



TRANSPARENCY COMMITTEE

SUMMARY

16 SEPTEMBER 2020

The legally binding text is the original French opinion version

amiodarone
CORDARONE 200 mg scored tablets

Reevaluation

► Key points

Favourable opinion for maintenance of reimbursement in the treatment and prevention of recurrences of supraventricular tachycardias and the prevention of recurrences of ventricular rhythm disorders (for more details, see MA).

► Role in the care pathway?

Supraventricular tachycardias

- Treatment of atrial fibrillation

Cardioversion should be considered to restore sinus rhythm in patients who remain symptomatic despite treatment to control heart rate. The restoration of sinus rhythm is not indicated in the event of asymptomatic AF or permanent AF.

Cardioversion falls within the scope of specialised management by a cardiologist. It may be pharmacological or electrical depending on the haemodynamic status and preference of the patient and must be combined with oral anticoagulant therapy.

Role of the medicinal product in the care pathway:

Only amiodarone has an MA in the treatment of atrial fibrillation.

Amiodarone remains a first-line therapy for the treatment of atrial fibrillation, considering the latest European guidelines and new clinical data confirming its efficacy for pharmacological cardioversion.

- Prevention of recurrences of atrial fibrillation

Antiarrhythmic treatment may be considered as long-term therapy to maintain sinus rhythm in the event of symptomatic recurrent paroxysmal or persistent AF. It is not generally initiated from the first episode of AF. Long-term antiarrhythmic treatment is aimed at improving symptoms and preventing recurrences of symptomatic AF. It falls within the scope of specialised management with a cardiological opinion and at least annual ECG monitoring. Catheter ablation may be a first-line therapeutic alternative in specific situations or a second-line alternative in the event of failure of medicinal treatment. It requires oral anticoagulant therapy and is reserved for cardiac rhythm specialists.

Role of the medicinal product in the care pathway:

In patients with paroxysmal or persistent atrial fibrillation, in combination with lifestyle and dietary measures and control of risk factors, amiodarone remains a first-line treatment for the maintenance of sinus rhythm in patients with concomitant heart disease (heart failure, coronary insufficiency), considering the latest European guidelines and new clinical data confirming its efficacy (with a high size effect) in the prevention of recurrences of atrial fibrillation compared to the control group (placebo or absence of treatment).

It is a second-line treatment in other patients due to its frequent pro-arrhythmic and extracardiac adverse effects, which ultimately corresponds to most situations.

In patients with permanent atrial fibrillation, the Committee reiterates that oral antiarrhythmic drugs no longer have a role in the prevention of recurrences.

- Other supraventricular tachycardias

The therapeutic strategy for the prevention of recurrences of supraventricular rhythm disorders apart from atrial fibrillation (focal atrial tachycardias, common atrial flutter, atrioventricular nodal re-entry tachycardia (AVNRT), atrioventricular re-entry tachycardia (AVRT)) is based on catheter ablation as a first-line approach. Medicinal treatment with beta-blockers or non bradycardia-inducing calcium channel blockers is recommended pending or following refusal or failure of ablation. The use of oral antiarrhythmic drugs has become marginal.

Role of the medicinal product in the care pathway:

Amiodarone is a last-resort treatment in focal atrial tachycardia and atrial flutter, in combination with lifestyle and dietary measures and control of risk factors.

The Committee considers that all the oral antiarrhythmic drugs concerned by the reevaluation no longer have a role in other types of supraventricular arrhythmia, including, in particular, nodal tachycardias or Bouveret-Hoffmann syndrome.

Prevention of recurrences of ventricular rhythm disorders

With the exception of certain specific cardiac diseases, the prevention of recurrences of ventricular arrhythmias is based on an implantable cardioverter defibrillator (ICD) and, more rarely, on antiarrhythmic drugs. The decision to implant an ICD requires the opinion of a cardiac rhythm specialist. Implantation is only considered in authorised centres in patients in whom the reasonable expectancy of survival with a satisfactory functional status is more than 1 to 2 years and in patients over 30 years of age.

Beta-blockers (excluding sotalol) are recommended as first-line treatment in patients with ventricular arrhythmia.

In the event of failure of or contraindication to beta-blockers, the European guidelines indicate antiarrhythmics. Antiarrhythmic drugs are used as an adjuvant therapy in the treatment of patients with ventricular arrhythmias. The choice of antiarrhythmic drug must take into account the causal disease and/or the associated heart condition.

Furthermore, interventional procedures are alternatives:

- The ablation of arrhythmogenic foci is considered as a second-line treatment of recurrent idiopathic ventricular tachycardias, following the failure of pharmacotherapy.
- Ablation is generally performed percutaneously (percutaneous catheter ablation), by the subepicardial route in rare cases and, in exceptional cases, surgically.
- Finally, other invasive or surgical treatments, such as myocardial revascularisation, ventricular aneurysm resection, sympathetic denervation, short-term mechanical circulatory support, heart

transplant, the use of a total artificial heart device or anaesthetic sedation, represent special situations, with implementation decided upon on a case-by-case basis following a specialised opinion.

Role of the medicinal product in the care pathway:

In the prevention of life-threatening recurrences of ventricular tachycardias, symptomatic and disabling documented ventricular tachycardias and ventricular fibrillations, new data on amiodarone do not call into question its already known efficacy. Hence oral amiodarone remains the reference preventive therapy, particularly in the presence of coronary insufficiency and/or impaired left ventricular function.

It should be noted that due to its adverse effects, it must be used with caution and its use is mainly recommended in patients who cannot have an ICD or refuse to have one implanted.

► Special recommendations

The Committee maintains its recommendation of reserving initial prescription to cardiologists, given:

- the need for pre-treatment screening with assessment of heart function, in particular involving the performance of an ECG and, if necessary, additional cardiac imaging,
- the need to evaluate the benefit of prescription, taking into account the clinical indication, the aetiology, the patient's comorbidities and, in particular, in view of:
 - the specific safety profile of oral antiarrhythmic drugs (pro-arrhythmic effects for all drugs and extracardiac effects for amiodarone),
 - the updated efficacy profile and the Committee's new guidelines concerning the role of each drug in the care pathway.

The Committee reiterates that if it is necessary to change treatment, any overlapping of prescriptions of antiarrhythmic drugs should be avoided, since this could exacerbate their toxicity.

COMMITTEE'S CONCLUSIONS

Clinical benefit

Supraventricular rhythm disorders

► Supraventricular rhythm disorders, primarily represented by atrial fibrillation, are serious conditions that can impair quality of life and be life-threatening for the patient, either immediately (sudden death) or following complications (heart failure, stroke).

► The proprietary medicinal product CORDARONE (amiodarone) is a curative and preventive treatment for recurrences of supraventricular rhythm disorders.

► The efficacy/adverse effects ratio of amiodarone remains high in the treatment and prevention of recurrences of supraventricular rhythm disorders given:

- new data confirming its efficacy for the pharmacological cardioversion of atrial fibrillation compared to placebo or the absence of treatment,
- its high effect size in the prevention of recurrences of atrial fibrillation compared to the control group (placebo or the absence of treatment),
- despite the absence of demonstration of a benefit on morbidity and mortality and its safety profile marked by frequent adverse effects (in particular pro-arrhythmic and extracardiac).

► There are therapeutic alternatives (see 08. Role in the care pathway).

► The proprietary medicinal product CORDARONE (amiodarone), in combination with lifestyle and dietary measures and control of risk factors:

- remains a first-line therapy for the treatment of atrial fibrillation,
- remains a first-line treatment for the prevention of recurrences of paroxysmal or persistent fibrillation following restoration of sinus rhythm only in patients **with associated structural heart disease** (heart failure, coronary insufficiency). It is a second-line treatment in other patients due to its frequent extracardiac adverse effects,
- is a last-resort treatment for the prevention of recurrences of focal atrial tachycardias and atrial flutter.

Public health impact

Considering:

- the seriousness of ventricular rhythm disorders,
- their prevalence,
- the partially met medical need,
- the absence of demonstration of an impact on mortality in view of the available data, which suggested an efficacy only on prevention of recurrences of AF compared with placebo (with a high effect size),
- the lack of robust new data demonstrating an impact on morbidity, quality of life or the organisation of care,
- the lack of additional response to the identified need,

CORDARONE (amiodarone) is unlikely to have an additional impact on public health.

Given all of these elements, the Committee considers that the clinical benefit of CORDARONE (amiodarone) remains substantial in the treatment of supraventricular tachycardia, and the prevention of recurrences of documented supraventricular tachycardia when the need for treatment has been established in the event of resistance or contraindication to other therapies.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products

approved for use in the indications “Treatment of supraventricular tachycardia” and “Prevention of recurrences of documented supraventricular tachycardia when the need for treatment has been established in the event of resistance or contraindication to other therapies”, and at the MA dosages.

Ventricular rhythm disorders

► Ventricular rhythm disorders are serious diseases that can cause haemodynamic instability and sudden cardiac death in the patient.

► The proprietary medicinal product CORDARONE (amiodarone) is a **preventive treatment** for recurrences of life-threatening ventricular rhythm disorders and/or disabling, symptomatic documented ventricular tachycardias.

► The efficacy/adverse effects ratio of amiodarone remains high in the prevention of recurrences of ventricular rhythm disorders, in view of new morbidity and mortality data that do not call into question the demonstrated efficacy in the prevention of sudden death.

► There are therapeutic alternatives (see 08. Role in the care pathway).

► The proprietary medicinal product CORDARONE (amiodarone), in combination with lifestyle and dietary measures and control of risk factors, remains a second-line treatment in the prevention of recurrences of disabling or life-threatening ventricular rhythm disorders due to its toxicity.

Public health impact

Considering:

- the seriousness of ventricular rhythm disorders,
- their prevalence,
- the partially met medical need,
- the absence of demonstration of an impact on morbidity and mortality,
- the lack of new data demonstrating an impact on quality of life or the organisation of care,
- the lack of additional response to the identified need,

CORDARONE (amiodarone) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CORDARONE (amiodarone) **remains substantial** in the prevention of recurrences of ventricular rhythm disorders.

The Committee issues a **favourable opinion** for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications “Prevention of recurrences of life-threatening ventricular tachycardias: treatment must be initiated in a hospital environment with monitoring, symptomatic and incapacitating documented ventricular fibrillation and ventricular tachycardias”, and at the MA dosages.