

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dronedarone Aristo 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dronedarone hydrochloride salt corresponding to 400 mg of dronedarone.

Excipient with known effect

Each tablet contains 108.92 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White, oblong shaped tablets with dimensions of 17.6 × 8.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dronedarone Aristo 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 (see sections 4.3 and 4.4), Dronedarone Aristo should only be prescribed after alternative treatment options have been considered.

Dronedarone Aristo must not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

4.2 Posology and method of administration

Treatment should be initiated and monitored only under specialist supervision (see section 4.4). Treatment with Dronedarone Aristo can be initiated in an outpatient setting.

Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting Dronedarone Aristo

There is limited information on the optimal timing to switch from amiodarone to Dronedarone Aristo. It should be considered that amiodarone may have a long duration of action after discontinuation due to its long half life. If a switch is envisaged, this should be done under the supervision of a specialist (see sections 4.3 and 5.1).

Posology

The recommended dose is 400 mg twice daily in adults. It should be taken as

- one tablet with the morning meal and
- one tablet with the evening meal.

Grapefruit juice should not be taken together with Dronedarone Aristo (see section 4.5).

If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose.

Special populations

Elderly

Efficacy and safety were comparable in elderly patients who did not suffer from other cardiovascular diseases and younger patients. In patients ≥ 75 years old, clinical signs of heart failure and ECG should be monitored on a regular basis when co-morbidities are present (see sections 4.3, 4.4 and 5.1). Although plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary (see sections 5.1 and 5.2).

Hepatic impairment

Dronedarone is contraindicated in patients with severe hepatic impairment because of the absence of data (see section 4.3 and 4.4). No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2).

Renal impairment

Dronedarone is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) < 30 ml/min) (see section 4.3). No dose adjustment is required in other patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of dronedarone in children aged below 18 years of age have not yet been established. No data are available.

Method of administration

Oral use.

It is recommended to swallow the tablet whole with a drink of water during a meal. The tablet cannot be divided into equal doses.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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)
- Bradycardia <50 beats per minute (bpm)
- Permanent AF with an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
- Patients in unstable hemodynamic conditions,
- History of, or current heart failure or left ventricular systolic dysfunction
- Patients with liver and lung toxicity related to the previous use of amiodarone
- Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir (see section 4.5)
- Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides (such as erythromycin), Class I and III antiarrhythmics (see section 4.5)
- QTc Bazett interval ≥ 500 milliseconds
- Severe hepatic impairment
- Severe renal impairment (CrCl <30 ml/min)
- Co-administration with dabigatran

4.4 Special warnings and precautions for use

Careful monitoring during dronedarone administration is recommended by regular assessment of cardiac, hepatic and pulmonary function (see below). If AF reoccurs discontinuation of dronedarone should be considered. Treatment with dronedarone should be stopped during the course of treatment, in case the patient develops any of the conditions which would lead to a contraindication as mentioned in section 4.3. Monitoring of co-administered medicinal products like digoxin and anti-coagulants is necessary.

Patients developing permanent AF during treatment

A clinical study in patients with permanent AF (AF duration for at least 6 months)

and cardiovascular risk factors was stopped early due to an excess of cardiovascular death, stroke and heart failure in patients receiving dronedarone (see section 5.1). It is recommended to perform ECGs serially, at least every 6 months. If patients treated with dronedarone develop permanent AF, treatment with Dronedarone Aristo should be discontinued.

Patients with history of, or current heart failure or left ventricular systolic dysfunction

Dronedarone Aristo is contraindicated in patients in unstable hemodynamic conditions, with history of, or current heart failure or left ventricular systolic dysfunction (see section 4.3).

Patients should be carefully evaluated for symptoms of Congestive Heart Failure. There have been spontaneously reported events of new or worsening heart failure during treatment with dronedarone. Patients should be advised to consult a physician if they develop or experience signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea. If heart failure develops, treatment with Dronedarone Aristo should be discontinued. Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with Dronedarone Aristo should be discontinued.

Patients with coronary artery disease

In patients with coronary artery disease, clinical signs of heart failure and ECG should be regularly monitored to detect early signs of heart failure. In ESC and ACC/AHA/HRS guidelines, dronedarone has a class IA recommendation in patients with paroxysmal/persistent AF and coronary artery disease.

Elderly

In elderly patients ≥ 75 years with multiple co-morbidities, clinical signs of heart failure and ECG should be monitored on a regular basis (see sections 4.2 and 5.1).

Women of child bearing potential and pregnancy

Dronedarone is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential should use effective methods of contraception during treatment with dronedarone and for 7 days after the final dose. Prior to initiating dronedarone, the prescriber should confirm that women of childbearing potential are not pregnant (see section 4.6).

Liver Injury

Hepatocellular liver injury, including life-threatening acute liver failure, has been reported in patients treated with dronedarone in the post-marketing setting. Liver function tests should be performed prior to initiation of treatment with dronedarone, after one week and after one month following initiation of treatment and then repeated monthly for six months, at months 9 and 12, and periodically thereafter. If alanine aminotransferase (ALT) levels are elevated $\geq 3 \times$ upper limit of normal (ULN), ALT levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be $\geq 3 \times$ ULN, treatment with dronedarone should be withdrawn. Appropriate investigation and close observation of patients should continue until normalisation of ALT.

Patients should immediately report any symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching) to their physician.

Management of plasma creatinine increase

An increase in plasma creatinine (mean increase 10 µmol/L) has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients. In most patients this increase occurs early after treatment initiation and reaches a plateau after 7 days. It is recommended to measure plasma creatinine values prior to and 7 days after initiation of dronedarone. If an increase in creatininemia is observed, serum creatinine should be re-measured after a further 7 days. If no further increase in creatinaemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. If serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.

An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE inhibitors or Angiotensin II Receptors Antagonists (AIIRAs). Larger increases in creatinine after dronedarone initiation have been reported in the postmarketing setting. Some cases also reported increases in blood urea nitrogen possibly due to hypoperfusion secondary to developing CHF (pre-renal azotaemia). In such cases dronedarone should be stopped (see sections 4.3 and 4.4). It is recommended to monitor renal function periodically and to consider further investigations as needed.

Electrolytes imbalance

Since antiarrhythmic medicinal products may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before initiation and during dronedarone therapy.

QT prolongation

The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation. These changes are linked to the therapeutic effect of dronedarone and do not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥ 500 milliseconds, dronedarone should be stopped (see section 4.3).

Based on clinical experience, dronedarone has a low pro-arrhythmic effect and has shown a decrease in arrhythmic death in the ATHENA study (see section 5.1). However, proarrhythmic effects may occur in particular situations such as concomitant use with medicinal products favouring arrhythmia and/or electrolytic disorders (see sections 4.4 and 4.5).

Respiratory, thoracic and mediastinal disorders

Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience. Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed treatment should be discontinued.

Interactions (see section 4.5)

Digoxin

Administration of dronedarone to patients receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with digoxin toxicity.

Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved. A synergistic effect on heart rate and atrioventricular conduction is also

possible.

Beta-blockers and calcium antagonists

The co-administration of beta-blockers or calcium antagonists with depressant effect on sinus and atrio-ventricular node should be undertaken with caution. These medicinal products should be initiated at low dose and up titration should be done only after ECG assessment. In patients already on calcium antagonists or beta blockers at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed.

Vitamin K antagonists

Patients should be appropriately anti-coagulated as per clinical AF guidelines. International Normalised Ratio (INR) should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label.

Potent CYP3A4 inducers

Potent CYP3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort are not recommended.

Statins

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

Grapefruit juice

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

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Dronedarone is primarily metabolised by CYP 3A4 (see section 5.2). Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact on dronedarone. Dronedarone is a moderate inhibitor of CYP 3A4, a mild inhibitor of CYP 2D6 and a potent inhibitor of P-glycoproteins (P-gp). Dronedarone therefore, has the potential to interact on medicinal products substrates of P-glycoproteins, CYP 3A4 or CYP 2D6. Dronedarone and/or its metabolites also have been shown to inhibit transport proteins of the Organic Anion Transporter (OAT), Organic Anion Transporting Polypeptide (OATP) and Organic Cation Transporter (OCT) families *in vitro*.

Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6.

A potential pharmacodynamic interaction can also be expected with beta-blockers, calcium antagonists and digitalis.

Medicinal products inducing torsades de pointes

Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides (such as erythromycin),

terfenadine and Class I and III antiarrhythmics are contraindicated because of the potential risk of proarrhythmia (see section 4.3).

In patients already taking beta-blockers at time of dronedarone initiation, an ECG should be performed and the dose of beta-blockers should be adjusted if needed (see section 4.4).

Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved (see section 4.4).

Effect of other medicinal products on Dronedarone Aristo

Potent CYP 3A4 inhibitors

Repeated doses of 200 mg ketoconazole daily resulted in a 17-fold increase in dronedarone exposure. Therefore, concomitant use of ketoconazole as well as other potent CYP 3A4 inhibitors such as itraconazole, voriconazole, posaconazole, ritonavir, telithromycin, clarithromycin or nefazodone is contraindicated (see section 4.3).

Moderate/weak CYP 3A4 inhibitors

- Erythromycin

Erythromycin, an oral macrolide, may induce torsades de pointes and, as such, is contraindicated (see section 4.3). Repeated doses of erythromycin (500 mg three times a day for 10 days) resulted in an increase in steady state dronedarone exposure of 3.8-fold.

- Calcium antagonists

Calcium antagonists, diltiazem and verapamil, are substrates and/or moderate inhibitors of CYP 3A4. Moreover, due to their heart rate-lowering properties, verapamil and diltiazem have the potential to interact with dronedarone from a pharmacodynamic point of view.

Repeated doses of diltiazem (240 mg twice daily), verapamil (240 mg once daily) and nifedipine (20 mg twice daily) resulted in an increase in dronedarone exposure of 1.7-, 1.4- and 1.2-fold, respectively. Calcium antagonists also have their exposure increased by dronedarone (400 mg twice daily) (verapamil by 1.4-fold, and nisoldipine by 1.5-fold). In clinical studies, 13% of patients received calcium antagonists concomitantly with dronedarone. There was no increased risk of hypotension, bradycardia and heart failure.

Overall, due to the pharmacokinetic interaction and possible pharmacodynamic interaction, calcium antagonists with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be used with caution when associated with dronedarone. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on calcium antagonists at time of dronedarone initiation, an ECG should be performed and the calcium antagonist dose should be adjusted if needed (see section 4.4).

- Other moderate/weak CYP 3A4 Inhibitors

Other moderate inhibitors of CYP3A4 are also likely to increase dronedarone exposure.

CYP 3A4 inducers

Rifampicin (600 mg once daily) decreased dronedarone exposure by 80% with no major change on its active metabolite exposure. Therefore, co-administration of rifampicin and other potent CYP 3A4 inducers such as phenobarbital, carbamazepine, phenytoin or St John's Wort is not recommended as they decrease dronedarone exposure.

MAO inhibitors

In an *in vitro* study MAO contributed to the metabolism of the active metabolite of dronedarone. The clinical relevance of this observation is not known (see sections 4.4 and 5.2).

Effect of Dronedarone Aristo on other medicinal products

Interaction on medicinal products metabolized by CYP 3A4

Dabigatran

When dabigatran etexilate 150 mg once daily was co-administered with dronedarone 400 mg twice daily, the dabigatran AUC₀₋₂₄, and C_{max} were increased by 100% and 70%, respectively. No clinical data are available regarding the co-administration of these medicinal products in AF patients. Their co-administration is contraindicated (see section 4.3).

Statins

Dronedarone can increase exposure of statins that are substrates of CYP 3A4 and/or P-gp substrates. Dronedarone (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4-fold and 2-fold respectively. It is predicted that dronedarone could also increase the exposure of lovastatin within the same range as simvastatin acid. There was a weak interaction between dronedarone and atorvastatin (which resulted in a mean 1.7-fold increase in atorvastatin exposure). There was a weak interaction between dronedarone and statins transported by OATP, such as rosuvastatin (which resulted in a mean 1.4-fold increase in rosuvastatin exposure).

In clinical trials, there was no evidence of safety concerns when dronedarone was co-administered with statins metabolised by CYP 3A4. However, spontaneously reported cases of rhabdomyolysis when dronedarone was given in combination with a statin (simvastatin in particular) have been reported, and, therefore, concomitant use of statins should be undertaken with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin label recommendations and patients monitored for clinical signs of muscular toxicity (see section 4.4).

Calcium antagonists

The interaction of dronedarone on calcium antagonists is described above (see section 4.4).

Immunosuppressants

Dronedarone could increase plasma concentrations of immunosuppressants (tacrolimus, sirolimus, everolimus and cyclosporine). Monitoring of their plasma concentrations and appropriate dose adjustment is recommended in case of coadministration with dronedarone.

Oral contraceptives

No decreases in ethinylestradiol and levonorgestrel were observed in healthy subjects receiving dronedarone (800 mg twice daily) concomitantly with oral contraceptives.

Interaction on medicinal products metabolised by CYP 2D

Beta blockers

Sotalol must be stopped before starting dronedarone (see sections 4.2 and 4.3).

Beta blockers that are metabolised by CYP 2D6 can have their exposure increased by dronedarone. Moreover, beta blockers have the potential to interact with dronedarone from a pharmacodynamic point of view. Dronedarone 800 mg daily increased metoprolol exposure by 1.6-fold and propranolol exposure by 1.3-fold (i.e. much below the 6-fold differences observed between poor and extensive CYP 2D6 metabolisers). In clinical studies, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers. Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, beta blockers should be used with caution concomitantly with dronedarone. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already taking beta blockers at time of dronedarone initiation, an ECG should be performed and the beta blocker dose should be adjusted if needed (see section 4.4).

Antidepressants

Since dronedarone is a weak inhibitor of CYP 2D6 in humans, it is predicted to have limited interaction on antidepressant medicinal products metabolised by CYP 2D6.

Interaction of P-gp substrates

Digoxin

Dronedarone (400 mg twice daily) increased digoxin exposure by 2.5-fold by inhibiting P-gp transporter. Moreover, digitalis has the potential to interact with dronedarone from a pharmacodynamic point of view. A synergistic effect on heart rate and atrio-ventricular conduction is possible. In clinical studies, increased levels of digitalis and/or gastrointestinal disorders indicating digitalis toxicity were observed when dronedarone was co-administered with digitalis. The digoxin dose should be reduced by approximately 50%, serum levels of digoxin should be closely monitored and clinical and ECG monitoring is recommended.

Interaction with medicinal products metabolised by CYP 3A4 and P-gp

Rivaroxaban

Dronedarone is likely to increase the exposure of rivaroxaban (a CYP3A4 and P-gp substrate) and consequently concomitant use may increase the risk of bleedings. Concomitant use of rivaroxaban and dronedarone is not recommended.

Apixaban

Dronedarone may increase the exposure of apixaban (a CYP3A4 and P-gp substrate). However, no dose adjustment for apixaban is required when co-administered with agents that are not strong inhibitors of both CYP3A4 and P-gp, such as dronedarone.

Edoxaban

In *in vivo* studies, edoxaban (a CYP3A4 and P-gp substrate) exposure was increased when administered with dronedarone. The edoxaban dose should be reduced according to the edoxaban label recommendations.

Interaction on warfarin and losartan (CYP 2C9 substrates)

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.

Losartan and other AIIRAs (Angiotensin II Receptor Antagonists)

No interaction was observed between dronedarone and losartan and an interaction between dronedarone and other AIIRAs is not expected.

Interaction on theophylline (CYP 1A2 substrate)

Dronedarone 400 mg twice daily does not increase the steady state theophylline exposure.

Interaction on metformin (OCT1 and OCT2 substrate)

No interaction was observed between dronedarone and metformin, an OCT1 and OCT2 substrate.

Interaction on omeprazole (CYP 2C19 substrate)

Dronedarone does not affect the pharmacokinetics of omeprazole, a CYP 2C19 substrate.

Interaction with clopidogrel

Dronedarone does not affect the pharmacokinetics of clopidogrel and its active metabolite.

Other information

Pantoprazole (40 mg once daily), a medicinal product which increases gastric pH without any effect on cytochrome P450, did not interact significantly on dronedarone pharmacokinetics.

Grapefruit juice (CYP 3A4 inhibitor)

Repeated doses of 300 ml of grapefruit juice three times daily resulted in a 3-fold increase in dronedarone exposure. Therefore, patients should be warned to avoid grapefruit juice beverages while taking dronedarone (see section 4.4).

4.7 Effects on ability to drive and use machines

Dronedarone has no or negligible influence on the ability to drive and use machines. However, ability to drive and use machines may be affected by adverse reactions such as fatigue.

4.8 Undesirable effects

Summary of the safety profile

Assessment of intrinsic factors such as gender or age on the incidence of any treatment emergent adverse reactions showed an interaction for gender (female patients) for the incidence of any adverse reactions and for serious adverse

reactions.

In clinical studies, premature discontinuation due to adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% in the placebo-treated group. The most common reasons for discontinuation of therapy with dronedarone were gastrointestinal disorders (3.2% of patients versus 1.8% in the placebo group).

The most frequent adverse reactions observed with dronedarone 400 mg twice daily in the 5 studies were diarrhoea (9%), nausea (5%) and vomiting (2%), fatigue and asthenia (7%).

Tabulated list of adverse reactions

The safety profile of dronedarone 400 mg twice daily in patients with atrial fibrillation (AF) or atrial flutter (AFL) is based on 5 placebo controlled studies, in which a total of 6,285 patients were randomised (3,282 patients received dronedarone 400 mg twice daily, and 2,875 received placebo). The mean exposure across studies was 13 months. In ATHENA study, the maximum follow-up was 30 months. Some adverse reactions were also identified during post marketing surveillance.

Adverse reactions are presented by system organ class.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
Immune system disorders				Anaphylactic reactions including angioedema
Nervous system disorders			Dysgeusia	Ageusia
Cardiac disorders	Congestive heart failure (see below)	Bradycardia (see sections 4.3 and 4.4)		
Vascular disorders				Vasculitis, including leukocytoclastic vasculitis
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease including pneumonitis and pulmonary fibrosis (see below)	
Gastrointestinal disorders		Diarrhoea Vomiting Nausea Abdominal pain Dyspepsia		

Hepatobiliary disorders		Liver function test abnormalities		Hepatocellular liver injury, including life-threatening acute liver failure (see section 4.4)
Skin and subcutaneous tissue disorders		Rashes (including generalised, macular, maculopapular) Pruritus	Erythemas (including erythema and rash erythematous) Eczema Photosensitivity reaction Dermatitis allergic Dermatitis	
General disorders and administration site conditions		Fatigue Asthenia		
Investigations	Blood creatinine increased* QTc Bazett prolonged #			

* ≥10% five days after treatment initiation (see section 4.4)

>450 msec in male >470 msec in female (see section 4.4)

Description of selected adverse reactions

In the 5 placebo controlled studies, CHF occurred in the dronedarone group with rates comparable with placebo (very commonly, 11.2% versus 10.9%). This rate should be considered in the context of the underlying elevated incidence of CHF in AF patients. Cases of CHF have also been reported in post-marketing experience (frequency not known) (see section 4.4).

Interstitial lung disease including pneumonitis and pulmonary fibrosis

In the 5 placebo controlled studies, 0.6% of patients in the dronedarone group had pulmonary events versus 0.8% of patients receiving placebo. Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience (frequency not known). A number of patients had been previously exposed to amiodarone (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, monitor the patient's cardiac rhythm and blood pressure. Treatment should be supportive and based on symptoms.

It is not known whether dronedarone and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

There is no specific antidote available. In the event of overdose, treatment should be supportive and directed toward alleviating symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cardiac therapy, antiarrhythmic class III,
ATC code: C01BD07

Mechanism of action

In animals, dronedarone prevents atrial fibrillation or restores normal sinus rhythm depending on the model used. It also prevents ventricular tachycardia and ventricular fibrillation in several animal models. These effects most likely result from its electrophysiological properties belonging to all four Vaughan-Williams classes. Dronedarone is a multichannel blocker inhibiting the potassium currents (including IK(Ach), IKur, IKr, IKs) and thus prolonging cardiac action potential and refractory periods (Class III). It also inhibits the sodium currents (Class Ib) and the calcium currents (Class IV). It non-competitively antagonises adrenergic activities (Class II).

Pharmacodynamic effects

In animal models, dronedarone reduces the heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect or weak increase on QTc-intervals, and with no change in HV- and QRS- intervals. It increases effective refractory periods (ERP) of the atrium, atrio-ventricular node, and ventricular ERP was slightly prolonged with a minimal degree of reverse frequency dependency.

Dronedarone decreases arterial blood pressure and myocardial contractility (dP/dt max) with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption.

Dronedarone has vasodilatory properties, in coronary arteries (related to the activation of the nitric oxide pathway) and in peripheral arteries.

Dronedarone displays indirect antiadrenergic effects and partial antagonism to adrenergic stimulation. It reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.

Clinical efficacy and safety

Reduction of risk of AF-related hospitalisation

The efficacy of dronedarone in the reduction of risk of AF-related hospitalisation was demonstrated in patients with AF or a history of AF and additional risk factors in the ATHENA multicenter, multinational, double blind, and randomised placebo-controlled study.

Patients were to have at least one risk factor (including age, hypertension, diabetes, prior cerebrovascular accident, left atrium diameter ≥ 50 mm or LVEF < 0.40) together with AF/AFL and sinus rhythm both documented within the last 6 months. Patients who received amiodarone within 4 weeks prior to randomisation were not included. Patients could be in AF/AFL or in sinus rhythm after spontaneous conversion or following any procedures.

Four thousand six hundred and twenty eight (4,628) patients were randomised and treated for up to 30 months maximum (median follow-up: 22 months) with either dronedarone 400 mg twice daily (2,301 patients) or placebo (2,327 patients), in addition to conventional therapy including beta-blockers (71%), ACE inhibitors or AIIRAs (69%) digitalis (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), chronic antiplatelet therapy (6%) and/or diuretics (54%).

The primary endpoint of the study was the time to first hospitalisation for cardiovascular reasons or death from any cause.

Patients ranged in age from 23 to 97 years and 42% were over 75 years old. Forty seven percent (47%) of patients were female and a majority was Caucasian (89%).

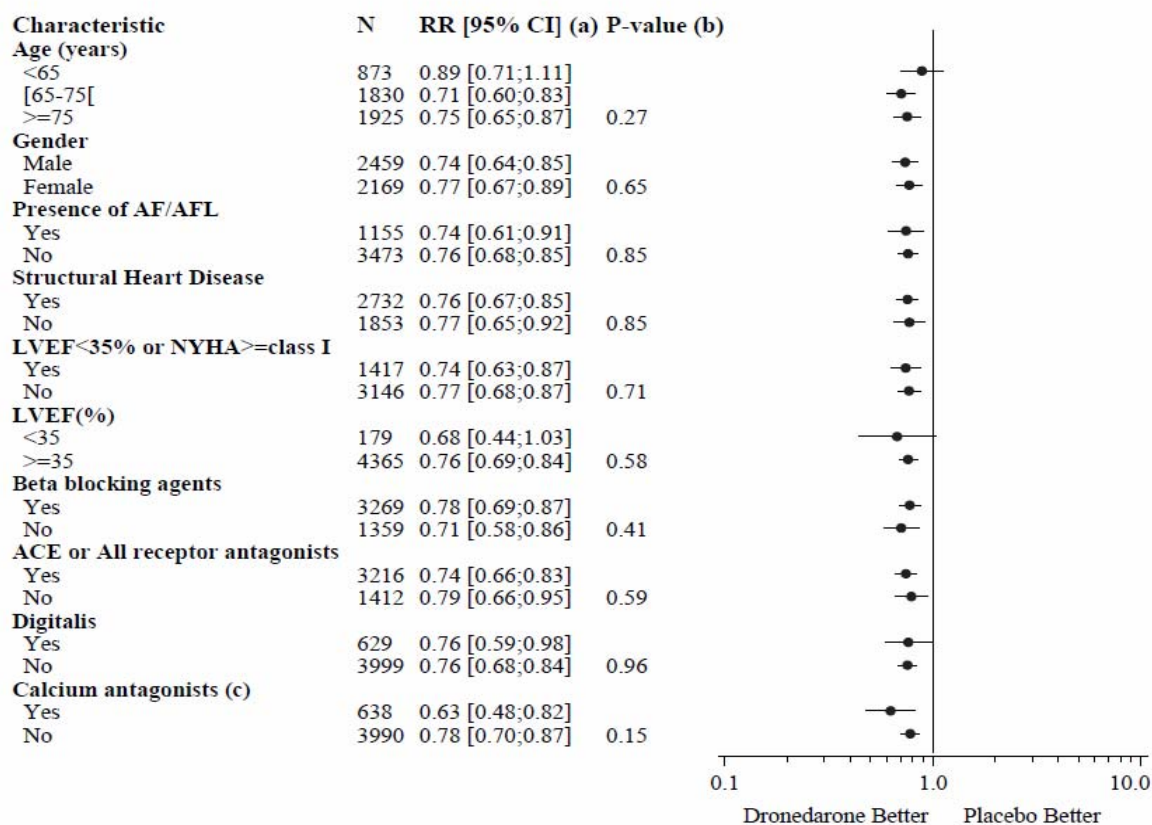
The majority had hypertension (86%) and structural heart disease (60%) (including coronary artery disease: 30%; congestive heart failure (CHF): 30%; LVEF<45%: 12%).

Twenty five percent (25%) had AF at baseline.

Dronedarone reduced the incidence of cardiovascular hospitalisation or death from any cause by 24.2% when compared to placebo ($p<0.0001$).

The reduction in cardiovascular hospitalisation or death from any cause was consistent in all subgroups, irrespective of baseline characteristics or medicinal products (ACE inhibitors or AIIRAs; beta-blockers, digitalis, statins, calcium antagonists, diuretics) (see figure 1).

Figure 1 - Relative Risk (RR) (dronedaronone 400 mg twice daily versus placebo) - first cardiovascular hospitalisation or death from any cause.



a Determined from Cox regression model

b P-value of interaction between baseline characteristics and treatment based on Cox regression model

c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

Similar results were obtained on the incidence of cardiovascular hospitalisation with a risk reduction of 25.5% ($p < 0.0001$).

During the course of the study, the number of deaths from any cause was comparable between the dronedarone (116/2,301) and placebo (139/2,327) groups.

Maintenance of sinus rhythm

In EURIDIS and ADONIS, a total of 1,237 patients with a prior episode of AF or AFL were randomised in an outpatient setting and treated with either dronedarone 400 mg twice daily ($n = 828$) or placebo ($n = 409$) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or AIIAs, chronic antiplatelet agents, diuretics, statins, digitalis, and calcium antagonists). Patients had at least one ECG-documented AF/AFL episode during the last 3 months and were in sinus rhythm for at least one hour and were followed for 12 months. In patients who were taking amiodarone, an ECG was to be performed about 4 hours after the first administration to verify good tolerability. Other antiarrhythmic medicinal products had to be withdrawn for at least 5 plasma half-lives prior to the first administration.

Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%), male (69%) patients. The most common co-morbidities were hypertension (56.8%) and structural heart disease (41.5%) including coronary heart disease

(21.8%).

In the pooled data from EURIDIS and ADONIS as well as in the individual trials, dronedarone consistently delayed the time to first recurrence of AF/AFL (primary endpoint). As compared to placebo, dronedarone lowered the risk of first AF/AFL recurrence during the 12-month study period by 25% ($p = 0.00007$). The median time from randomised to first AF/AFL recurrence in the dronedarone group was 116 days, i.e. 2.2-fold longer than in the placebo group (53 days).

The DIONYSOS study compared the efficacy and safety of dronedarone (400 mg twice daily) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) over 6 months. A total of 504 patients with documented AF were randomised, 249 received dronedarone and 255 received amiodarone. Patients ranged in age from 28 to 90 years, 49% were more than 65 years old. The incidence of the primary efficacy endpoint defined as first recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy at 12 months was 75% in the dronedarone group and 59% in the amiodarone group (hazard ratio = 1.59, log-rank p -value <0.0001). AF recurrence was 63.5% versus 42%, respectively. Recurrences of AF (including absence of conversion) were more frequent in the dronedarone group, whereas premature study drug discontinuations due to intolerance were more frequent in the amiodarone group. The incidence of the main safety endpoint defined as the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or gastrointestinal specific events or premature study drug discontinuation following any adverse event was reduced by 20% in the dronedarone group compared to the amiodarone group ($p = 0.129$). This reduction was driven by the occurrence of significantly fewer thyroid and neurological events and a trend for less skin or ocular events, and fewer premature study drug discontinuations compared to the amiodarone group. More gastrointestinal adverse events, mainly diarrhoea, were observed in the dronedarone group (12.9% versus 5.1%).

Patients with symptoms of heart failure at rest or with minimal exertion within the previous month, or who were hospitalised for heart failure during the previous month.

The ANDROMEDA study was conducted in 627 patients with left ventricular dysfunction, hospitalised with new or worsening heart failure and who had had at least one episode of shortness of breath on minimal exertion or at rest (NYHA class III or IV) or paroxysmal nocturnal dyspnoea within the month before admission. Patients ranged in age from 27 to 96 years, 68% were more than 65 years old. The study was stopped prematurely due to an observed imbalance of deaths in the dronedarone group [$n = 25$ versus 12 (placebo), $p = 0.027$] (see sections 4.3 and 4.4).

Patients with Permanent Atrial Fibrillation:

The PALLAS study was a randomised placebo-controlled study investigating the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors (patients with congestive heart failure ~ 69%, coronary heart disease ~ 41%, prior stroke or TIA ~ 27%; LVEF $\leq 40\%$ ~ 20.7% and patients ≥ 75 years with hypertension and diabetes ~ 18%). The study was prematurely stopped after randomization of 3149 patients (placebo = 1577; dronedarone = 1572) due to the significant increase in heart failure (placebo = 33; dronedarone = 80; HR = 2.49 (1.66-3.74)); stroke [placebo = 8; dronedarone = 17; HR = 2.14 (0.92-4.96)] and cardiovascular death [placebo = 6; dronedarone = 15; HR = 2.53 (0.98-6.53)] (see sections 4.3 and

4.4).

5.2 Pharmacokinetic properties

Absorption

Following oral administration in fed condition, dronedarone is well absorbed (at least 70%). However due to presystemic first pass metabolism, the absolute bioavailability of dronedarone (given with food) is 15%. Concomitant intake of food increases dronedarone bioavailability by on average 2- to 4-fold. After oral administration in fed conditions, peak plasma concentrations of dronedarone and the main circulating active metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5. The steady state mean dronedarone C_{max} is 84-147 ng/ml and the exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5- to 3.0-fold increase with respect to C_{max} and AUC.

Distribution

The *in vitro* plasma protein binding of dronedarone and its N-debutyl metabolite is 99.7% and 98.5% respectively and is not saturable. Both compounds bind mainly to albumin. After intravenous (IV) administration the volume of distribution at steady state (V_{ss}) ranges from 1,200 to 1,400 L.

Biotransformation

Dronedarone is extensively metabolised, mainly by CYP 3A4 (see section 4.5). The major metabolic pathway includes N-debutylation to form the main circulating active metabolite followed by oxidation, oxidative deamination to form the inactive propanoic acid metabolite, followed by oxidation, and direct oxidation. Monoamine Oxidases contribute partially to the metabolism of the active metabolite of dronedarone (see section 4.5). The N-debutyl metabolite exhibits pharmacodynamic activity but is 3 to 10-times less potent than dronedarone. This metabolite contributes to the pharmacological activity of dronedarone in humans.

Elimination

After oral administration, approximately 6% of the labelled dose is excreted in urine mainly as metabolites (no unchanged compound excreted in urine) and 84% are excreted in faeces mainly as metabolites. After intravenous administration the plasma clearance of dronedarone ranges from 130 to 150 L/h. The terminal elimination half-life of dronedarone is around 25-30 hours and that of its N-debutyl metabolite around 20-25 hours. In patients, dronedarone and its metabolite are completely eliminated from the plasma within 2 weeks after the end of a 400 mg twice daily-treatment.

Special populations

The pharmacokinetics of dronedarone in patients with AF is consistent with that in healthy subjects. Gender, age and weight are factors that influence the pharmacokinetics of dronedarone. Each of these factors has a limited influence on dronedarone.

Gender

In female patients, dronedarone exposures and its N-debutyl metabolite exposure are on average 1.3- to 1.9-fold higher as compared to male patients.

Elderly

Of the total number of subjects in clinical studies of dronedarone, 73% were 65 years of age and over and 34% were 75 years of age and over. In patients aged 65 years of age and over, dronedarone exposures are 23% higher in comparison with patients aged below 65 years of age.

Hepatic impairment

In subjects with moderate hepatic impairment, dronedarone unbound exposure is increased by 2-fold. That of the active metabolite is decreased by 47% (see section 4.2).

The effect of severe hepatic impairment on the pharmacokinetics of dronedarone was not assessed (see section 4.3).

Renal impairment

The effect of renal impairment on dronedarone pharmacokinetics has not been evaluated in a specific study. Renal impairment is not expected to modify the pharmacokinetics of dronedarone because no unchanged compound was excreted in urine and only approximately 6% of the dose was excreted in urine as metabolites (see section 4.2).

5.3 Preclinical safety data

Dronedarone had no genotoxic effects, based on one in vivo micronucleus test in mice and four *in vitro* tests.

In 2-year oral carcinogenicity studies, the highest dronedarone dose administered for 24 months was 70 mg/kg/day in rats and 300 mg/kg/day in mice.

Observations were increased incidence of mammary gland tumors in female mice, histiocytic sarcomas in mice and hemangiomas at the mesenteric lymph node level in rats, all at the highest tested dose only (corresponding to an exposure of 5 to 10 times that of the human therapeutic dose).

Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man. None of these observations was considered relevant for humans.

In chronic toxicity studies, slight and reversible phospholipidosis (accumulation of foamy macrophages) was observed in mesenteric lymph nodes mainly in the rat. This effect is considered specific to this species and not relevant to humans.

Dronedarone caused marked effects on embryo-foetal development at high doses in rats, such as increased post-implantation losses, reduced foetal and placental weights, and external, visceral and skeletal malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose,
Maize starch, Pregelatinized
Crospovidone,
Lactose Monohydrate,
Silica Colloidal anhydrous,
Magnesium stearate.

Tablet coat
Hypromellose (E464),
Macrogol (E1521),
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque PVC-Aluminium or opaque PVC/PE/PVDC-Aluminium blisters.

Dronedarone Aristo is available in pack sizes of 20, 20x1, 40, 40x1, 50, 50x1, 60, 60x1, 100 and 100x1 film-coated tablets in blisters and in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Straße 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 40546/0149

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/10/2023

10 DATE OF REVISION OF THE TEXT

28/08/2025