Improving patient outcomes in atrial fibrillation—revisions to the ESC guideline: *A focus on the role of dronedarone*

Discussion group:

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- **Nicholas Peters (NP), Professor of Cardiology and Head of Cardiac Electrophysiology, Imperial College London; Consultant Cardiologist, Imperial College Healthcare NHS Trust (St Mary's Hospital)**
- **Derick Todd (DT), Consultant Cardiologist, Liverpool Heart and Chest Hospital NHS Foundation Trust**
- **Matt Fay (MF), GP, Westcliffe Medical Centre, Shipley, North Bradford Primary Care Trust; and GPwSI in Cardiology**

Background

The aim of the discussion was to bring together a group of healthcare professionals with varying levels of involvement and expertise in managing atrial fibrillation (AF), to discuss the recently revised European Society of Cardiology (ESC) guideline.[1] There was a specific focus on positioning of dronedarone within the guideline.

Guideline

JC: Discuss the rationale for the positioning of dronedarone in the ESC guideline: what are the principles governing the choice of an anti-arrhythmic drug?

NP: Choice is governed by the principles of safety and efficacy. Safety is particularly important with atrial arrhythmia when dealing with ventricular arrhythmogenesis. When considering an anti-arrhythmic drug, an overriding concern is whether it is safe from the point of view of producing ventricular pro-arrhythmia. It is also important to consider how effective the drug is in respect of the atrial arrhythmia. There are now outcome data for dronedarone that suggest it is beneficial for patients with additional risk factors, such as structural heart disease and vascular disease.[2]

MF: The view from primary care is that we must not only treat for improved symptom control, but we must see the cost savings within the health economy, such as those resulting from a reduction in hospital admissions and attendance at GP clinics. It is not purely a question of whether the patient feels better; more solid outcome measures are needed to show that cost savings are being made. However, first and foremost has to come the benefit to the patient of symptom management, with safety being of paramount concern, followed by efficacy.

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DT: As well as safety and effectiveness, tolerability and suitability for the patient, possible side-effects, and other co-morbidities and issues should be considered.

Round-table recommendation

- Safety and efficacy are paramount when choosing an anti-arrhythmic drug.

JC: What changes have been made to prescribing recommendations in the ESC guideline—how do these affect the positioning of dronedarone in the ESC guideline algorithm on choice of anti-arrhythmic drug (see Figure 1, p.3)?

This algorithm divides patient populations by underlying aetiology, as follows:

- minimal or no heart disease
- significant underlying heart disease, which is subdivided into patients with:
  - hypertension-induced hypertrophy
  - coronary artery disease (CAD)
  - congestive heart failure (CHF).

Minimal or no heart disease

DT: The decision to put dronedarone, flecainide, propafenone, and sotalol together seems reasonable, and they are arranged with regard to safety and efficacy. As far as cost effectiveness within the health economy is concerned, dronedarone is more costly than the other three and this could have been reflected in the algorithm. Nevertheless it can be a viable first choice for the right people within this group. Many older patients, who would fit in with the NICE guidance treatment criteria,[3] seem to have minimal heart disease and many doctors would feel more comfortable treating them with dronedarone because of the drug's safety profile. I would prefer to use dronedarone first-line for a 75-year-old patient with symptomatic AF for whom I cannot exclude heart disease and who may have a background risk for hypertension.

NP: Cost consideration was not a criterion for the ESC guideline, but this algorithm (Figure 1, p.3) needs to be viewed in the context of the importance of cost efficacy to the healthcare system. Although the proven outcome benefits for dronedarone in contrast to the other drugs mentioned is not so relevant for patients with minimal or no heart disease, where prognosis is generally good, the placing of drugs for this group of patients seems wholly appropriate.

MF: I also agree that the drugs are properly placed. It is important for guidelines to show the expert view in an ideal world. Recommendations must then be implemented in local practice where cost effectiveness and whether health authorities can afford the drugs can be taken into account. Guidelines should not reflect that, but should concentrate on where the evidence base places therapies.

JC: In this case, for patients with minimal or no heart disease, the ESC guideline does not make a distinction between dronedarone, flecainide, propafenone, and sotalol, which are all recommended as potential first-line drugs ahead of amiodarone, which has an extra cardiac side-effect profile. All those drugs listed had similar efficacy with regard to the recurrence of AF.

Significant underlying heart disease

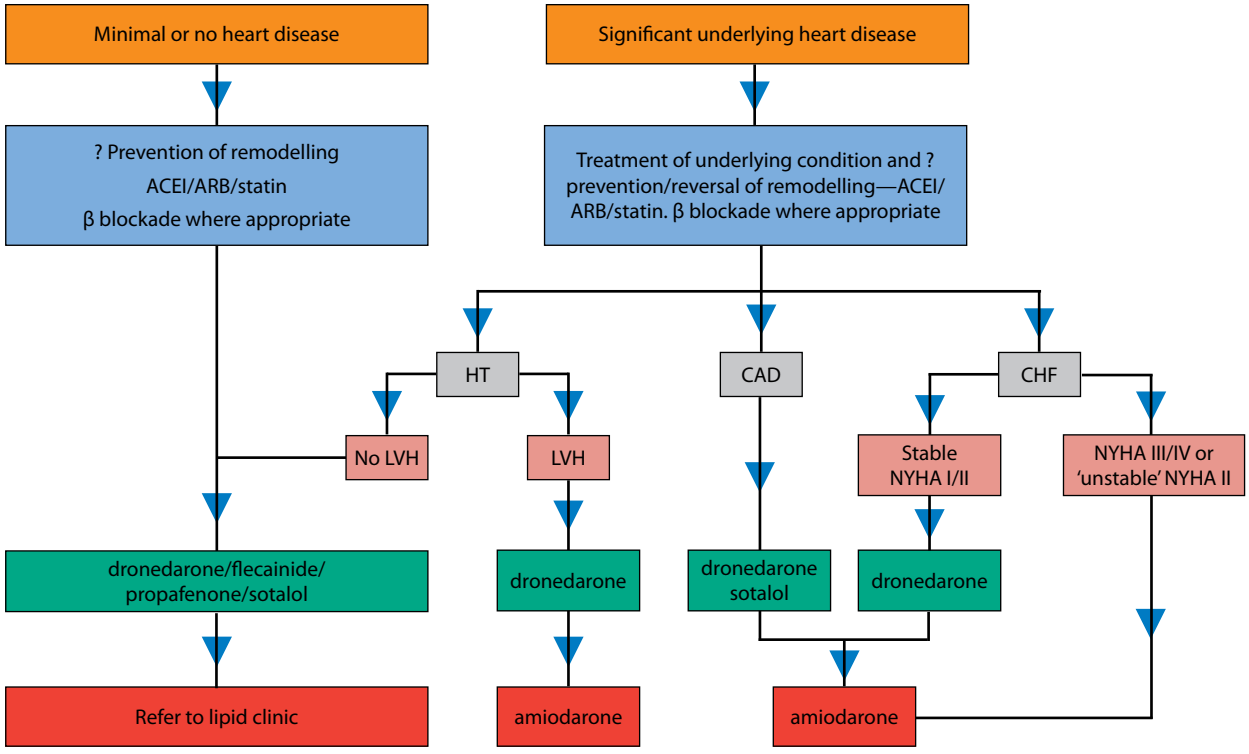
Congestive heart failure

JC: Patients with heart failure are subdivided into those with stable New York Heart Association (NYHA[4]) I/II, for whom dronedarone is recommended ahead of amiodarone, and patients with NYHA III/IV or 'unstable' NYHA II, where dronedarone is bypassed (see Figure 1, p.3). When we were drawing up the ESC guideline, there was much discussion whether stable heart failure groups NYHA I/II/III should all be recommended to receive dronedarone. However, after correspondence from reviewers, NYHA III was moved to a group not receiving dronedarone.

DT: We have to remember that there were some unfavourable data for dronedarone in heart failure populations (as cited in the ANDROMEDA study for example[5]). Safety is the primary concern for use of these drugs and it is appropriate that dronedarone is bypassed for the NYHA III/IV or 'unstable' NYHA II heart failure population. It can be difficult to classify patients according to NYHA groups when they initially present with symptomatic AF—their uncontrolled heart rate may not be a result of ongoing heart failure, and the initial classification according to NYHA may become very transient. They may initially experience shortness of breath, which will improve greatly when the heart rate is controlled, and there may not be much left ventricular dysfunction. However, it is better to err on the side of caution in this group and prefer amiodarone to dronedarone.

NP: I would like to endorse the earlier point that in an elderly patient, where the presence of structural heart disease is not known and it may be inappropriate to undertake investigations, it is correct to err in favour of dronedarone for safety reasons. However,

Figure 1: Choice of anti-arrhythmic drug according to underlying pathology



ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; HT=hypertension; LVH=left ventricular hypertrophy; CAD=coronary artery disease; CHF=congestive heart failure; NYHA=New York Heart Association.
unstable=cardiac decompensation within the prior 4 weeks. Anti-arrhythmic agents are listed in alphabetical order within each treatment box.
?=evidence for 'upstream' therapy for prevention of atrial remodelling still remains controversial.

AJ Camm, P Kirchhof, G Lip et al, for the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010; **31**: 2369–2429. Reproduced with kind permission.

I think that dividing the grouping of patients with CHF as it is done in the algorithm is overcautious. Based on my interpretation of available evidence, I would have preferred to have stable NYHA I/II and NYHA III grouped together and then NYHA IV or 'unstable' NYHA II/III on the right of the diagram, but a wide margin of safety has been incorporated into the ESC guideline. I would expect that future revisions to the guideline might change the groupings.

Coronary artery disease

DT: I think the ESC was slightly generous in its positioning of sotalol, which could have been placed as second-line treatment, below dronedarone. I have found sotalol to cause some problems with patients in the past so I have tended to avoid it, and current data back that up.[6]

NP: As an electrophysiologist I dislike sotalol. For treatment of AF in CAD I would consider dronedarone alone as first-line treatment, with amiodarone as the second-line choice. In the light of the recent data on sotalol,[6] I would expect dronedarone to appear on its own as first-line option in a future revision of the algorithm.

MF: I agree with the comments on sotalol and it is my normal practice to avoid its use whenever I can. Dronedarone now presents a good alternative to sotalol and avoids moving straight to amiodarone use, which I have been reticent to do. The problem with sotalol use in primary care is that its use as a beta-blocker may possibly not have been monitored as closely as other drugs and it may have problems that have been overlooked.

JC: Sotalol was retained in the guideline because, in some countries, it is the predominant anti-arrhythmic drug; for example, the majority of anti-arrhythmic drug prescriptions in Sweden are for sotalol. It was therefore decided not to drop sotalol but to explain that it should be used with caution. There was little previous evidence of any difference in effect between dronedarone and sotalol with regard to prevention of recurrences of AF, so it was decided to place the two drugs together as first-line treatments, in order to leave amiodarone as the drug of last resort. However, since publication of

the ESC guideline, recent analyses of potential serious cardiovascular outcomes from treatment with sotalol and amiodarone are both worse than with dronedarone.[7]

Hypertension-induced hypertrophy

JC: In the 2006 ESC guideline only amiodarone was available as a treatment for patients with hypertension-induced left ventricular hypertrophy as there was evidence that Class III drugs were associated with hypertrophic situations, particularly hypertension treated with diuretics. There was some basic science suggesting that sotalol was not suitable for that group of patients. There is much evidence of the use of dronedarone in the hypertensive patient population because many of the patients in the ATHENA, EURIDIS, and ADONIS trials had hypertension, but there was no systemic documentation of hypertrophy.[2,8] The guideline development group decided to include dronedarone under that group where amiodarone was the only other alternative treatment. However, there is little data on the use of dronedarone in patients with documented hypertrophy.

MF: We get into a complex area when we begin to discuss different structural heart disease. However I think the drugs are appropriate as placed.

Round-table recommendations

- Although cost is sometimes taken into account when formulating guideline recommendations, it should not be the criterion for assessing the effectiveness of medications
- Results from recent analyses suggest that dronedarone should be the first-line treatment for CAD as sotalol was found to be associated with worse potentially serious cardiovascular outcomes.

Identifying the right treatment for the right patient

JC: In the context of the ESC guideline on management of AF, which patients are more appropriate for treatment with dronedarone?

NP: Local PCT formulary restrictions mean that dronedarone still cannot be prescribed freely in my area. It has been used for patients with additional risk factors as a first-line anti-arrhythmic agent in line with the algorithm (see Figure 1, p.3). If co-prescribed with anticoagulants, such as warfarin, amiodarone can have a destabilising effect, which dronedarone does not, but that is not an important issue when deciding on the right treatment.

DT: By the time patients are referred on to specialists they have often already failed on a few drugs, so dronedarone may be the next option available. I have used dronedarone for:

- some patients with moderately symptomatic AF rather than severely symptomatic AF, who were changed from an amiodarone prescription as it was agreed that dronedarone would retain the beneficial effect that amiodarone has when rhythm control fails
- some patients following ablation, who had been on amiodarone but had severely symptomatic AF; switching to dronedarone allowed for some protection if breakthrough AF episodes occurred
- older patients without structural heart disease—these patients can often be referred for ablation, and dronedarone is a viable alternative.

I have discussed dronedarone use with patients in their 70s on the basis that there is now a safe pharmacological alternative to ablation that is likely to avoid hospitalisation as a result of AF episodes. Dronedarone can be used rather than amiodarone for 2–3 weeks preceding cardioversion.

MF: I have also been using dronedarone for older people (>70 years of age) who are otherwise very fit and active and who clearly do not have other structural cardiac issues that would become evident with their activity levels. I would feel very uncomfortable opting for the other Class I agents for these patients, nor would I want to use amiodarone in this case because of the limits its side-effects would place on their lifestyles. I have used dronedarone almost as a first-line agent in this group where I have not considered cardiac investigation to be warranted, but where I have not felt comfortable moving to other agents in case of covert coronary disease or structural heart disease. Some younger patients have continued with flecainide, despite some side-effects, to avoid ablation. However, many of them switched to dronedarone once it became available, hoping for a reduction in the side-effects they experienced with flecainide.

In my area we have a good working relationship with the anticoagulation service. If their local anticoagulation services are not good, cardiologists may need to take that into consideration. They have to be absolutely confident that the anticoagulation service available to them will pick up on any co-prescription issues.

JC: The ESC guideline writers expected local users to take into account what they could afford with regard to use of dronedarone, and consequently the guideline is more liberal in its indications concerning choice of patient than the NICE recommendations.

JC: How can we ensure dronedarone use targets those patients who will benefit most from treatment?

MF: I think we have to have dronedarone being used in a situation where it can be prescribed by experts. That may be pathway driven, but I am concerned that dronedarone may be viewed as a low side-effect version of amiodarone, especially by more junior colleagues within secondary care. I would want assurance from an acute provider that they restrict use of dronedarone to those who understand its use and the cost implications of the drug within the community. That would probably restrict prescription writing to consultant cardiologists and some elderly care physicians. As a GP, I would not want it to have been prescribed without consultant input for a patient in secondary care, who subsequently comes back into the primary care sector.

Improving patient outcomes

JC: A key focus of the NHS quality, innovation, productivity, and prevention (QIPP) agenda is reducing hospitalisation—does the group feel that dronedarone should be considered in order to reduce cardiovascular hospitalisations in appropriate AF patients as it states in the ESC guideline?

DT: One of the beauties of dronedarone is that it is a drug that does not aim for perfection in AF control, and it is reasonable to accept that what you are aiming for is, on balance, an improvement, and more of an outcome-based strategy. You look not just for whether the patient has AF, but also when they have AF and how they cope with that AF. I ask patients to grade themselves and if they give themselves 10/10 in sinus rhythm and 2/10 in AF, I will tell them that something like dronedarone will stop them falling to 2/10. Hopefully they will then maintain a level around 6/10, sufficient to keep them out of hospital, which it is crucial to avoid if possible, and dronedarone can help to achieve that. Improvements in cardiovascular outcomes represent a strong motivation and patients are reassured to be told there is evidence of reduction, which is not something one has been able to say about other medications. There are also data indicating improved outcomes in stroke,[2] and I have used dronedarone in some patients who have had strokes with AF and who have symptomatic ongoing AF.

NP: To some extent it was timely and inspired to mandate the pivotal trials with dronedarone to look at these outcome endpoints. When it comes to a healthcare system, these are the important drivers, both in terms of cost efficacy of a treatment and in terms of a patient's outcomes. Avoidance of acute medical care, and hospitalisation in particular, is where the major savings and patient benefits are going to come from. To measure improvement in treatment outcomes at the level of the regulatory authorities, by mandating outcome studies, is the right way to provide the appropriate measures. If pivotal studies are not run along those lines, you end up without any measurable effect that any clinician can latch on to with any degree of certainty and comfort. I think the data that exist for dronedarone are very supportive of its use in terms of QIPP, given the likelihood of a positive cost efficacy analysis.

MF: GPs need to be moved away a little from that comfort zone where they can do a test that reassures them they are achieving population effect. Some aspects will need to be taken on faith, particularly in the primary prevention agenda. The ATHENA study clearly demonstrated reductions in hospitalisation,[2] but we cannot afford to implement blanket prescribing of dronedarone to all patients with AF. However, we may be able to identify subgroups where the cost/benefit analysis may show advantages, such as for frequent hospital attenders or people with very high cardiovascular risk profiles. We need to make sure that this is a cost-effective medication at its current list price. However, I have not yet seen the cost efficacy data for that.

JC: With a drug like dronedarone, which may not be a very powerful anti-arrhythmic agent, you may have recurrences of arrhythmia and still have a major chance of reducing cardiovascular hospitalisations and other outcomes, but this is very difficult to measure for an individual patient. In addition to reducing cardiovascular outcomes, particularly hospitalisations, dronedarone may also reduce cardiovascular mortality.

Round-table recommendation

- It is important to avoid hospitalisation of patients with AF if possible, and the improved outcomes with dronedarone can help to achieve this.

The ESC guideline on management of AF: the GP perspective

JC: From a GP's perspective, how clear is the ESC guideline? Would easy access to this guidance help GPs understand AF management better?

MF: I think this ESC guideline offers very safe treatment for AF by putting the patient's symptoms at the heart of the recommendations. They put the risk of stroke and the need for more aggressive anticoagulation therapy up front before getting into discussions of rate and rhythm. Other factors that should be considered alongside coexisting heart disease and cardiovascular disease, including diabetes, are also covered, and the guideline also deals very nicely with when we should aim to end the arrhythmia.

On the whole, I think the ESC guideline is very clear, but many GPs will be unaware of it. It also currently lacks a very clear executive summary that could be easily released to GPs, who might get bogged down in the full guideline. We must remember that when we talk about the GP, we are not only including colleagues in primary care, but also elderly care physicians and secondary care clinicians in acute medical practice whose speciality is not in cardiology. Therefore a short summary should be available for all those who come into contact with AF as a general part of their particular care area.

JC: The pocket guidelines version, which is substantially abbreviated, and other formats, are now available from the ESC website (**www.escardio.org/guidelines-surveys/esc-guidelines/Pages/atrial-fibrillation.aspx**).

Round-table recommendation

- The availability of a brief summary of the guideline should benefit GPs.

Implications for the future

JC: The aim is for a joined-up service between primary and secondary care for patients with AF—how far will the new guideline go towards achieving this aim?

With regard to the joined-up service, in my area of London we have guidance on the use of dronedarone, which specifies what the primary care physician will follow and what the secondary care physician will do. For example the secondary care physician will decide that it will be used and write the first prescription, and subsequent prescriptions are then written by the GP, but only after measurements of renal function have been made, and a new baseline value has been derived for creatinine. Regular liver function testing is now recommended.[9]

DT: We have the same protocol, which is a good way to go with the use of a new drug. I think that the join up between primary, secondary, and tertiary care for AF is greatly improved now that there is more available to primary care in terms of pharmacology. Before dronedarone was available, there was not much of a basis for anti-arrhythmic drug treatment in primary care or that could be used with much confidence. The advent of a newer, safer drug presents the opportunity for primary care to engage more with AF and that is good for patients, and it brings primary and secondary care together in AF management. Dronedarone has prompted, by necessity, an increased interaction between the two.

MF: Particularly in the UK, AF is on the rise and the advent of dronedarone gives the perfect opportunity for distance consultation. The GP could write to the consultant in secondary care and ask whether the medication would benefit a particular patient. The advice could then come to the clinician and the patient without the need for a face-to-face specialist consultation.

NP: There are several layers of physician, including GPs and general cardiologists, before you get to specialists and electrophysiologists, and in future we may see very few patients who are not already on dronedarone before they walk through the specialist's door.

JC: Does this ESC guideline provide a good foundation for the revision of the NICE AF guideline, which is scheduled for 2011?

NP: I think there is a mismatch between the AF guidelines from NICE and the ESC. They differ in one significant factor: the NICE guideline incorporates some cost-efficacy considerations, which the ESC guideline does not. Cost will always be an additional factor for NICE to consider, although it does not affect which patients are more appropriate to receive dronedarone. Although NICE may use the same evidence base, they may not use the ESC guideline per se to help drive their recommendations. I consider the ESC guideline, which accords completely with my approach to the management of AF, to be very sensible.

DT: The ESC guideline is an excellent commonsense document. I would like it to be a foundation for the revision of the NICE guideline, but I do not expect that. As an independent body, NICE will make its own recommendations. It is more likely that the NICE TA on dronedarone[3] will form a basis for the revised NICE AF guideline. The 2006 NICE management of AF guideline is now so old that it must be reviewed in 2011 and there will be many areas to address, including ablation, which is now in the spotlight.

MF: There is a cohort of patients with structural heart disease or coronary heart disease for whom the next options within the current NICE recommendations are beta-blockers then amiodarone.[10] However, when the potential side-effects are discussed with them they may be unwilling to accept them. Evidence of further risk factors would allow prescription of dronedarone in line with NICE recommendations, however those investigations are not always possible and there are always exceptions. In my view the NICE guideline did not fully consider the unpleasant aspects in some respects of taking amiodarone, however they had to consider the costs of dronedarone. The NICE guidance includes beta-blockers as first-line therapy,[10] which are not necessarily correctly placed, demoting dronedarone to second line[3] when in reality it is an appropriate first-line treatment.

The ESC guideline has put a couple of significant irritations in the way of NICE: one of those is adoption of the CHA_2DS_2-VASc* risk score over $CHADS_2$* as used by NICE in TA197; the other is the inclusion of dronedarone, as it has. Those irritations may trigger the NICE review of its AF guideline and I agree that it will do that in its own way. However, the nature of the sign up to the ESC guideline by various professional bodies in lieu of a more up-to-date recommendation, means that these organisations will follow the ESC guideline because it outdates that from NICE.

Round-table recommendation

- The NICE clinical guideline on AF has not been amended since 2006 and revision is now needed, and is planned for 2011.

Conflicts of interest

John Camm has spoken for and advised sanofi-aventis.
Matt Fay has received fees from sanofi-aventis for speaking at events, and for acting as consultant for developing information to be used for the education of primary care clinicians.
Nicholas Peters is a member of the sanofi-aventis Global Advisory Board for anti-arrhythmic products and development.
Derick Todd has received fees from sanofi-aventis for speaking at events.

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*CHA_2DS_2-VASc=cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); $CHADS_2$=cardiac failure, hypertension, age, diabetes, stroke (doubled)

MULTAQ ▼ Prescribing Information

See Summary of Product Characteristics before prescribing.

Presentation: White, oblong shaped tablets containing 400mg dronedarone.

Indication: Use in adult clinical stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Dosage: Adults and Elderly: 400mg twice daily, one tablet with the morning meal and one tablet with the evening meal. Not recommended under 18 years.

Contraindications: Hypersensitivity to dronedarone or excipients; second or third degree atrio-ventricular block or sick sinus syndrome (except when used with a functioning pacemaker); bradycardia < 50 beats per minute; unstable haemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding to NYHA Class IV and unstable Class III patients); co-administration with cytochrome P450 (CYP) 3A4 inhibitors (such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir); co-administration with products inducing torsades de pointes (such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides (such as erythromycin), Class I and III anti-arrhythmics); QTc Bazett interval ≥ 500 milliseconds; severe hepatic impairment; severe renal impairment (CrCL < 30ml/min).

Warnings: Not recommended in stable patients with recent (1 to 3 months) NYHA Class III heart failure or Left Ventricular Ejection Fraction < 35%. Patients should be advised to consult a physician if they develop or experience worsening signs or symptoms of heart failure, discontinuation of Multaq may need to be considered if heart failure develops. Liver function tests should be performed prior to initiation of treatment with dronedarone and then repeated monthly for 6 months, at months 9 and 12, and periodically thereafter. If ALT (alanine aminotransferase) levels are elevated ≥3 x upper limit of normal (ULN), ALT levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 x ULN, treatment should be discontinued. Appropriate investigation and close observation of patients should continue until normalisation of ALT. Measure creatinine clearance values 7 days after initiating dronedarone and use these as the new reference baseline, as in increase in creatininemia may be expected. An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE inhibitors or Angiotensin II Receptor Antagonists (AIIRAs). Correct any potassium or magnesium deficiency before initiation and during treatment. The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec). These changes do not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥ 500 milliseconds, dronedarone should be stopped. Dronedarone has a low pro-arrhythmic effect; however, proarrhythmic effects may occur in particular situations such as concomitant use with medicinal products favouring arrhythmia and/or electrolytic disorders. Patients with galactose intolerance should not take dronedarone as it contains lactose. Not recommended in pregnancy. Individual clinical assessment needed in lactation.

Drug Interactions: Contraindicated with products inducing torsades de pointes and potent CYP 3A4 inhibitors. Not recommended with potent CYP3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort. Patients should be warned to avoid grapefruit juice beverages while taking dronedarone. Caution when used with calcium antagonists and beta-blockers (if initiating either, start at the lowest dose and increase according to ECG response; if established on treatment, monitor with ECG and adjust dose(s) as necessary), statins (consider lower starting and maintenance doses and monitor for signs of muscle toxicity), sirolimus, tacrolimus, and digoxin (digoxin dose should be reduced by approximately 50%). No interactions observed with oral contraceptives, warfarin, theophylline, antidepressants, metformin, omeprazole, clopidogrel, pantoprazole or losartan.

Side Effects (see SPC for full details): Nervous system disorders: dysgeusia (uncommon), aguesia (rare); Cardiac disorders: Congestive heart failure (very common), bradycardia (common); Gastrointestinal disorders: diarrhoea, nausea, vomiting, abdominal pains, dyspepsia (common); Hepatobiliary disorders: Liver function test abnormalities (common), hepatocellular liver injury, including life-threatening acute liver failure (rare); Skin and subcutaneous disorders: rashes and pruritus (common), erythemas, eczema, photosensitivity, dermatitis – including allergic (uncommon); General disorders: fatigue, asthenia (common); Investigations: increased blood creatinine, prolonged QTc Bazett (very common).

Legal category: POM

Product Licence Numbers:
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