Duet®	Two separate tablets	Estradiol 1mg, 2mg Estradiol 1mg, 2mg	Norethisterone 1mg	Estradiol daily x 16 days Estradiol+norethisterone daily x 12 days	M	2
Femoston®	Two separate tablets	Estradiol 1mg, 2mg Estradiol 1mg, 2mg	Dydrogesterone* 10mg	Estradiol daily x 14 days Estradiol+dydrogesterone daily x 14 days	M	2
Evorel® Sequi	Two separate patches	Estradiol 50microgram/24hrs Estradiol 50microgram/24hrs	Norethisterone 170microgram/24hrs	Estradiol patch twice weekly x 2 weeks Combined patch twice weekly x 2 weeks	M	2
Continuous combined (***unsuitable for use in perimenopause or within 12 months of the last period***)						
Kliovance®	Tablet	Estradiol 1mg	Norethisterone 500microgram	One tablet daily	X	1
Elleste Duet® Conti	Tablet	Estradiol 2mg	Norethisterone 1mg	One tablet daily	X	1
Femoston® Conti	Tablet	Estradiol 0.5mg Estradiol 1mg	Dydrogesterone* 2.5mg Dydrogesterone* 5mg	One tablet daily	X	1
Bijuve®	Capsule (contains gelatine)	Estradiol 1mg	Progesterone micronised* 100mg	One capsule daily	X	1
Evorel® Conti	Patch	Estradiol 50microgram/24hrs	Norethisterone 170microgram/24hrs	One patch twice weekly	X	1

Preparation	Formulation	Oestrogen	Progestogen	Dose	Bleed	No. of Rx charges[#]
Women with uterus						
Progestogens** (required if taking unopposed oestrogen and no Mirena® coil or other 52mg LNG-IUS)						
Medroxyprogesterone acetate (generic) Note: 'off label' indication	Tablet	N/A	Medroxyprogesterone 2.5mg, 5mg and 10mg	Sequential: Two tablets daily for the last 14 days of each 28-day oestrogen HRT cycle. Continuous combined regimen: 2.5mg/5mg po daily	**M**	**1**
Utrogestan®	Capsule (contains gelatine and soybean lecithin)	N/A	Progesterone micronised 100mg	**Licensed dose:** Two capsules daily at bedtime, for twelve days in the last half of each therapeutic cycle (beginning on day 15 of the cycle and ending on day 26). Withdrawal bleeding may occur in the following week Alternatively one capsule at bedtime from day 1 to day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule **Unlicensed dose**: Sequential regimen***: Two capsules every night for 2 out of 4 weeks Continuous regimen: One capsule every night.	**M** (No bleed if taking continuous regimen)	**1**

[#] The HRT prepayment certificate, introduced on 1 April 2023, saves money for those who pay 3 or more HRT prescription charges within 12 months; note this only applies to products licensed for HRT, see list here. Full details are in the DHSC guidance (Mar 23). We advise 3 months initial prescribing of HRT preparations; once stable 6 monthly on a 12 month repeat, in line with the annual review. Prescribers also need to be mindful of any serious shortage protocols (SSPs) in place that may limit the duration to a 3 month's supply.

*These progestogens are less androgenic and are sometimes better tolerated than norethisterone but are more expensive.
**For further information see BMS guidance: Progestogens and endometrial protection and Management of unscheduled bleeding on hormone replacement therapy
***Commonly accepted practice as dosing regime is easier to remember and therefore improves adherence.

For HRT dosage equivalent see BMS guidance. A rule of thumb for transdermal estradiol products:
1 50microgram patch **or** 1mg Sandrena® sachet
2 pumps Oestrogel®

3 sprays Lenzetto® (this is the maximum licensed dose)