# Dronedarone *(Multaq®)* (TLS Amber with Shared Care)

For the treatment and management of atrial fibrillation

**AREAS OF RESPONSIBILITY FOR SHARING OF CARE**

This shared care agreement outlines how the responsibilities for managing the prescribing of **dronedarone for atrial fibrillation** might be shared between the secondary care specialist and general practitioner (GP).GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.
The doctor who prescribes this medication legally assumes clinical responsibility for dronedarone and the consequences of its use.

**RESPONSIBILITIES AND ROLES**

**Secondary care – specialist**

1. To confirm the patient has no contra-indications to treatment and consider the relevance of any cautions.
2. To undertake monitoring of the patient's renal and hepatic function prior to initiation of dronedarone and confirm the absence of severe renal and hepatic failure.
3. To discuss the benefits and possible side-effects of treatment with the patient, advising women of child bearing age to use reliable contraceptive methods whilst taking dronedarone
4. To advise patient to immediately report to their physician if they develop or experience:
    - symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching)
    - Breathlessness and non-productive cough
    - Swollen feet or legs, trouble breathing when lying down or sleeping, shortness of breath when moving around, or weight increase
5. To initiate dronedarone for the licensed indication in accordance with the manufacturer's Summary of Product Characteristics (SPC) and provide at least 28 days supply.
6. To assess potential adverse events, including monitoring plasma potassium at 7 and 14 days after initiation, LFTs at day 7 and at 1 month and plasma creatinine at day 7 and report any adverse events to the MHRA.
7. To discuss the possibility of sharing prescribing and monitoring of dronedarone with the patient's GP; to provide a copy of this shared care agreement for their consideration and not to transfer prescribing responsibility until the GP has formally agreed to share care in this way.
8. To advise on the clinical relevance of concomitant medication after initiation of dronedarone, as well as potential drug interactions (e.g. with dabigatran, digoxin, beta-blockers etc).
9. To ensure that arrangements are in place for GPs to obtain advice and support where needed.
10. To undertake regular follow up of the patient at 3 and 9 months post discharge then annually.
11. To arrange for an annual a 12 lead ECG, to assess the patient's response to, and stability on, dronedarone and monitor for any side-effects e.g. QTc prolongation.
12. To communicate promptly with the GP the results of any monitoring undertaken in secondary care and any changes to treatment made by the specialist.

**Primary care - general practitioner**

1. To reply to the request from secondary care to share care as soon as possible.
2. To ensure a full understanding of their responsibilities for managing patients with atrial fibrillation on dronedarone, including monitoring and side-effects in line with the SPC.
3. To prescribe dronedarone at the dose at which the patient's treatment has been stabilised, after communication with the secondary care specialist.
4. To report to, and seek advice from, the secondary care specialist if any aspect of the patient's care is of concern.
5. To refer the patient back to the secondary care specialist if the patient's condition deteriorates.

   ***Particular attention should be paid to symptoms that could indicate liver injury symptoms of developing heart failure and interstitial lung disease.*** To arrange for liver function tests to be monitored, in accordance with the monitoring schedule.
6. To arrange for plasma creatinine to be monitored in accordance with the monitoring schedule.

   ***Dronedarone is expected to increase plasma creatinine by approx. 10 micromol/l at the time of initiation. This does not reflect a change in underlying renal function and should not necessarily trigger the discontinuation of other drugs, especially ACE inhibitors or Angiotensin II Receptor Antagonists (AIIRAs).***

***Prior to sharing prescribing and monitoring of dronedarone, the GP and secondary care specialist should agree a threshold for increase in plasma creatinine that would prompt patient referral back to secondary care. As further change in creatinine levels is unlikely to be due to dronedarone, it should also prompt investigation for other causes of renal disease.***

7. To monitor plasma potassium levels and plasma magnesium levels in accordance with the monitoring schedule.
8. To report any adverse effects to the MHRA & specialist.

**Patient or carer**

1. Report to the specialist or GP if he/she does not have a clear understanding of the treatment.
2. Share any concerns in relation to treatment with dronedarone.
3. Present rapidly to the GP or secondary care specialist should their condition significantly worsen.
4. Notify the GP or secondary care specialist if physical activity causes shortness of breath or if he/she has shortness of breath while at rest or after a small amount of exercise.
5. The patient must notify the GP or secobdary care specialist if they develop any of the following:
   - symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching)
   - Breathlessness and non-productive cough
   - Swollen feet or legs, trouble breathing when lying down or sleeping, shortness of breath when moving around, or weight increase
6. Immediately report to the GP or secondary care specialist symptoms indicative of liver injury (such as sustained new-onset abdominal pain, ↓ appetite, nausea, vomiting, fever, malaise, tiredness, jaundice, dark urine or itching).
7. Report any other adverse effects to the specialist or GP whilst taking dronedarone

**BACK UP ADVICE AND SUPPORT**

| | *Telephone No.* | *Bleep* | *Fax* | *Email* |
|---|---|---|---|---|
| Dr Paul Foley<br>Consultant Cardiologist | 01793 646214 | - | - | paul.foley@gwh.nhs.uk |
| GWH Medicines Information | 01793-605029 | - | - | medicines.information@gwh.nhs.uk |

**SUPPORTING INFORMATION**

**Licensed indication**

Dronedarone (Multaq®) is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile dronedarone should only be prescribed after alternative treatment options have been considered.

**Place in treatment pathways**

Guidance on the management of atrial fibrillation has been issued by NICE http://guidance.nice.org.uk/CG36.
NICE has also produced a technology appriasal for dronedarone: Dronedarone for the treatment of non-permanent atrial fibrillation https://www.nice.org.uk/guidance/ta197.
Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation:

- whose atrial fibrillation is not controlled by first-line therapy (usually including betablockers), that is, as a second-line treatment option and after alternative options have been considered and
- who have at least 1 of the following cardiovascular risk factors:
  hypertension requiring drugs of at least 2 different classes
  diabetes mellitus
  previous transient ischaemic attack, stroke or systemic embolism
  left atrial diameter of 50mm or greater or
  age 70 years or older and
  who do not have left ventricular systolic dysfunction and who do not have a history of, or current, heart failure.

**Dosage and administration**

In adults, the recommended dose of dronedarone is 400 mg twice daily, with breakfast and evening meal. Do not take with grapefruit juice.

Refer to SPC for more detailed information on missed doses and prescribing in renal impairment, hepatic impairment, children and elderly. http://www.medicines.org.uk

**Contraindications and cautions**

Dronedarone is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Bradycardia <50 beats per minute (bpm)

- Second- or third- degree atrio-ventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Patients in unstable hemodynamic conditions,
- Concomitant potent cytochrome P 450 (CYP) 3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir)
- Medicinal products inducing torsades de pointes (such as phenothiazines, cisapride, bepridil, tricyclic antidepressants), terfenadine, certain oral macrolides (such as erythromycin), and Class I and III antiarrhythmics
- QTc Bazett interval ≥500 milliseconds
- Severe hepatic impairment or severe renal impairment (CrCl <30ml/min)
- Co-administration with dabigatran

Dronedarone should be used with caution in patients on MAO inhibitors, beta-blockers or digoxin.

Refer to SPC for more detailed information on contraindication and precautions http://www.medicines.org.uk

**Side-effects**

*Very common (≥1/10):*

- Congestive heart failure, increased plasma creatinine*, prolonged QTc interval #

*Common (≥1/100 to <1/10):*

- Bradycardia, diarrhoea, vomiting, nausea, abdo pain, dyspepsia, LFT abnormalities, rashes, pruritus, fatigue, asthenia

*Uncommon (≥1/1,000 to <1/100):*

- Dysgeusia, erythemas, eczema, photosensitivity reaction, allergic dermatitis, dermatitis, Interstitial lung disease including pneumonitis and pulmonary fibrosis

*Rare (≥1/10,000 to <1/1,000):*

- Ageusia, hepatocellular liver injury (including life-threatening acute liver failure), Vasculitis, including leukocytoclastic vasculitis, Anaphylactic reactions including angioedema

[* ≥10% five days after treatment initiation; # >450 msec in male >470 msec in female]

In clinical trials, the most frequently observed adverse reactions with dronedarone 400 mg po bd were diarrhoea, nausea, vomiting, fatigue and asthenia.

Refer to the SPC for a full list of adverse effects & further information http://www.medicines.org.uk.

Dronedarone has black triangle (▼) status, so all suspected adverse reactions (including those not considered to be serious, those already well recognised and those where the causal link is uncertain) should be reported to the MHRA. http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con108718.pdf

**Monitoring**

| *Parameter* | *Frequency of monitoring* | *Action* |
|---|---|---|
| Liver function tests | monthly for 6 months, at 9 months, at 12 months and then annually. | If ALT is elevated to ≥3 upper limit of normal (ULN), re-check level in 48-72 hrs.<br>If ALT is then confirmed as ≥3 ULN, contact Specialist for urgent advice on other treatment options then stop dronedarone. |
| Plasma creatinine | at 6 months and 12 months then annually. | If Cr is less than agreed threshold for this patient, take no further action.<br>If Cr is more than agreed threshold for this patient, refer to Specialist for review. |
| Plasma potassium and plasma magnesium | at 6 months and 12 months then annually. | Correct any deficiency if it occurs.<br>Refer back to Specialist for review if deficiency persists or frequently recurs. |

Electrolytes imbalance

Since anti-arrhythmic medicines may be ineffective or even arrhythmogenic in patients with hypokalaemia, potassium or magnesium deficiency should be corrected before initiation, and during, dronedarone therapy.

**Drug interactions**

Patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Dronedarone will increase plasma levels of digoxin, and thus may precipitate symptoms and signs of digoxin toxicity. Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved. A synergistic effect on heart rate and atrio-ventricular conduction is possible.

Beta-blockers and calcium antagonists with depressant effect on sinus and AV node should be co-administered with caution. In patients on dronedarone, they should be initiated at low dose, and titrated only after ECG assessment. In patients on calcium

antagonists/ beta blockers at time of dronedarone initiation, an ECG should be performed and doses adjusted if necessary.

Medicines which induce torsades de pointes (such as phenothiazines and tricyclic antidepressants), certain oral macrolides (such as erythromycin), and Class I & III antiarrhythmics are contraindicated due to risk of proarrhythmia.

Statins should be used with caution. Lower starting and maintenance doses of statins should be considered, and patients monitored for clinical signs of muscular toxicity.

MAO inhibitors may decrease clearance of the active metabolite of dronedarone, and should be used with caution.

Concomitant potent CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St John's Wort) are not recommended.
Warfarin and other vitamin K antagonists
Dronedarone (600 mg twice daily) increased by 1.2-fold S-warfarin with no change in R-warfarin and only a 1.07 increase in International Normalised Ratio (INR).
However, clinically significant INR elevations (≥5) usually within 1 week after starting dronedarone were reported in patients taking oral anticoagulants. Consequently, INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label.

NOACs
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.
Apixaban: No information about concomitant use.
Edoxoaban: See SPC for dose adjustment when used concomitantly with dronedarone.
Dabigatran: Contra-indicated.

Dronedarone tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

Refer to the SPC for more detailed information on drug interactions http://www.medicines.org.uk.

**Cost**
At September 2015 MIMS dronedarone will cost primary care £821 per patient per year.

**References**
1. NICE TA 197: Dronedarone for the treatment of non-permanent atrial fibrillation. National Institute for Health and Clinical Excellence. August 2010 (updated Dec 2012). https://www.nice.org.uk/guidance/ta197
2. MHRA safety warning: **Dronedarone (Multaq▼): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements** Medicines and Healthcare Products Regulatory Agency. October 2011. https://www.gov.uk/drug-safety-update/dronedarone-multaq-cardiovascular-hepatic-and-pulmonary-adverse-events-new-restrictions-and-monitoring-requirements
3. Summary of Product Characteristics. Multaq. Sanofi- Aventis. http://www.medicines.org.uk/EMC/medicine/22894/SPC/Multaq+400mg+tablets/

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