Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

# Public Assessment Report

# UKPAR

# Flecainide Acetate 50 mg and 100 mg Tablets

# (flecainide acetate)

# UK Licence No: PL 25298/0137-8

# Brown & Burk UK Ltd

# Lay Summary
## Flecainide Acetate 50 mg and 100 mg Tablets
## (flecainide acetate)

This is a summary of the Public Assessment Report (PAR) for Flecainide Acetate 50 mg and 100 mg Tablets (PL 25298/0137-8). For ease of reading, this medicinal product will collectively be referred to as Flecainide Acetate Tablets in this Lay Summary.

This summary explains how Flecainide Acetate Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Flecainide Acetate Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Flecainide Acetate Tablets and what are they used for?**
Flecainide Acetate Tablets are generic medicines. This means that they are similar to 'reference medicines' already authorised in the UK called Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Ltd; PL 15142/0078-9).

Flecainide Acetate tablets are used to treat:

- Arrhythmias (irregular heart beat)
- Tachycardia (heart beat too fast)
- Atrial fibrillation (rapid contractions of muscles in the heart).

**How do Flecainide Acetate Tablets work?**
Flecainide Acetate Tablets contain the active ingredient flecainide acetate, which belongs to a group of medicines called anti-arrhythmics. This medicine works by controlling the rate and rhythm of the heart.

**How are Flecainide Acetate Tablets used?**
Flecainide Acetate Tablets are taken by mouth.

Patients must take this medicine exactly as a doctor or pharmacist has told them. They must check with their doctor or pharmacist if they are not sure.

**Adults:**
**Supraventricular arrhythmias (Irregular heart beat that starts in the upper chambers of the heart)**
- Flecainide Acetate 50mg tablets: The usual dose is one tablet twice a day.
- Flecainide Acetate 100mg tablets: The usual dose is half a tablet twice a day.

A doctor may prescribe up to a total dose of 300 mg daily (3 x 100 mg tablets or 6 x 50 mg tablets).

**Ventricular arrhythmias (Irregular heart beat that starts in the lower chambers of the heart)**
- Flecainide Acetate 50mg tablets: The usual dose is two tablets twice a day.

• Flecainide Acetate 100mg tablets: The usual dose is one tablet twice a day.

**The elderly and patients with kidney or heart problems:**
• For elderly patients, and patients with kidney or heart problems, the doctor may tell them to take a lower dose.

While patients are taking this medicine, a doctor may ask them to have check-ups. These are to make sure that the medicine is working properly and that the dose they are taking is right for them.

**Use in Children:**
• Flecainide Acetate tablets are not recommended for children under 12 years of age, However, dairy products such as milk, infant formula and possibly yoghurt, may reduce how much flecainide is absorbed in children and infants.

Flecainide Acetate Tablets can only be obtained on prescription from a doctor.

For further information on how Flecainide Acetate Tablets are used, please see the Summaries of Product Characteristics and package leaflet available on the MHRA website.

**How have Flecainide Acetate Tablets been studied?**
Because Flecainide Acetate Tablets are generic medicines, studies have been limited to tests to determine that they are bioequivalent to the reference medicines, Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Ltd; PL 15142/0078-9). Two medicines are bioequivalent when they produce the same levels of the active substance in the body**.**

**What are the benefits and risks of Flecainide Acetate Tablets?**
As Flecainide Acetate Tablets are generic medicines of the reference medicines, Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Ltd; PL 15142/0078-9), their benefits and risks are taken as being the same as those for the reference medicines**.**

**Why are Flecainide Acetate Tablets approved?**
It was concluded that, in accordance with EU requirements, Flecainide Acetate Tablets have been shown to have comparable quality and to be bioequivalent to Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Ltd; PL 15142/0078-9). Therefore, the view was that, as for the reference products, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Flecainide Acetate Tablets?**
A risk management plan has been developed to ensure that Flecainide Acetate Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Flecainide Acetate Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

## Other information about Flecainide Acetate Tablets

Marketing Authorisations were granted in the UK on 26 January 2018.

The full PAR for Flecainide Acetate Tablets follows this summary.

This summary was last updated in March 2018.

# Table of Contents

# I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brown & Burk UK Ltd, Marketing Authorisations for the medicinal products Flecainide Acetate 50 mg and 100 mg Tablets (PL 25298/0137-8) on 26 January 2018. These products are prescription-only medicines (POM), indicated for:

a) AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways.

b) Paroxysmal atrial fibrillation in patients with disabling symptoms when treatment need has been established and in the absence of left ventricular dysfunction (see 4.4, Special warnings and special precautions for use). Arrhythmias of recent onset will respond more readily.

c) Symptomatic sustained ventricular tachycardia.

d) Premature ventricular contractions and/or non-sustained ventricular tachycardia which are causing disabling symptoms, where these are resistant to other therapy or when other treatment has not been tolerated.

Flecainide Acetate tablets can be used for the maintenance of normal rhythm following conversion by other means.

Flecainide Acetate tablets are for oral administration

These applications were submitted as abridged national applications, according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products. The applicant has cross-referred to Tambocor 50 mg and 100 mg Tablets, which were originally authorised to 3M Health Care Limited (PL 00068/0102 & PL 00068/0152) on 07 April 1983 and 28 April 1992 respectively. These licenses underwent changes of ownership procedures to Valeant Pharmaceuticals Limited (PL 19166/0078-9) on 13 October 2007 and then to the current marketing authorisation holder, Meda Pharmaceuticals Ltd (PL 15142/0078-9), on 13 July 2010 and 24 March 2010 respectively.

Flecainide Acetate tablets contain the active substance flecainide which slows conduction through the heart, having its greatest effect on His Bundle conduction. It also acts selectively to increase anterograde and particularly retrograde accessory pathway refractoriness. Its actions may be reflected in the electrocardiography (ECG) by prolongation of the PR interval and widening of the QRS complex. The effect on the JT interval is insignificant.

No new non-clinical studies were conducted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

A bioequivalence study was submitted to support these applications comparing the applicant's test product Flecainide Acetate 100 mg Tablets and the reference product, Tambcor 100 mg tablets (Meda Pharma BV) in healthy adult, human subjects under

fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of originator products that have been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Flecainide Acetate 50 mg and 100 mg Tablets outweigh the risks and Marketing Authorisations were granted.

# II QUALITY ASPECTS

## II.1 Introduction

The products are presented as tablets and contain 50 mg and 100 mg flecainide acetate, as active substance. The excipients present are silicified microcrystalline cellulose, croscarmellose sodium, maize starch and magnesium stearate.

All the excipients used in the manufacture of the proposed formulations comply with their respective European Pharmacopoeia monographs with the exception of silicified microcrystalline cellulose which complies with the United States Pharmacopeia. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contains animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

The finished products are packaged in polyvinylchloride (PVC)/polyvinylidenechloride (PVdC) aluminium blister packs containing 20, 28, 30, 40, 50, 56, 60, 84, 90, 100 112, 120, 168 and 180 tablets.

Not all pack sizes may be marketed.

The Marketing Authorisation Holder committed to get the mock-ups approved for unmarketed pack sizes before those packs are commercially marketed.

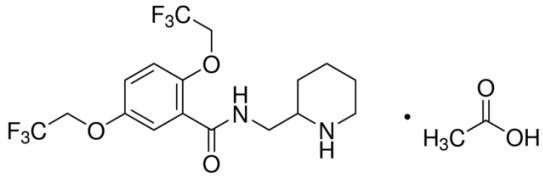
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

## II.2 Drug Substance

INN: **Flecainide acetate**

Chemical Name: (N-[(RS)-piperidine-2-ylmethyl]-2,5-bis(2,2,2 trifluoroethoxy)benzamide acetate

Structure:



Molecular formula: $C_{17}H_{20}F_6N_2O_3.C_2H_4O_2$

Molecular weight: 474.40 g/mol

Appearance: White or almost white crystalline powder, very hygroscopic in nature.

Solubility: Soluble in water and in ethanol. It is freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid.

Flecainide acetate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, flecainide acetate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

## II.3 Medicinal Product

### Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious, tablets that are bioequivalent to the reference products, Tambocor 50 mg and 100 mg Tablets (Meda Pharma BV).

Comparative dissolution profiles have been presented for the proposed and reference products.

### Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated at production scale and has shown satisfactory results. approval.

### Finished Product Specifications

The finished product specifications are acceptable. The test methods have been described and have been adequately validated. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for all working standards used.

### Stability of the products

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from the studies support a shelf-life of 24 months, with no special storage conditions.

Suitable post approval stability commitments have been provided.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended from a pharmaceutical point of view.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of flecainide acetate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

## III.2 Pharmacology

Not applicable for these product type. Refer to section 'III.1; Introduction' detailed above.

### III.3 Pharmacokinetics
Not applicable for these product type. Refer to section 'III.1; Introduction' detailed above.

### III.4 Toxicology
Not applicable for these product type. Refer to section 'III.1; Introduction' detailed above.

### III.5 Environmental Risk Assessment (ERA)
Since Flecainide Acetate 50 mg and 100 mg Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

### III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical point of view.

# IV CLINICAL ASPECTS
## IV.1 Introduction
The clinical pharmacology of flecainide acetate is well-known. With the exception of bioequivalence data, no new clinical data have been submitted and none are required for applications of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

## IV.2 Pharmacokinetics
In support of these applications, the Marketing Authorisation holder has submitted the following bioequivalence study:

**An open label, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, bioequivalence study of Flecainide Acetate 100 mg Tablets and Tambcor 100 mg Tablets (Meda Pharma BV) in healthy adult, human subjects under fasting conditions.**

Blood samples were collected before dosing and up to and including 72.0 hours after drug administration. The study periods were separated by a wash-out period of 11 days.

## Results

**Bioequivalence results for log-transformed test/reference ratio with 90% Confidence Intervals:**

| Pharmacokinetic parameter | 90% Confidence Intervals | Acceptance Range |
|---|---|---|
| $C_{max}$ (ng/mL) | (94.51%; 105.85%) | 80.00%-125.00% |
| $AUC_t$ (ng.hr/mL) | (91.15%; 104.83%) | 80.00%-125.00% |

The 90% confidence intervals of the test/reference formulations for $AUC_t$ and $C_{max}$ values lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Bioequivalence has been shown between the test product (Flecainide Acetate 100 mg Tablets), and the reference product Tambcor 100 mg Tablets (Meda Pharma BV) under fasting conditions.

**Biowaiver**

As the 50 mg and 100 mg strength products meet all the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for the 100 mg tablet can be extrapolated to the other strength i.e. 50 mg tablet. Therefore, bioequivalence has been shown between the 50 mg and 100 mg strengths of the test products and their respective reference products.

## IV.3 Pharmacodynamics

No new pharmacodynamics data are required for these applications and none have been submitted.

## IV.4 Clinical efficacy

No new clinical efficacy data are required for these applications and none have been submitted.

## IV.5 Clinical safety

No new clinical safety data are required for these applications and none have been submitted.

## IV.6 Risk Management Plan (RMP)

The Marketing Authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Flecainide Acetate 50 mg and 100 mg Tablets.

**A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:**

| Safety Concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | **Important identified risks** | |
| Proarrhythmic effects | The risk of Proarrhythmic effects associated with the use of Flecainide Acetate is described as posology 4.2, contraindications for use in section 4.3, Special warnings and precautions for use in section 4.4, Interaction with other medicinal products and other forms of interaction in section 4.5 Undesirable effects in section 4.8 of the SPC & before you take Flecainide acetate in section 2 , section 3 how to take Flecainide Acetate tablets<br>section 4 possible side effects and appropriate advice is provided to the prescriber to | None |

| | | |
|---|---|---|
| | minimise this risk. | |
| Adverse hemodynamic effects, including cardiac failure | The risk of adverse hemodynamic effects, including cardiac failure associated with the use of Flecainide Acetate is described as contraindicated in section 4.3 special warnings and precautions for use in section 4.4, Interaction with other medicinal products and other forms of interaction in section 4.5 Undesirable effects in section 4.8 and overdose 4.9 of the SPC & before you take Flecainide acetate in section 2 , section 3 how to take Flecainide Acetate tablets section 4 possible side effects and appropriate advice is provided to the prescriber to minimise this risk. | None |
| **Important Potential risks** | | |
| Interaction | The risk of Interaction associated with the use of Flecainide Acetate described as Interaction with other medicinal products and other forms of interaction in section 4.5, and overdose section 4.9 of the SPC. before you take Flecainide acetate in section 2 and appropriate advice is provided to prescriber to minimise this risk. | None |
| **Missing information** | | |
| Exposure during pregnancy | The risk associated with the use of Flecainide Acetate use Exposure during pregnancy described as pregnancy in section 4.6 and 5.3 section of the SPC & before you take Flecainide acetate in section 2 appropriate advice is provided to the prescriber to minimise this risk. | None |
| Use in the pediatric population <12 year old | The risk associated with the use of Flecainide Acetate Use in the pediatric population <12 year old, described as posology section4.2 and special warnings and precautions for use in section 4.4 of the SPC & before | None |

| | | |
|---|---|---|
| | you take Flecainide acetate in section 2 appropriate advice is provided to the prescriber to minimise this risk. | |

### IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications.

## V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

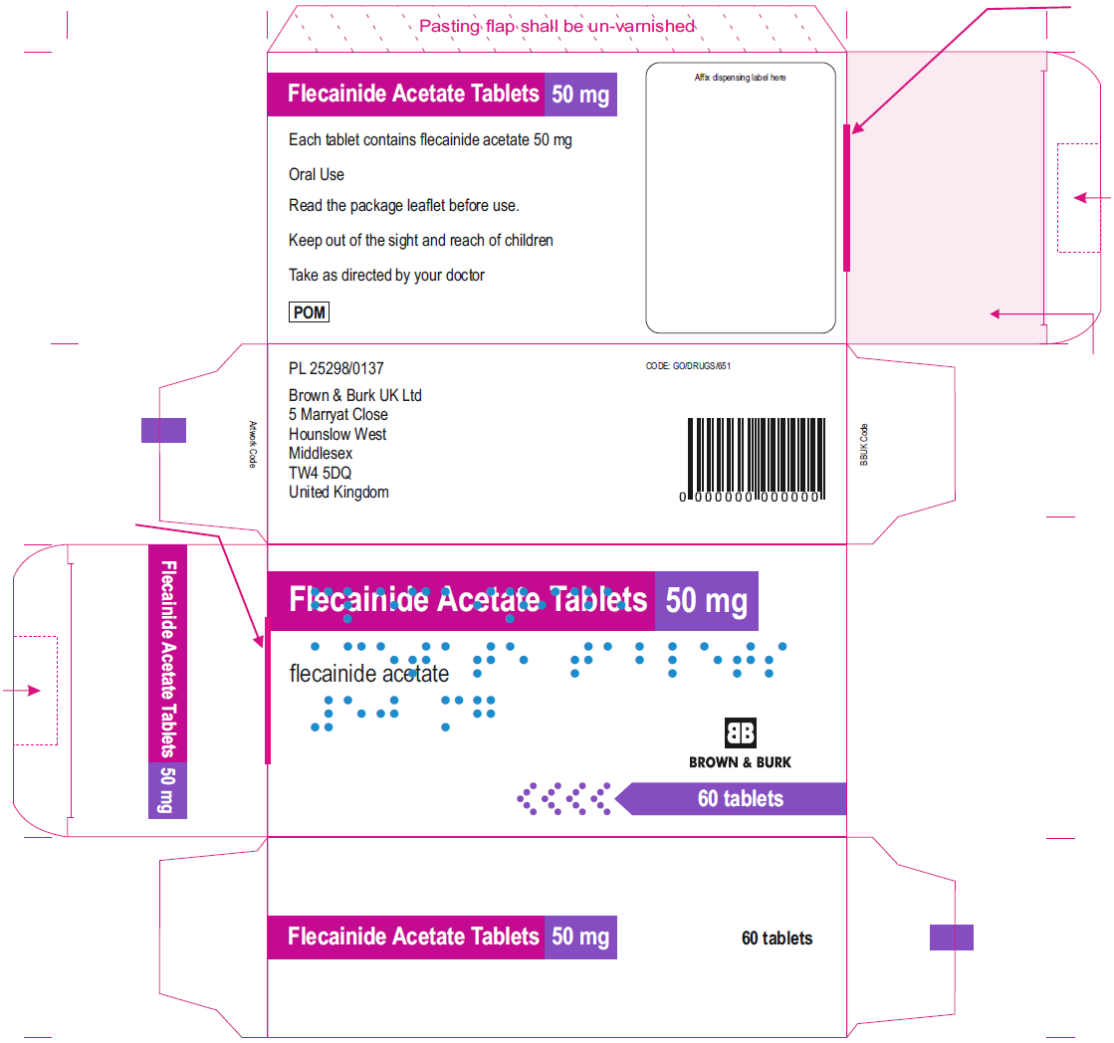
## VI Overall conclusion, benefit/risk assessment and recommendation

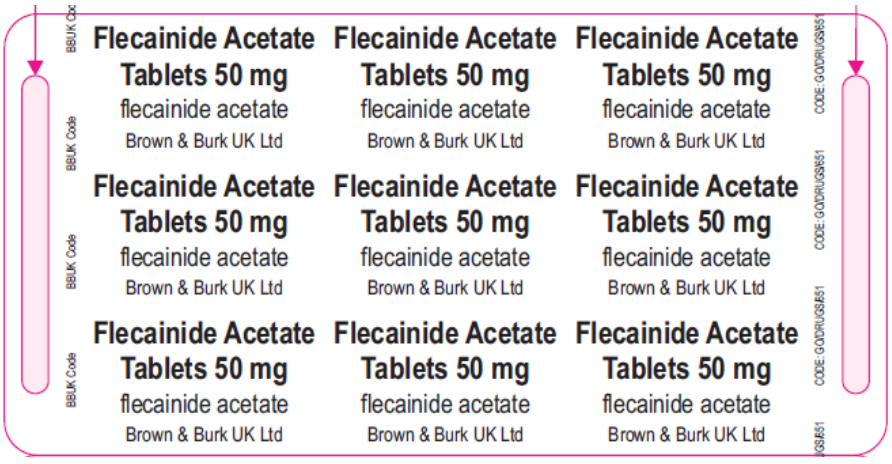
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the proposed products are bioequivalent to the authorised reference products. Extensive clinical experience with flecainide acetate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

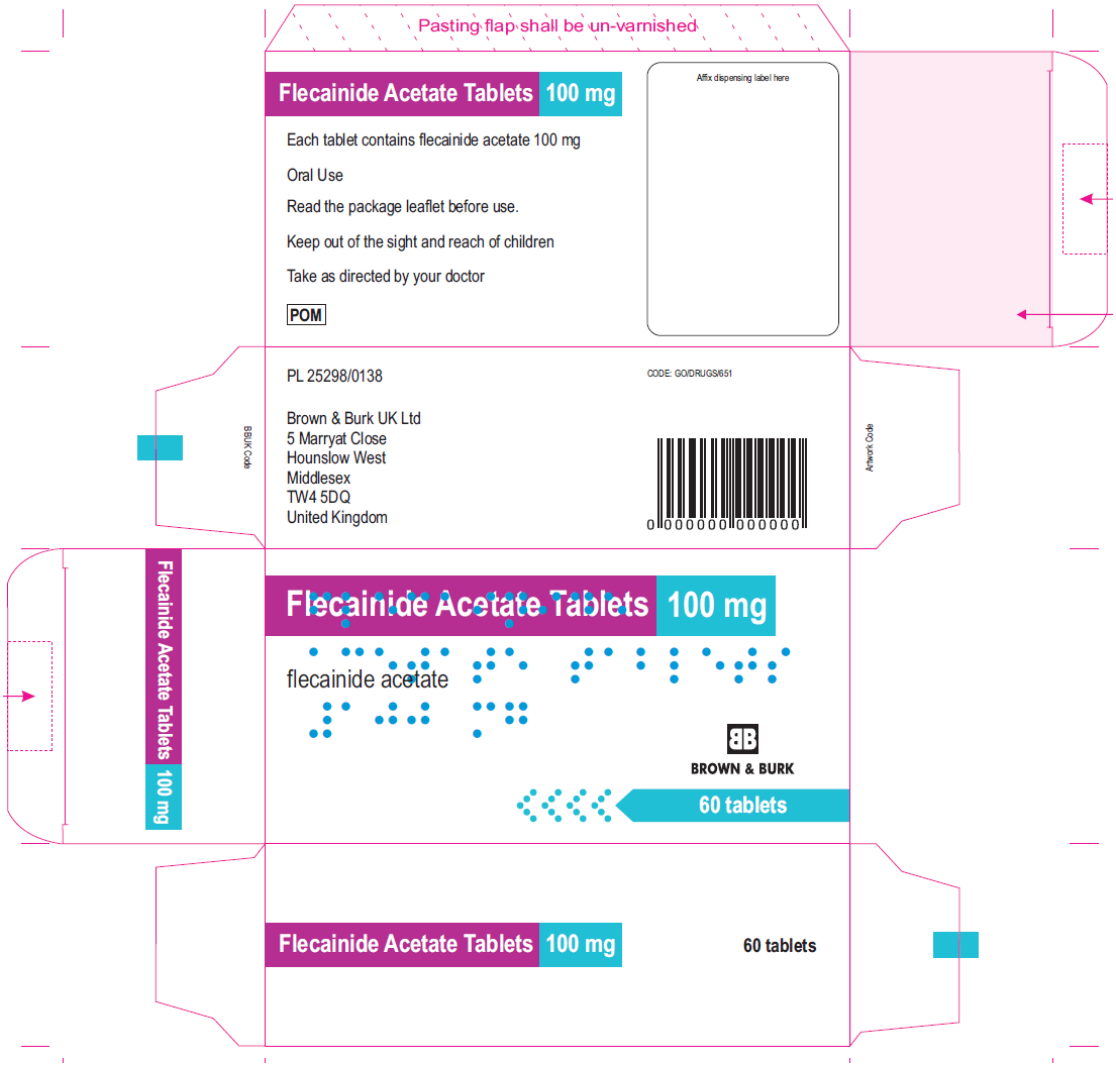
# Summary of Product Characteristics, Patient Information Leaflet & Labels

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

The current approved labelling is provided below:




Pasting flap shall be un-varnished
Flecainide Acetate Tablets 100 mg
Each tablet contains flecainide acetate 100 mg
Oral Use
Read the package leaflet before use.
Keep out of the sight and reach of children
Take as directed by your doctor
POM
Affix dispensing label here
PL 25298/0138
CODE: GO/DRUGS/651
Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom
BBUK Code
Artwork Code
Flecainide Acetate Tablets 100 mg
flecainide acetate
BROWN & BURK
60 tablets
Flecainide Acetate Tablets 100 mg
60 tablets


Flecainide Acetate Tablets 100 mg
flecainide acetate
Brown & Burk UK Ltd
BBUK Code
CODE: GO/DRUGS/651

# Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |