

Amiodarone for patients with Atrial Fibrillation

Version: 3
Date issued: 22 March 2023
Review Date: January 2026
Key words: AF, Amiodarone

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Abbreviations

ALT	Alanine transaminase
BPM	Beats per minute
CCF	Congestive cardiac failure
CXR	Chest X-ray
ECG	Electrocardiogram
H&E	History & Examination
HRCT	High resolution computed tomography
INR	International normalised ratio
LFT	Liver function tests
MHRA	Medicines and Healthcare Products Regulatory Agency
PAF	Paroxysmal atrial fibrillation
PFT	Pulmonary function tests
T3	Liothyronine sodium
T4	Levothyroxine sodium
TFT	Thyroid function tests
TSH	Thyroid stimulating hormone
U&E	Urea and electrolytes
VT	Ventricular tachycardia
WPW	Wolf Parkinson White

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INDICATIONS FOR USE

Amiodarone is a class III antiarrhythmic drug (Vaughan-Williams classification) that reduces the incidence of arrhythmias by increasing the duration of the refractory period of the cardiac action potential prolonging the QT interval. It also slows heart rate and cardiac action potential conduction through inhibition of beta receptors and ion channels in a similar manner to antiarrhythmic drugs from classes IA, II and IV.

Amiodarone can be used to treat many different types of arrhythmia but serious side effects, including fatal pulmonary toxicity, restrict its use clinically. It is therefore reserved for the treatment of severe rhythm disorder not responding to other therapies or when other treatments cannot be used.

Indications may include:

- Atrial Fibrillation and Flutter when other drugs cannot be used
- Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome
- Tachyarrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias. Also ventricular fibrillation when other drugs cannot be used.

Contraindications:

- Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifasicular or trifasicular block) or sinus node disease, amiodarone should only be used in these cases in conjunction with a permanent or temporary pacemaker.
- Known hypersensitivity to *iodine*, amiodarone or to any of the excipients.

Cautions:

- Evidence or history of thyroid dysfunction. TSH should be performed prior to therapy in all patients.

Initiation/dosage

Only a cardiologist or specialist should initiate treatment with oral amiodarone and duration of treatment should be specified. Oral loading dose (Adult) 200mg 3 times daily for 1 week, reduced to 200mg twice daily for a further week, followed by maintenance of 200mg daily or the minimum required to control the arrhythmia.

IV Loading in hospital: Dilute 300mg of amiodarone to 250 ml bag of 5 % Glucose and infused over 1 hour. (BNF recommends 5mg/kg initially so consider reduced dose in patients <60kg). Followed by an infusion of 900mg amiodarone in 500ml or 1 litre bag of 5% Glucose over 23 hours. (Consider using dose of 15mg/kg for patients <60kg)
Max IV dose in 24 hours is 1.2g

Please note this document does not discuss the administration details of amiodarone in cardiac arrest (refer to ALS algorithm European Resuscitation Council 2015).

ADMINISTRATION

Amiodarone is irritant, acidic and may cause peripheral vein damage when given intravenously. It should be administered through a central line or PICC line where possible.

Loading doses can be administered via a yellow or blue peripheral cannula which should be sited in the biggest vein available as far down the arm as possible, or back of the hand with points of flexion in the wrists and inner elbow being the last resort for placement. An infusion pump check list must be used to monitor the infusion hourly for signs of phlebitis.

When repeated doses or continuous infusions are anticipated, administration by central route is recommended.

The decision to place a central line is a clinical one and will depend on the following factors:

- The patients' condition
- The urgency of the situation
- The availability of suitable veins
- The difficulties and problems associated with central venous access
- The concentration of the amiodarone*
- The duration of the infusion*

The clinician must take into account the high numbers of phlebitis associated with peripheral administration (see below) when making a decision on which route to use. **The decision must be clearly documented in the clinical notes.**

*Amiodarone concentrations greater than 3mg/ml in glucose 5% have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5mg/ml or less appear to be less irritating. IV concentrations of more than 2mg/ml should not be given peripherally for more than 1 hour.

Consideration should be given as to whether the maintenance dose needs to be given intravenously or whether it can be given orally following the IV loading dose. This will depend on the response to the loading dose and the patients' haemodynamic status (300mg IV = 600mg orally).

Cannulas must be flushed with 5 % glucose following infusion.

ORAL

If control has been achieved intravenously and maintenance is considered necessary intravenously then follow the oral regime below. The overlap period should be 16-24hours.

If patient has received greater than 24hours of the intravenous loading regimen a dose reduction of the initial oral dose is suggested.

- Calculate the total IV dose received
- Double the dose to give equivalent oral dose
- Subtract from this figure 200mg for each day of IV therapy
- If <2400mg follow normal oral loading
- If 2400-4200mg start on 200mg bd for one week then od maintenance
- If >4200mg go straight to 200mg od maintenance.

An oral loading dose is necessary even when the patient has been adequately "loaded" intravenously. This is because amiodarone has a large volume of distribution and a long half-life. The high initial plasma levels quickly dissipate as the drug binds to the peripheral lipophilic tissues, thus a prolonged loading regime is required. Because the absorption of oral amiodarone is very slow, and its elimination, in the early stages of therapy relatively fast, there is a risk of significant fall in plasma amiodarone levels if iv therapy were to be stopped when oral therapy started; the period of maximum risk is the first 24 hours of oral therapy. It is therefore advisable that iv therapy is phased out gradually allowing an overlap period.

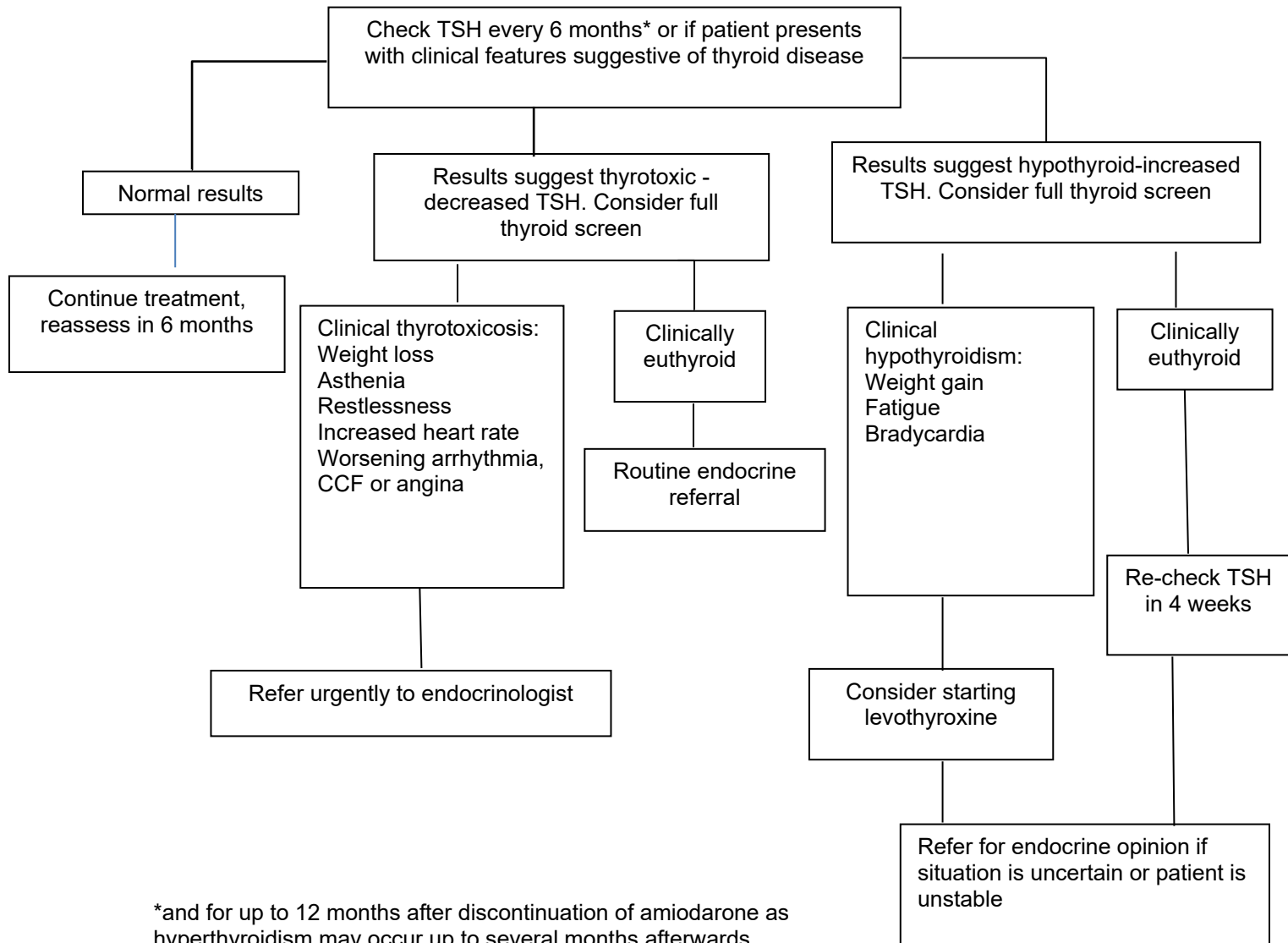
MONITORING REQUIREMENTS

Monitoring at baseline and during initiation is the responsibility of secondary care. Consultants will make an assessment and amend other medications to minimise the risk of bradycardia or other adverse effects as appropriate. Further monitoring is the responsibility of primary care upon agreement of shared care.

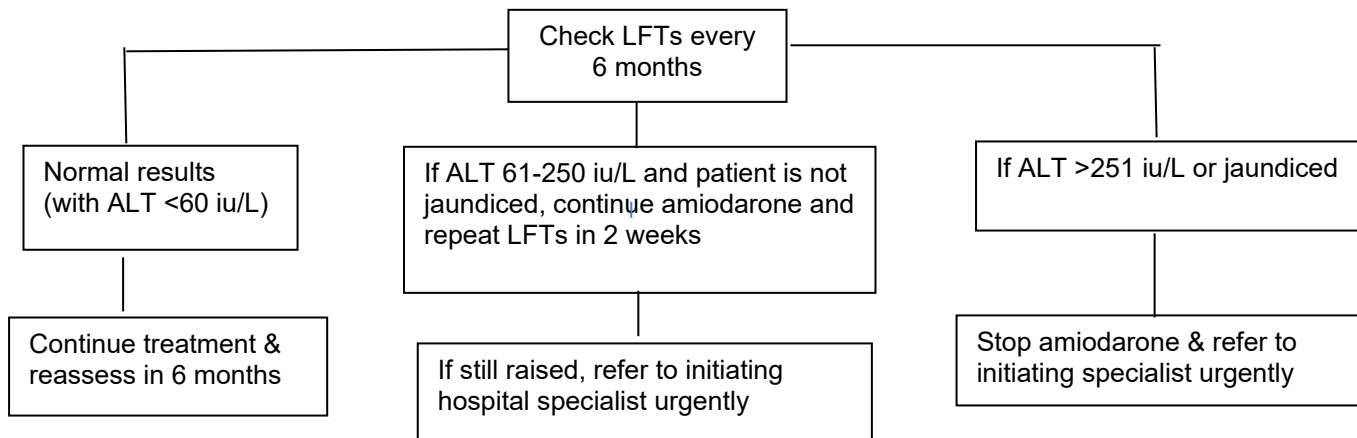
	Baseline	Loading	Monitoring frequency
History & examination	*		Continue annually
Adverse effects	*	*	Continue every 6 months ¹
Heart rate & ECG	*	*	Continue annually ²
TSH	*		Continue every 6 months and for up to 12 months after discontinuation ³
U&Es	*		Continue every 6 months
LFTs	*	*	Continue every 6 months
Digoxin level (if applicable)	*	*	Assess serum digoxin levels if dose increased or toxicity is suspected
INR (if applicable)	*	*	More frequent monitoring of INR both during and after amiodarone treatment (initially weekly for first 7 weeks)
CXR	*		Also if any suspected pulmonary toxicity
Eye examination			Assess if new or worsening visual symptoms occur.

1. At each review visit ask about breathlessness and non-productive cough, related to possible pulmonary toxicity.
2. ECG is valuable for detecting transition from paroxysmal AF to permanent AF which may occur 'silently.'
3. An increase of up to 40% above the baseline T4 is a normal effect of amiodarone. This occurs approximately 2 months after initiation and does not require discontinuation if there is no clinical or further biological evidence (TSH) of thyroid disease. If TFTs are borderline repeat test in 6 weeks. In the event of thyrotoxicosis seek the urgent advice of an endocrinologist.

THYROID FUNCTION TEST ALGORITHM



LIVER FUNCTION TEST ALGORITHM



DRUG INTERACTIONS

Amiodarone inhibits metabolism through several cytochrome P450 pathways, causing interactions with many commonly used drugs. Due to the long half-life of amiodarone, the onset of drug interactions may be slow after initiating amiodarone, and interactions may be observed for several months after discontinuation of amiodarone.

Concomitant use with amiodarone contraindicated	
Anti-arrhythmics	Class Ia anti-arrhythmic drugs ie Disopyramide and Class III anti-arrhythmic drugs ie Sotalol, prolong the QT interval therefore increase the risk of torsades de pointes
Antibacterial drugs	Parental Erythromycin, Co-trimoxazole, and Pentamidine injection prolong the QT interval
Antidepressants	Lithium and tricyclics ie Doxepin, Amitriptyline prolong the QT interval. Manufacturer of Citalopram and Escitalopram states concomitant use of class III antiarrhythmics (amiodarone) that prolong the QT interval is contraindicated
Anti-psychotics	Chlorpromazine, Fluphenazine, Pimozide, Haloperidol, Amisulpiride all prolong the QT interval
Antihistamines	Prolong the QT interval
Anti-malarials	Quinine, Mefloquine, Chloroquine prolong the QT interval
Concomitant use with amiodarone not recommended or should be avoided	
Antivirals	Avoid combination therapy containing Simeprevir and Sofosbuvir due to risk of severe bradycardia and heart block; unless other antiarrhythmics cannot be given
Beta-Blocker	Potential of negative chronotropic properties and conduction slowing effects may occur. Concomitant administration is not recommended.
Calcium-Channel Inhibitors	Rate lowering calcium channel inhibitors ie Diltiazem, Verapamil potentiate negative chronotropic properties and conduction slowing effects may occur. Concomitant administration is not recommended.
Fluroquinolone	Ie Levofloxacin may prolong QT interval. Concomitant use of amiodarone should be avoided.
Grapefruit & Grapefruit juice	Inhibit cytochrome P450 3A4 and may increase the plasma concentration of amiodarone therefore should be avoided.
Laxatives	Stimulant laxatives ie Bisacodyl, Senna may cause hypokalaemia and increase the risk of torsades de pointes. Concomitant administration is not recommended.
Concomitant use with amiodarone are cautioned	
Anticoagulants	Warfarin clearance is reduced. This can lead to sudden and pronounced increase in INR. Interaction reaches its peak in 6-7 weeks. Decrease Warfarin dose by 33-50% and monitor the INR weekly, tailoring the Warfarin dose to the INR target. Amiodarone increases the exposure to Dabigatran increasing the risk of bleeding. Adjust the dosage of Dabigatran according to manufacturers' advice (note dose may be different for different clinical indications).
Cardiac Glycosides	Plasma level of Digoxin approximately doubles over weeks after commencement of amiodarone. Halve Digoxin dose and monitor Digoxin level if applicable.
Ciclosporin	Plasma level of Ciclosporin increased when used with amiodarone. A reduction in the dose of Ciclosporin may be necessary.
Drugs may cause hypokalaemia/hypomagnesaemia	Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia: and/or hypomagnesaemia ie Diuretics, Systemic corticosteroids, Tetracosactrin, IV Amphotericin, Aminophylline, Theophylline.
Lipid-regulating	Increased risk of myopathy with Simvastatin (do not exceed 20mg OD).
Phenytoin	Plasma level of Phenytoin increased with amiodarone. Phenytoin dosage should be reduced in signs of overdosage and plasma levels may be measured.

ADVERSE EFFECTS

The following list is not exhaustive, please see Summary of Product Characteristics (SPC), available at www.medicines.org.uk

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Patients on long term treatment should be carefully supervised because these reactions may be delayed. The minimum effective maintenance dose should be given because undesirable effects are usually dose related. Because of long half-life of amiodarone, clinical problems may occur up to a year (e.g., photosensitivity) after stopping the drug (hyperthyroidism may occur up to several months after discontinuation).

Adverse effect	Frequency %	Diagnosis	Management
Suspected pulmonary toxicity (suggested by new or worsening cough and/or shortness of breath)	2 -17% (common)	CXR and ECG to exclude alternative diagnoses	If no clear cause for cough/SOB found, or if pulmonary toxicity is still a possibility, refer urgently to initiating cardiologist or respiratory physician.
Hyperthyroidism	2% (common)	TSH	See algorithm
Hypothyroidism	6% (common)	TSH	See algorithm
Liver toxicity	1% (common)	LFTs	See algorithm
Optic neuropathy	0.13% (very rare)	Ophthalmologic examination	If optic neuropathy/neuritis is suspected, refer urgently to ophthalmologist and discuss possibility of stopping amiodarone & prescribing alternative antiarrhythmic therapy with patient's cardiologist.
Neurological symptoms (e.g., tremor, ataxia)	Common	History, examination	Reduce dose. Rarely (0.3%) peripheral neuropathy may occur in people on long-term amiodarone.
Proarrhythmia	<1% (uncommon)	ECG	Stop amiodarone.
Bradycardia	2-4% (common)	Examination, ECG	If severe, discuss with cardiologist whether to stop amiodarone or insert pacemaker.
Nausea, anorexia	30% (very common)	History + examination	Commonly occur with loading doses - reduce dosage.
Corneal micro-deposits	>90% (very common)	Slit-lamp examination	None. Most patients on amiodarone develop this (reversible on withdrawal of treatment) which rarely interfere with vision but driver may be dazzled by headlights at night.
Photosensitivity	4-9% (very common)	History + examination	Shield from light and use a wide spectrum sunscreen during treatment and for several months after discontinuation.
Blue skin discolouration	<9% (very common)	Examination	Reduce dosage

APPENDIX 1: GUIDELINES FOR STOPPING LONG-TERM AMIODARONE TREATMENT

Amiodarone is a very effective antiarrhythmic drug often used in the treatment of paroxysmal atrial fibrillation (PAF) and ventricular tachycardia (VT). Unlike most other antiarrhythmics it is safe in heart failure. Its use is limited by side-effects, some of them life-threatening. The risk of these side-effects increases with time and with dose. It seems sensible therefore to ask from time to time whether the drug is still indicated and whether the dose can be reduced. The following is a simple guide to establishing whether amiodarone should be continued at its present dose, or whether treatment can be reduced or withdrawn completely.

Step 1: Establish the original indication for amiodarone therapy

- Paroxysmal Atrial Fibrillation (PAF)
- Permanent AF
- Ventricular Tachycardia (VT)
- Wolff-Parkinson-White Syndrome (WPW)
- Palpitations of uncertain cause

Step 2: Review diagnosis & need for amiodarone in light of current status

PAF

The natural history of PAF is for it to become chronic at some stage (25% in 5 years). This may happen 'silently.' AF can be considered permanent when the patient has been shown to be in AF on two occasions and no longer reports symptoms of cardiac rhythm change. When a patient develops permanent AF the amiodarone should be stopped and heart rate controlled with beta blockers, calcium channel blockers or digoxin. The usual amiodarone dose in PAF is 200mg OD. If a patient has been very stable for a year or more this can be reduced to 100mg.

Permanent AF

Very occasionally it is necessary to use amiodarone for rate control in permanent AF. As other rate control options (eg. AV nodal ablation plus pacemaker insertion) could be considered, all patients on amiodarone for rate control should initially be under the care of a cardiologist. Once a patient has been stable for two years it is worth considering reducing or stopping amiodarone without necessarily referring back to hospital. The long terminal half-life of amiodarone means that it will take months before its effect on AV node conduction has gone completely.

VT

Patients with symptomatic VT should remain on amiodarone in the long term unless they develop significant side-effects. Patients with internal cardiac defibrillators (ICDs) are often also on amiodarone to reduce the frequency of shocks. Some patients are started on amiodarone for VT at the time of an acute illness. Any patient who has been completely well for two years with no suggestion of recurrent VT should be referred to a cardiologist for review of the long-term need for amiodarone.

WPW

Amiodarone is rarely used for WPW, unless an electrophysiologist has been unsuccessful in ablating an accessory pathway. Some WPW patients were started on amiodarone before the modern era of percutaneous treatments. Some are happy to stay on amiodarone but they should be given the opportunity to discuss definitive treatment with an electrophysiologist.

Palpitation

Patients should not be started on amiodarone unless there is a clearly defined electrophysiological diagnosis. If a patient was started on amiodarone because of suspicion of VT but has been stable for two years they should be reviewed by a cardiologist. If the indication was just palpitations then the amiodarone should be stopped.

Step 3: Stopping Amiodarone

- Amiodarone can be stopped abruptly.
- Amiodarone has a long half life. Plasma concentrations fall by 50% in the first two weeks but it may then take a further six months before it is eliminated completely.
- Ventricular rate control and AF: if resting heart rate is <110bpm review in two weeks to consider increasing dose of other rate slowing drugs (the plasma level of digoxin will decrease upon withdrawal of amiodarone). If resting heart rate is >110bpm add in or increase beta blocker, digoxin, rate-limiting calcium channel blocker. A further review of heart rate at three months after stopping amiodarone is sensible.
- Due to the long half-life of amiodarone, clinical problems (eg. Hypothyroidism, photosensitivity) may occur/persist for up to a year after stopping the drug. TSH should be monitored for up to twelve months after discontinuation.
- Warfarin: the INR will decrease upon stopping amiodarone. In most cases it is sufficient to repeat the INR one week after stopping in expectation that a dose increase may be necessary.

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FULL VERSION CONTROL RECORD

Version:	3.0
Guidelines Lead(s):	Andrea Lavous, Lead Arrhythmia Nurse
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Library check completed:	N/A
Ratified at:	Drugs and Therapeutics Committee, February 2023
Date Issued:	22 March 2023
Review Date:	January 2026
Pharmaceutical dosing advice and formulary compliance checked by:	Ann Parker, Cardiology Pharmacist
Key words:	AF, Amiodarone

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date. This guideline is for use in Frimley Health Trust hospitals only. Any use outside this location will not be supported by the Trust and will be at the risk of the individual using it.

Version Control Sheet

Version	Date	Guideline Lead(s)	Status	Comment
1.0 (FPH)	August 2012			
2.0	August 2014			
1.0 (FHFT)	May 2017			
2.0	Sept 2018	Andrea Lavous	Final	
3.0	Jan 2023	Dr Mark Norman	Final	