NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA197; Dronedarone for the treatment of non-permanent atrial fibrillation

This guidance was issued in August 2010.

The review date for this guidance is March 2013.

1. Recommendation

The guidance should be incorporated into the ongoing update of NICE clinical guideline 36 'Atrial fibrillation', once the wording of the guidance has been amended to reflect the changes to the UK marketing authorisation for dronedarone. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost-effectiveness of dronedarone within its licensed indication for the treatment of atrial fibrillation and atrial flutter.

3. Current guidance

1.1 Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation only in people:

• whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, and

• who have at least one of the following cardiovascular risk factors:

− hypertension requiring drugs of at least two different classes

− diabetes mellitus

− previous transient ischaemic attack, stroke or systemic embolism

− left atrial diameter of 50 mm or greater

− left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or

− age 70 years or older, and

• who do not have New York Heart Association (NYHA) class III or IV heart failure.

1.2 People who do not meet the criteria in section 1.1 who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

Following safety concerns, the European Medicines Agency has reviewed and amended the marketing authorisation for dronedarone. This has resulted in a more restricted marketing authorisation than was originally appraised in TA197. However, the evidence suggests that reviewing the guidance would not be of value to the NHS. There is no new evidence to indicate that dronedarone would be less safe or less effective in the population that meets the revised marketing authorisation. Consequently, if considered in line with the revised marketing authorisation, it is likely that dronedarone would still be considered clinically and cost effective and continue to be recommended for this population. Therefore, it is proposed that the wording of recommendation 1.1 in TA197 is amended to reflect the changes in the UK marketing authorisation and the guidance re-issued accordingly.

The Centre for Clinical Practice is currently updating NICE clinical guideline 36 'Atrial Fibrillation' and it is recommended that TA197 be incorporated into the update of CG36, once the wording of recommendation 1.1 has been amended to reflect the revised marketing authorisation. Any change in the treatment pathway, and therefore the relevant comparators for dronedarone would be identified during the guideline update.

In the meantime, a warning about the restricted use of dronedarone should be placed on TA197 webpage of the NICE website.

5. Implications for other guidance producing programmes

The Centre for Clinical Practice is currently updating CG36 and the draft scope proposes to update the pharmacological management section of the guideline. It is therefore deemed appropriate to incorporate TA197 Dronedarone for the treatment of non-permanent atrial fibrillation once the wording of recommendation 1.1 has been amended.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from April 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

7. Summary of evidence and implications for review

Since the ATHENA trial[2], which was reviewed during the development of TA197, no new evidence has been published that is directly relevant to the population described in TA197 as eligible for treatment with dronedarone. There were three registered and unpublished trials identified during this review, but none were considered relevant to the remit of TA197 or this review. However, new evidence has been generated that is indirectly relevant to the eligible population and has resulted in the marketing authorisation being amended.

The PALLAS trial (NCT01151137) began enrolment in July 2010; however, the data monitoring committee recommended that the study be terminated for safety reasons in July 2011. Connolly et al (2011) reported that, among patients with permanent atrial fibrillation and additional cardiovascular risk factors who receive dronedarone, there was a highly significant doubling in the rate of the first composite coprimary outcome (stroke, myocardial infarction, systemic embolization or death from cardiovascular causes). It should be noted that the study population had permanent AF, which is not directly relevant to the population considered in the development of TA197.

When TA197 was published in August 2010, dronedarone had a marketing authorisation for:

> the treatment of adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Following the early termination of the PALLAS trial, the European Medicines Agency (EMA) reviewed and revised the marketing authorisation:

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

Several additional contraindications, precautions and special warnings have also been added to the revised SPC, including the need for greater monitoring of liver and renal function. Patients must be successfully cardioverted to sinus rhythm prior to treatment with dronedarone.

The impact on TA197

Two elements of section 1.1 of the guidance contradict the revised marketing authorisation, either directly or by implication. Firstly, the recommendation presently

[2] ATHENA - a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalisation or death from any cause in patients with atrial fibrillation/atrial flutter; NCT00174785

states that dronedarone should be a treatment option for patients with left ventricular ejection fraction less than 40% (but does note that the original summary of product characteristics [SPC] did not recommend dronedarone for people with left ventricular ejection fraction less than 35%). However, dronedarone is now contraindicated in all patients with left ventricular systolic dysfunction. Secondly, the recommendation states dronedarone should not be a treatment option for patients with New York Heart Association (NYHA) class III or IV heart failure. This could imply that dronedarone is a treatment option for patients with other types of heart failure; however, the revised marketing authorisation states that it is contraindicated in all patients with current or previous heart failure. Therefore, there is a risk that patients will continue to be treated in line with the recommendation in TA197, but outside of the marketing authorisation.

The revisions to dronedarone's marketing authorisation have also had the following effects:

- The eligible patient population now smaller, and possibly different, to that addressed in the assessment for TA197.
- The marketing authorisation now supports the use of dronedarone only after alternative treatment options have been considered. The comparators in the appraisal for TA197 were sotalol, class 1c drugs and amiodarone.

These changes could mean that the cost-effectiveness model considered in the development of TA197 may no longer be wholly accurate; however, there is no new evidence to indicate that the incremental cost-effectiveness ratio (ICER) for dronedarone would increase such that it would no longer be cost-effective use of NHS resources.

Given the change in marketing authorisation, dronedarone may be more likely to be used as a third-line (or subsequent) treatment (that is, after both beta-blockers and an alternative antiarrhythmic agent). However, the optimal sequencing of treatments is unclear at this stage. The European public assessment report for dronedarone states:

"The existence of comparative efficacy and safety data between the different anti-arrhythmics would facilitate the clear identification of the exact patient population who can derive greater benefit from dronedarone treatment. However, this information not being available, the Committee considered that the therapeutic indication of Multaq needs to be significantly revised to ensure that it is only used after consideration of other anti-arrhythmic agents."

During the development of TA197, the Evidence Review Group indicated that dronedarone may more cost-effective when used at later points in the treatment pathway but noted that the submission did not consider the cost effectiveness of dronedarone at different time points within the treatment pathway (for example, as a second-line treatment after failure of an alternative first-line antiarrhythmic).

The Centre for Clinical Practice is currently updating NICE clinical guideline 36 'Atrial Fibrillation'. If the review of NICE clinical guideline 36 investigates treatment sequencing and results in a change to the treatment pathway, this may impact on the relevant comparators for dronedarone. Several new treatments for atrial fibrillation

have recently been referred to, or appraised by, NICE including dabigatran, rivaroxaban, apixaban and vernakalant. None of these technologies are relevant comparators for dronedarone (either they are not antiarrhythmic drugs or are for acute treatment).

It is anticipated that this review of CG36 will be published mid-2014. In addition, the European Society of Cardiology (ESC) is undertaking a focused review of its 2010 guidelines for the management of atrial fibrillation.

Recommendation

There is no new evidence to indicate that, if considered in line with the revised marketing authorisation, the incremental cost-effectiveness ratio (ICER) for dronedarone would increase such that it would not be cost-effective use of NHS resources. Therefore undertaking a review of guidance would not be of value for the NHS.

The safety concerns arising from the current recommendation in TA197 contradicting the revised marketing authorisation should be addressed in a pragmatic way that does not require a full review of TA197.

It is proposed that the wording of recommendation 1.1 in TA197 is amended to reflect the changes in the UK marketing authorisation (see table below) and the guidance re-issued.

Current recommendation in TA197 (2010)	**Suggested revised recommendation in TA197 (to be reissued in 2012)**
1.1 Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation only in people: • whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, and • who have at least one of the following cardiovascular risk factors: − hypertension requiring drugs of at least two different classes − diabetes mellitus − previous transient ischaemic attack, stroke or systemic embolism − left atrial diameter of 50 mm or greater − left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or − age 70 years or older, and • who do not have New York Heart Association (NYHA) class III or IV heart failure.	1.1 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 beta-blockers), that is, as a second-line treatment option and after alternative options have been considered, and • who have at least one of the following cardiovascular risk factors: − hypertension requiring drugs of at least two different classes − diabetes mellitus − previous transient ischaemic attack, stroke or systemic embolism − left atrial diameter of 50 mm or greater or − age 70 years or older, and • who do not have left ventricular systolic dysfunction, and • who do not have history of, or current heart failure.

Because the Centre for Clinical Practice is currently updating NICE clinical guideline 36 ‘Atrial Fibrillation’, it is recommended that TA197 be incorporated into the update of CG36, once the wording of recommendation 1.1 has been revised to reflect the revised marketing authorisation. In the meantime, a warning about the restricted use of dronedarone should be placed on TA197 webpage of the NICE website.

8. Implementation

A submission from Implementation is included in Appendix 3.

The costing template published alongside TA197 estimated 5,610 patients would receive treatment with dronedarone once TA197 was fully implemented. If a linear uptake was assumed, over a 5-year period, the estimated annual cost at 18 months would be approximately £1.4 million. Current expenditure is approximately £500,000 per year.

The uptake data provided by the implementation team shows that approximately 2500 units of dronedarone are dispensed in the community each month (source: ePACT). There is no recent data available for the number of units dispensed by Hospital pharmacies (source: IMS).

Based on the available date, it is unclear whether the treatment is well established and embedded in the NHS. It may be that use is significantly less than anticipated due to the safety concerns that were raised by the PALLAS trial.

There is no data to suggest that dronedarone is being used outside of the recommendations in TA197.

9. Equality issues

No equality and diversity issues were identified during the development of TA197.

GE paper sign off: Helen Knight, Associate Director, 25 May 2012

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	**No**
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	**No**
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	**No**
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	**No**

Options	Consequence	Selected – 'Yes/No'
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	**YES**, TA197 should be incorporated into the ongoing update of NICE clinical guideline 36 'Atrial fibrillation' once the wording of the recommendations has been amended to reflect changes in the marketing authorisation and the guidance has been re-issued; **however**, if the revised Clinical Guideline looks at treatment sequences and alters the treatment pathway, this may impact on the relevant comparators for dronedarone. In addition, a warning should be urgently placed on the NICE website regarding the revised UK marketing authorisation.
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	**NO**; however, if the revised Clinical Guideline looks at treatment sequences and alters the treatment pathway, this may impact on the relevant comparators for dronedarone.

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**No**

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Chronic heart failure. Quality Standard. Published: June 2011.

The management of atrial fibrillation. CG36. Published: June 2006. Review date: August 2011. Review decision: The guideline should be updated at this time (December 2011). An update of this guideline is currently in the process of being scheduled into the work programme.

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. TA249. Published: March 2012.

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. TA256. Published: May 2012.

Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias (review of TA11). TA95. Published: January 2006. Review date: July 2007, deferred to July 2010. Review decision: A combined review of both TA95 and TA120 (Cardiac resynchronisation therapy for the treatment of heart failure) should be planned into the appraisal work programme.

Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block. TA88. Published: February 2005. Review date: September 2011. Review decision: A review will be planned into the work programme and a revised remit will be sought to clarify the indications.

In progress

The management of atrial fibrillation (update). Clinical Guideline. Expected date of publication: TBC. Consultation on draft scope: 2-31 May 2012.

Atrial Fibrillation Quality Standard. Referred: March 2012.

Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation with one or more risk factor for stroke or systemic embolism [ID500]. Referred: November 2011. Expected date of issue: February 2013

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481]. Expected date of issue: September 2013.

WatchBP Home A for diagnosing and monitoring hypertension and detecting atrial fibrillation. Medical Technologies guidance. Expected date of issue: August 2012.

Suspended/terminated

Vernakalant for the treatment of rapid conversion of recent onset atrial fibrillation = 7 days [ID454]. Referred: May 2011. Suspended: June 2011 following receipt of manufacturer data.

Clopidogrel in combination with aspirin for the prevention of vascular events in people with atrial fibrillation [ID95]. Referred: July 2009. Removed from work programme: February 2011.

Ximelagatran for the treatment and prevention of stroke and other thromboembolic complications associated with atrial fibrillation [ID376]. Referred: October 2000. Suspended: 2005.

Atrial fibrillation - idraparinux sodium [ID375]. Referred: November 2005. Removed from work programme: July 2007

In topic selection[3]

[redacted]

[3] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Details of changes to the indications of the technology

Indication considered in original appraisal	Current indication (at the time of this review proposal)
Dronedarone has a marketing authorisation for the treatment of adult clinically stable patients with a history of, or current, non-permanent atrial fibrillation to prevent recurrence of atrial fibrillation or to lower ventricular rate. The SPC states that because of the unexplained results of the ANDROMEDA study, the use of dronedarone in unstable patients with NYHA class III and IV heart failure is contraindicated. There is also a recommendation in the SPC (under 'special warnings and precautions for use') which states that because of limited experience in stable patients with recent (1 to 3 months) NYHA class III heart failure or with left ventricular ejection fraction less than 35%, the use of dronedarone is not recommended in these patients. The recommended dosage of dronedarone is 400 mg twice daily. Dronedarone is available in 400 mg tablets and comes in packs of 20 tablets or 60 tablets. Source: TA197 (Aug 2010)	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 (see sections 4.3 and 4.4), Multaq should only be prescribed after alternative treatment options have been considered. MULTAQ should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure. Multaq is now also contraindicated in heart failure of all NHYA classes (I-IV) and in those patients who have left ventricular systolic dysfunction (LVSD). Source: SPC (18 January 2012)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
None identified	

Registered and unpublished trials

None identified

Additional information

European Medicines Agency (30 January 2012) Revised European public assessment report (EPAR) for Multaq.

National Prescribing Centre (28 November 2011) Dronedarone increases the risk of heart failure, stroke and death compared to placebo in people with permanent AF. NPC Rapid Review.

MHRA (October 2011) Dronedarone (Multaq): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements. Drug Safety Update 5(3).

National Prescribing Centre (29 September 2011) EMA recommends restricting the use of dronedarone. NPC Rapid Review.

European Medicines Agency (September 2011) European Medicines Agency recommends restricting use of Multaq

European Society of Cardiology (2010) Guidelines for the management of atrial fibrillation.

References

Connolly, S (2011) Dronedarone in High-Risk Permanent Atrial Fibrillation. *The New England Journal of Medicine.* 365: 2268-76

Appendix 3 – Implementation submission

1 Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index

This section presents Hospital Pharmacy Audit Index (HPAI) data on the cost and volume of Dronedarone prescribed and used in hospitals between January 2007 and March 2011.

Figure 1 Volume of Dronedarone prescribed in hospitals in England between January 2007 and March 2011

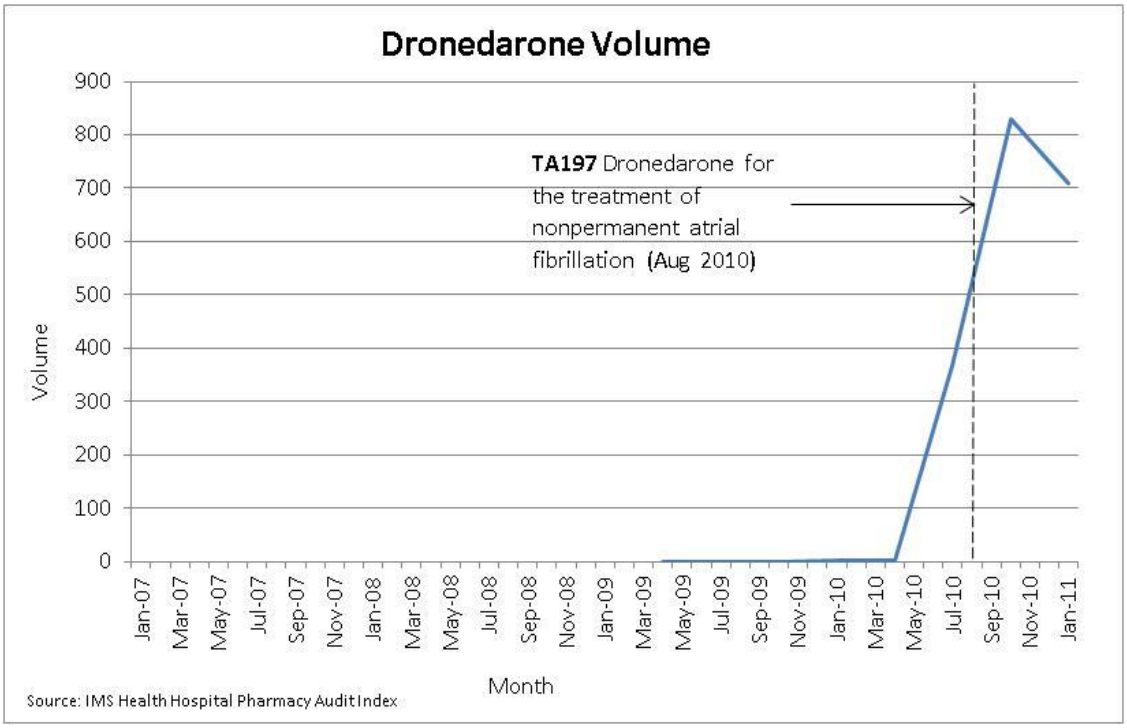
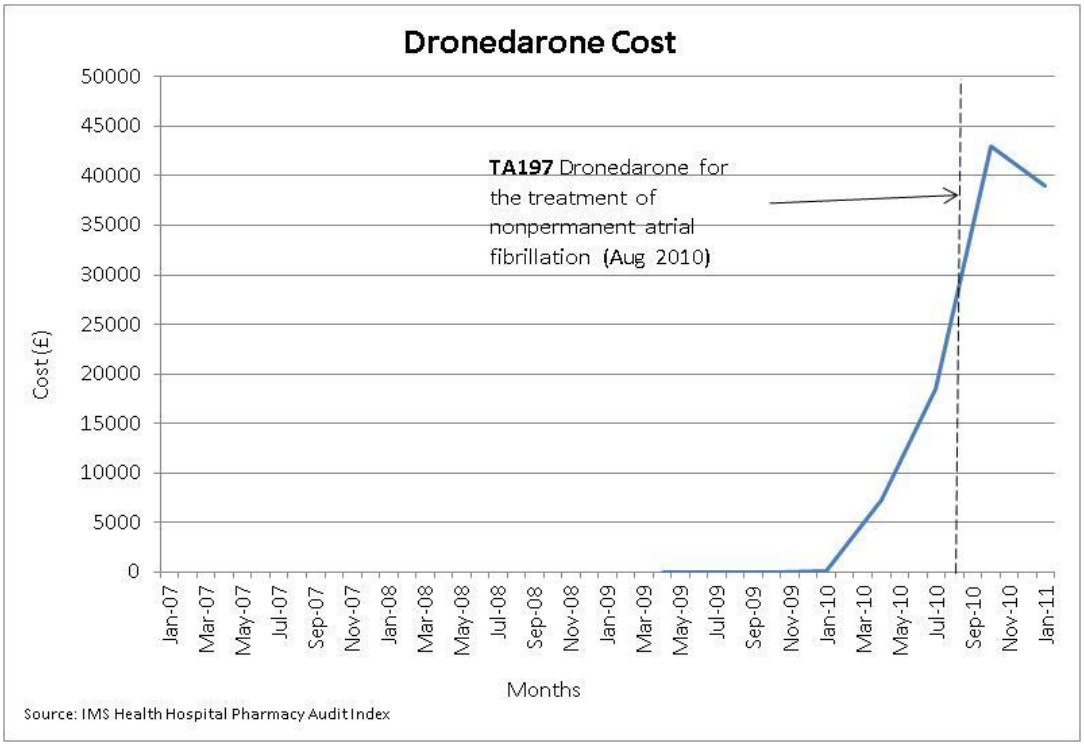


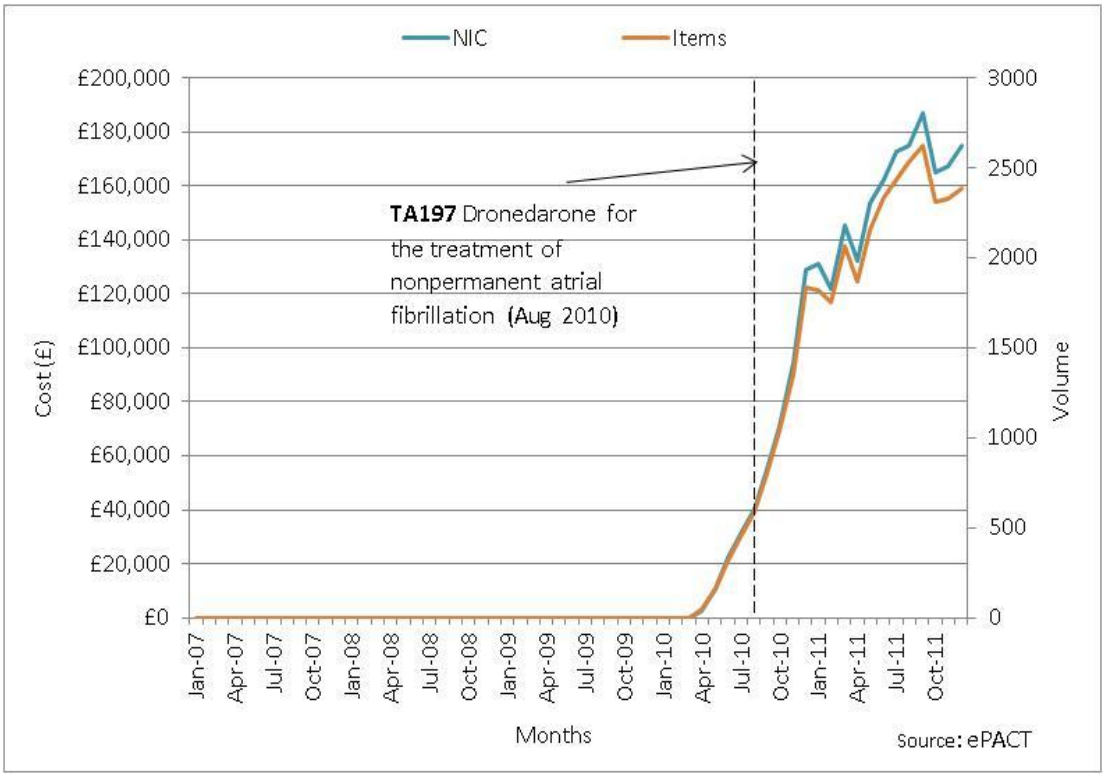
Figure 2 Net ingredient cost (£) of Dronedarone prescribed in hospitals in England between January 2007 and March 2011



1.2 ePACT and hospital ePACT

This section presents electronic Prescribing Analysis and Cost Tool data on the net ingredient cost and the number of prescription items prescribed in primary care and hospitals that have been dispensed in the community.

Figure 3 Cost and volume of Dronedarone prescribed in primary care and hospitals that has been dispensed in the community between January 2007 and December 2011



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

Nothing to add at this time.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

Appendix 4: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.