# Shared care protocol

## Amiodarone for patients within adult services

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| Version: | RDTC v1.0 | Replaces version: | LSCMMG combined amiodarone and dronedarone SCG version 1.1 |
| Clinical content last reviewed: | October 2023. | Next review date: | October 2025 |

| Version | Date published | Changes since previous version |
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| RDTC v1.0 | 7th December 2023 | Hyperlinks updated to link to current resources. Minor amendments to wording and grammar, for clarity. Advice added:<br>• Consider tests for thyroid peroxidase antibodies at baseline; monitor TFTs until stable at initiation; monitor INR for at least 7 weeks in warfarinised patients and more regularly thereafter; consider checking transfer factor if respiratory symptoms occur.<br>• Advice from MHRA Drug Safety Update (March 2022), particularly to consider CT scan in patients with respiratory symptoms and link to patient card.<br>• Additional clarity on which drugs affecting QTc interval are contraindicated.<br>• Updated advice on management of thyroid dysfunction to align with guidance from the Association of Clinical Biochemistry, British Thyroid Association, and British Thyroid Foundation. |
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**Local review and adoption**

| Local approval | Date |
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| Local content added | 2nd May 2024 |
| Approved for use by LSCMMG | 9th May 2024 |
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Clinical content has been reviewed and updated by the RDTC on the date indicated above. Every effort is made to keep the content up to date. These templates are provided to the North West and North East and Yorkshire ICBs for localisation and approval through standard ICB processes. The most recent version is available on the RDTC website at https://rdtc.nhs.uk/publication-type/shared-care/.

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## Shared Care Protocol

### Amiodarone for patients within adult services

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| **1. Background** | Amiodarone is used in the treatment of arrhythmias, as detailed in section 2. It has an important place in the treatment of severe cardiac rhythm disorders where other treatments either cannot be used or have failed. Amiodarone has potentially serious adverse effects and its use requires regular monitoring.<br>Due to the significant safety concerns, NHS England (NHSE) guidance advises that prescribers should not initiate amiodarone in primary care for any new patients. In exceptional circumstances, if there is a clinical need for amiodarone to be prescribed, this must be initiated by a specialist and only continued under a shared care arrangement. Amiodarone should only be prescribed when other treatment cannot be used or have failed, or is in line with NICE clinical guidance Atrial fibrillation: NG196. NICE defines the place in therapy of amiodarone in NG196, and has made a "Do not do" recommendation: "Do not offer amiodarone for long-term rate control".<br>Where there is an existing cohort of patients taking amiodarone who are not currently under shared care, it is recommended that these patients be reviewed to ensure that prescribing remains safe and appropriate and a shared care arrangement is introduced.<br>This document applies to adults aged 18 and over. |
| **2. Licensed and agreed off-label indications** | Licensed indications:<br>• Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.<br>• Atrial flutter fibrillation / atrial fibrillation when other drugs cannot be used.<br>• All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias and ventricular fibrillation when other drugs cannot be used. |
| **3. Locally agreed indications** | In addition to the above, licensed indications, LSCMMG have agreed to the follow use for shared care:<br>Use for post operative atrial fibrillation (post-CABG; note: only if it has been decided that treatment should continue long-term following post operative review).<br>**Please note:** If being initiated for post operative atrial fibrillation (post-CABG) shared care should only be initiated if it has been decided that treatment should continue long-term following the post operative follow up appointment. Secondary care is responsible for supplying amiodarone until the follow up appointment, which is usually six-weeks. |
| **4. Initiation and ongoing dose regime** | Transfer of monitoring and prescribing to primary care is normally after at least 1 month, and when the patient's dose has been optimised and with satisfactory investigation results for at least 1 month.<br>The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.<br>All dose or formulation adjustments will be the responsibility of the specialist unless directions have been discussed and agreed with the primary care clinician.<br>Termination of treatment will be the responsibility of the specialist.<br><br>**Initial stabilisation:**<br>200mg three times per day for one week, then reduce to 200mg twice per day for one week.<br>Amiodarone is initiated with a loading dose in order to achieve adequate tissue levels rapidly. Rarely, the specialist team may use an alternative loading regimen. |

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| | **The loading period must be prescribed by the initiating specialist.**<br><br>**<u>Maintenance dose (following initial stabilisation):</u>**<br>200mg per day, or less if appropriate. The minimum dose required to control the arrhythmia should be used.<br>Rarely, a higher maintenance dose may be required. The maintenance dose should be reviewed regularly, particularly if it exceeds 200mg per day.<br>**The initial maintenance dose must be prescribed by the initiating specialist.**<br><br>**Conditions requiring dose adjustment:**<br>Although there is no evidence that dose requirements for elderly patients are lower, they may be more susceptible to bradycardia and conduction defects if too high a dose is prescribed. The minimum effective dose should be used. Particular attention should be paid to monitoring thyroid function. |
| **5. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialist** | Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in the immediate future will prescribing and monitoring be transferred to primary care.<br><br>**<u>Baseline investigations:</u>**<br>• Thyroid function tests (TFTs; free T4, free T3 and TSH). Consider testing for thyroid peroxidase antibodies for people with elevated TSH.<br>• Liver function tests (LFTs, particularly transaminases)<br>• Urea and electrolytes (U&Es, including magnesium and potassium)<br>• Electrocardiogram (ECG)<br>• Chest X-ray<br>• For patients taking warfarin: monitor international normalised ratio (INR) at baseline and during dose stabilisation period, in close collaboration with the anticoagulant clinic or other appropriate service.<br>• For patients taking digoxin: clinical monitoring is recommended and the digoxin dose should be halved. Digoxin levels should be monitored appropriately and the dose titrated.<br><br>**<u>Initial monitoring:</u>**<br>• Where results are borderline, monitor TFTs every six weeks until stable.<br>• For patients taking warfarin: monitor INR for at least 7 weeks, in close collaboration with the anticoagulant clinic or other appropriate service.<br><br>**<u>Ongoing monitoring:</u>**<br>• ECG (at least annually)<br>• If respiratory symptoms or toxicity suspected: chest X-ray, high resolution CT scan, and pulmonary function tests including, where possible, transfer factor.<br>After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 6 remains appropriate. |

## 6. Ongoing monitoring requirements to be undertaken by primary care

If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.

| **Monitoring** | **Frequency** |
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| • Thyroid function tests (free T4, free T3 and TSH)<br>• LFTs (particularly transaminases)<br>• U&Es (including magnesium and potassium) | Perform all tests every 6 months during treatment, and 6 months after discontinuation.<br>Thyroid function should continue to be monitored for up to 12 months after discontinuation, with frequency determined clinically. |
| ECG | At least annually |
| For patients taking warfarin: INR | More frequent INR monitoring is required by the patient's usual warfarin monitoring service during treatment and after discontinuation. The warfarin dose should be adjusted according to the INR as required. |

## 7. Pharmaceutical aspects

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| Route of administration: | Oral |
| Formulation: | Tablets; 100mg and 200mg |
| Administration details: | Maintenance dose can be given once daily, however doses >200 mg daily (including loading period) may be given as split doses to minimise nausea.<br>If necessary, tablets may be crushed and dispersed in water or fruit juice, but have a bitter taste (unlicensed). Different brands may disperse in water at notably different rates. The solution for injection is irritant and should not be given orally. |
| Other important information: | The half-life of amiodarone is very long, with an average of 50 days (range 20-100 days). Side effects slowly disappear as tissue levels fall. Following drug withdrawal, residual tissue bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered.<br>Grapefruit juice should be avoided during treatment with oral amiodarone and for several months after discontinuation (see section 9). |

| **8. Cautions and contraindications** | This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.<br><br>**Contraindications:**<br>• Sinus bradycardia and sino-atrial heart block; severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease (unless pacemaker fitted) |
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| | • History of thyroid dysfunction. Use of amiodarone may be considered in patients who are euthyroid, after case-by-case assessment of the risks and benefits and with appropriate monitoring.<br>• Known hypersensitivity to iodine or amiodarone, or any of the excipients (including patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption)<br>• Concurrent use with certain medicines that may prolong the QT interval or increase the risk of Torsades de Pointes, e.g. moxifloxacin, Class Ia anti-arrhythmic drugs such as quinidine, class III anti-arrhythmic drugs such as sotalol, intravenous erythromycin, co-trimoxazole or pentamidine injection, some anti-psychotics e.g. chlorpromazine, fluphenazine, pimozide, haloperidol, amisulpride, lithium and tricyclic anti-depressants e.g. doxepin, amitriptyline, certain antihistamines e.g. terfenadine, anti-malarials e.g. quinine, mefloquine, chloroquine<br>• Pregnancy - except in exceptional circumstances (see section 12)<br>• Breastfeeding<br><br>**Cautions:**<br>• Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system; it is subject to a number of cautions. Because these reactions may be delayed, patients on long-term treatment should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given. See MHRA advice. |
| **9. Significant drug interactions** | The following list is not exhaustive. Please see BNF & SPC for comprehensive information and recommended management.<br><br>**Amiodarone is associated with a large number of interactions, some of which are significant enough to contraindicate concurrent use, require dose adjustment and/or additional monitoring (see section 8).**<br><br>Amiodarone is an enzyme inhibitor and can increase exposure to a number of medicines including:<br>• P-glycoprotein (PgP) substrates (e.g. digoxin, dabigatran)<br>• CYP2C9 substrates (e.g. warfarin, phenytoin)<br>• CYP3A4 substrates (e.g. ciclosporin, statins, fentanyl, sildenafil, colchicine)<br>• CYP2D6 substrates (e.g. flecainide)<br><br>Amiodarone interacts with other medicines that:<br>• prolong the QT interval (e.g. clarithromycin, fluoroquinolones) and increase the risk of Torsades de Pointes (see section 8)<br>• lower heart rate (e.g. beta-blockers, calcium channel blockers)<br>• induce hypokalaemia (e.g. diuretics, stimulant laxatives)<br>• induce hypomagnesaemia (e.g. diuretics, systemic corticosteroids)<br><br>Other interactions include:<br>• CYP3A4 and CYP2C8 inhibitors: may increase exposure to amiodarone (e.g. cimetidine, letermovir, ritonavir, darunavir, grapefruit juice) |

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| | • Sofosbuvir with daclatasvir; sofosbuvir and ledipasvir: risks of severe bradycardia and heart block when taken with amiodarone; see MHRA advice.<br>• Simeprevir with sofosbuvir: risk of severe bradycardia and heart block see MHRA advice.<br><br>**Due to the long half-life of amiodarone, there is potential for drug interactions to occur for several weeks/months after treatment has been discontinued.** See SPC for information on managing interactions. |

**10. Adverse effects and management**

As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance**.** For information on incidence of ADRs see relevant SPCs.

**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** www.mhra.gov.uk/yellowcard.

**The most serious toxicity with amiodarone is seen with long-term use and patients may therefore present first to primary care. Due to the long half-life of amiodarone, there is potential for adverse effects to occur for several weeks/months after treatment has been discontinued.**

| **Adverse effect** | **Management** |
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| Electrolyte deficiency:<br>hypokalaemia / hypomagnesaemia | Continue amiodarone. Correct deficiency as per local guidelines. Review other medicines that may be contributing to a deficiency. |
| **Cardiovascular effects:**<br>Bradycardia:<br>Heart rate 50 - 60bpm without symptoms | Continue amiodarone. Repeat monitoring. No action required unless symptoms develop or heart rate decreases further. |
| Heart rate 50bpm or less, or 60bpm or less with symptoms | Discuss with specialist team; dose reduction may be required. |
| Worsening of arrhythmia, new arrhythmia, or heart block | **Stop amiodarone.** Urgent referral to initiating specialist. |
| **Thyroid dysfunction**:<br>Borderline results according to local reference range | Continue amiodarone. Repeat test after 6 weeks. |
| Hyperthyroidism / thyrotoxicosis:<br>high T4, normal/high T3, low (less than 0.1 mU/L) or undetectable TSH | **Stop amiodarone.** Urgent referral to initiating specialist and endocrinologist. |
| Hypothyroidism:<br>low T4, high TSH | Continue amiodarone. Inform initiating specialist. Consider starting levothyroxine based on initiating specialist's advice. Monitor levothyroxine according to local pathways. |

| Adverse effect | Management |
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| Subclinical hypothyroidism<br>normal T4, raised TSH; clinical features not overtly manifest | Contact specialist team for advice, which may include input from endocrinology services.<br>Anticipate the need for additional monitoring, investigations and potentially thyroid hormone replacement based on specialist recommendations. |
| **Ophthalmological effects:**<br>Optic neuropathy / neuritis;<br>blurred or decreased vision | **Stop amiodarone.** Urgent referral to initiating specialist and ophthalmology. |
| Corneal micro-deposits:<br>Blueish halos when looking at bright lights, with no blurred or decreased vision.<br>Micro-deposits are usually limited to the area under the pupil, and usually only discernible by slit-lamp examination. | Continue amiodarone; reversible on discontinuation. The deposits are considered essentially benign and do not require discontinuation of amiodarone.<br>Encourage annual optician visits. |
| **GI disturbance**: nausea, anorexia, vomiting, taste disturbance | Continue amiodarone. May require dose reduction; discuss with specialist if persistent. |
| **Hepatotoxicity**:<br>abnormal LFTs +/- symptoms of hepatic injury (e.g. hepatomegaly, weakness, ascites, jaundice) | If serum transaminases elevated >3xULN but no symptoms of hepatic injury continue amiodarone and – repeat LFTs in 2 weeks. If still elevated may require dose reduction; discuss with specialist.<br>If serum transaminases >5xULN or any symptoms of hepatic injury- **stop amiodarone**. Urgent referral to initiating specialist and hepatologist. |
| **Neurological symptoms**:<br>Extrapyramidal tremor, ataxia, peripheral neuropathy, myopathy | Continue amiodarone. May require dose reduction; discuss with specialist. |
| **Pulmonary toxicity**: including pneumonitis or fibrosis<br>new/worsening cough, shortness of breath or deterioration in general health (e.g. fatigue, weight loss, fever) | **Stop amiodarone.** Urgent referral to initiating specialist and respiratory specialist. Admission may be required. |
| **Skin and subcutaneous tissue disorders**:<br>life threatening or even fatal cutaneous reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) | **Stop amiodarone.** Urgent referral to dermatology, inform initiating specialist. |
| Photosensitivity | Continue amiodarone. Reinforce appropriate self-care e.g. sun avoidance and purchasing of a broad spectrum sunscreen (at least SPF30). |
| Skin discolouration (blue/grey):<br>occurs in unprotected, light exposed skin | Continue amiodarone. May require dose reduction; discuss with specialist.<br>Reinforce self-care measures (as for photosensitivity above). Pigmentation slowly disappears following treatment discontinuation. |

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| **11. Advice to patients and carers**<br><br>The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual drugs. | **The patient should be advised to <u>stop taking amiodarone</u> and report any of the following signs or symptoms to their primary care prescriber without delay:**<br>• New or worsening breathlessness, or non-productive cough<br>• Deterioration in general health (e.g. fatigue, fever, weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in menstrual periods, swelling of the neck (goitre), nervousness, irritability, restlessness, or decreased concentration)<br>• New or worsening visual disturbances<br>• Progressive skin rash +/- blisters or mucosal lesions<br>• Signs and symptoms of bradycardia or heart block, e.g. dizziness, fatigue, fainting, shortness of breath, chest pain or palpitations, confusion or trouble concentrating, uneven or erratic heartbeat<br>• yellowing of the skin or eyes (jaundice), feeling tired or sick, loss of appetite, stomach pain, or high temperature<br><br>**The patient should be advised:**<br>• To use appropriate self-care against the possibility of phototoxic reactions: e.g. sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use a broad spectrum sunscreen (at least SPF30). These measures should be continued for the duration of therapy and for several months after discontinuation.<br>• If taking a statin and amiodarone, to report any signs of unexplained muscle pain, tenderness, weakness or dark coloured urine.<br>• Avoid grapefruit and grapefruit juice while taking amiodarone and for several months after discontinuation.<br>• Although there have been no case reports on enhanced hepatoxicity with alcohol, patients should be advised to moderate their alcohol intake to no more than 14 units per week while taking amiodarone.<br>• Always read the Patient Information Leaflet provided with medicines and follow the advice on other medicines to avoid and what to do a side effect occurs.<br><br>**Patient information**:<br>• A patient card is available for all patients that take amiodarone. This card includes important information on the most serious and potentially life-threatening side-effects (and their symptoms) that may occur during treatment with amiodarone and also reminds patients of the potential for drug to drug interactions.<br>• British Heart Foundation – anti-arrhythmics |
| **12. Pregnancy, paternal exposure and breastfeeding** | It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.<br><br>**Pregnancy**:<br>Due to the risk of neonatal goitre, amiodarone should only be prescribed in pregnancy if there is no alternative. Under these circumstances prescribing and monitoring will be the responsibility of the initiating specialist. |

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| | **Breastfeeding**:<br>Amiodarone is excreted into the breast milk in significant quantities; breast feeding is considered contraindicated due to the potential risk of iodine-associated adverse effects in the infant.<br>• Information for healthcare professionals: UK Drugs in Lactation Advisory Service |
| **13. Specialist contact information and arrangements for referral** | The specialist team should:<br>• make contact with the patient's GP requesting them to prescribe under a shared care agreement as soon as practicably possibly after the initial supply has been provided to the patient. Please note secondary care retains responsibility for monitoring and supply until the GP has agreed to prescribe under this shared care agreement.<br>• Share the results of any blood monitoring with primary care.<br>• Reassess the patient after 3 months for clinical response.<br>• Prior to entering into a shared-care agreement, secondary care will advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment.<br>• Secondary care should ensure that clear backup arrangements exist for GPs to obtain advice if required. |
| **14. Additional information** | Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details. |
| **15. References** | 1. British National Formulary. Accessed via https://bnf.nice.org.uk/ on 18/10/23.<br>2. Amiodarone hydrochloride 200 mg tablets. Ennogen Pharma Ltd. Date of revision of the text: 14/02/23. Accessed via https://www.medicines.org.uk/emc/ on 28/10/23.<br>3. Amiodarone hydrochloride 100 mg tablets. Accord Healthcare Ltd. Date of revision of the text: 27/01/22. Accessed via https://products.mhra.gov.uk/ on 18/10/23.<br>4. Amiodarone hydrochloride 200 mg tablets. Accord Healthcare Ltd. Date of revision of the text: 27/01/22. Accessed via https://products.mhra.gov.uk/ on 18/10/23.<br>5. Amiodarone hydrochloride 200mg tablets (Amiodarone Milpharm). Aurobindo Pharma- Milpharm Ltd. Date of revision of the text 14/08/2020. Accessed via https://www.medicines.org.uk/emc/ on 15/01/2021.<br>6. NHS England. Items which should not routinely be prescribed in primary care: policy guidance. August 2023. Last updated October 2023. Accessed via https://www.england.nhs.uk/long-read/items-which-should-not-routinely-be-prescribed-in-primary-care-policy-guidance/ on 18/10/23.<br>7. NICE. NG196: Atrial fibrillation: diagnosis and management. Last updated June 2021. Accessed via https://www.nice.org.uk/guidance/ng196 on 28/04/21.<br>8. Specialist Pharmacy Service. Lactation Safety Information: Amiodarone. Last reviewed 05/07/21. Accessed via https://www.sps.nhs.uk/medicines/amiodarone/ on 18/10/23.<br>9. Specialist Pharmacy Service – Medicines Monitoring. Published July 2021. Accessed via https://www.sps.nhs.uk/monitorings/amiodarone-monitoring/ on 18/10/23.<br>10. LiverTox. Amiodarone. Last updated 01/03/2016. Accessed via https://www.ncbi.nlm.nih.gov/books/NBK548109/ 18/10/23. |

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| | 11. NEWT Guidelines: amiodarone. Last updated February 2019. Accessed via https://www.newtguidelines.com/ on 18/10/23<br>12. MHRA Drug Safety Update: Sofosbuvir with daclatasvir; sofosbuvir and ledipasvir: risks of severe bradycardia and heart block when taken with amiodarone. May 2015. Accessed via https://www.gov.uk/drug-safety-update/sofosbuvir-with-daclatasvir-sofosbuvir-and-ledipasvir-risks-of-severe-bradycardia-and-heart-block-when-taken-with-amiodarone on 18/10/23<br>13. MHRA Drug Safety Update: Simeprevir with sofosbuvir: risk of severe bradycardia and heart block when taken with amiodarone. August 2015. Accessed via https://www.gov.uk/drug-safety-update/simeprevir-with-sofosbuvir-risk-of-severe-bradycardia-and-heart-block-when-taken-with-amiodarone on 18/10/23<br>14. MHRA Drug Safety Update: Amiodarone (Cordarone X): reminder of risks of treatment and need for patient monitoring and supervision. March 2022. Accessed via https://www.gov.uk/drug-safety-update/amiodarone-cordarone-x-reminder-of-risks-of-treatment-and-need-for-patient-monitoring-and-supervision on 17/10/2023.<br>15. UK Guidelines for the Use of Thyroid Function Tests. The Association for Clinical Biochemistry, British Thyroid Association, and British Thyroid Foundation. July 2006. Accessed via https://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf on 26/10/2023<br>16. NICE NG145: Thyroid disease: assessment and management. Last updated 26 October 2023. Accessed via https://www.nice.org.uk/guidance/ng145/ on 05/12/23. |
| **16. To be read in conjunction with the following documents** | • Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/<br>• NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/<br>• General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care<br>• NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/. |