Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Flecainide acetate 50 mg tablets
Flecainide acetate 100 mg tablets

(Flecainide acetate)

Procedure No: UK/H/6829/001-002/DC

UK Licence Number: PL 11311/0592-0593

Tillomed Laboratories Limited

LAY SUMMARY

Flecainide acetate 50 mg tablets
Flecainide acetate 100 mg tablets

This is a summary of the Public Assessment Report (PAR) for Flecainide acetate 50 mg tablets (PL 11311/0592; UK/H/6829/001/DC) and Flecainide acetate 100 mg tablets (PL 11311/0593; UK/H/6829/002/DC). It explains how Flecainide acetate 50 mg tablets and Flecainide acetate 100 mg tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Flecainide acetate 50 mg tablets and Flecainide acetate 100 mg tablets.

The product will be referred to as 'Flecainide acetate tablets' throughout the remainder of this public assessment report (PAR).

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 a 'generic medicine'. This means that Flecainide acetate tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Tambocor 50 mg and 100 mg Tablets (Teva UK; PL 00289/2210-11).

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?
This medicine contains the active ingredient called 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?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The patient's doctor will choose the dose that is right for their condition. Usually the treatment with Flecainide will be started in hospital. If the patient has switched from a different formulation (e.g. from an injection of Flecainide) the doctor should do so with caution and monitor the patient closely.

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

The 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 your heart)
• Flecainide acetate 50 mg tablets: The usual dose is two tablets twice a day.
• Flecainide acetate 100 mg tablets: The usual dose is one tablet twice a day.

The doctor may prescribe up to a total dose of 400 mg daily (4 x 100 mg tablets or 8 x 50 mg tablets)
The elderly and patients with kidney or heart problems:
• For elderly patients, and patients with kidney or heart problems, the doctor may tell you to take a lower dose. While the patient is taking this medicine, the doctor may ask the patient to have check-ups. These are to make sure that the medicine is working properly and that the dose the patient is taking is right for them.

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 acetate is absorbed in children and infants.

For further information on how Flecainide acetate tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Flecainide acetate tablets have been shown in studies?
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 (Teva UK; PL 00289/2210-11). Two medicines are bioequivalent when they produce the same levels of the active substance in the body**.**

What are the possible side effects of Flecainide acetate tablets?
As Flecainide Acetate Tablets are generic medicines of the reference medicines, Tambocor 50 mg and 100 mg Tablets (Teva UK; PL 00289/2210-11), their benefits and risks are taken as being the same as those for the reference medicines**.**

For a full list of all the side effects reported with Flecainide Tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

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 (Teva UK; PL 00289/2210-11). 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 (RMP) 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 (SmPC) and the package leaflet for Flecainide acetate tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/ reviewed continuously.

Other information about Flecainide acetate tablets

Germany (DE), Italy (IT) the UK agreed to grant Marketing Authorisations on 13 August 2018. Following a subsequent national phase in the UK, Marketing Authorisations were granted on 04 September 2018.

The full PAR for Flecainide acetate tablets follows this summary.

For more information about treatment with Flecainide acetate tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Tillomed Laboratories Limited, marketing authorisations for the medicinal product Flecainide acetate 50 mg tablets (PL 11311/0592; UK/H/6829/001/DC) and Flecainide acetate 100 mg tablets (PL 11311/0593; UK/H/6829/002/DC). 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 using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany (DE) and Italy (IT) as Concerned Member States (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal products for these applications are 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 Meda Pharmaceuticals Ltd (PL 15142/0078-9), on 13 July 2010 and 24 March 2010 respectively and then to the current marketing authorisation holder Teva UK limited (PL 00289/2210-11) on 13 November 2017.

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.

One bioequivalence study (an open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study in healthy adult volunteers) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical studies were conducted which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considered that the applications could be approved at the end of procedure on 13 August 2018. Following a subsequent national phase in the UK, Marketing Authorisations were granted on 04 September 2018.

II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as a tablet containing 50 mg or 100 mg flecainide acetate per tablet. Other ingredients consist of the pharmaceutical excipients; microcrystalline cellulose (PH 101), microcrystalline cellulose (PH 102), croscarmellose sodium and magnesium stearate.

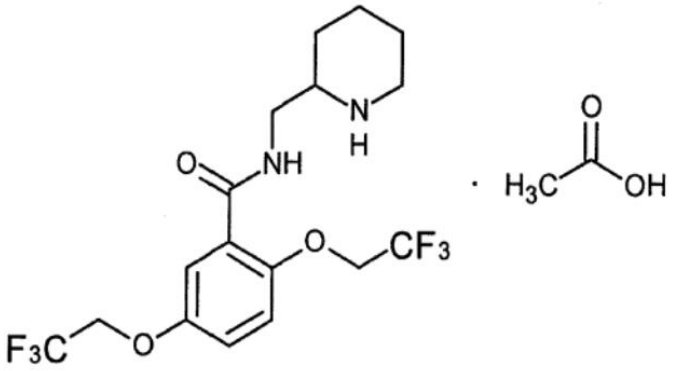
The product is packaged in aluminium/polyvinyl chloride/ polyvinylidene chloride (Alu-PVC/PVdC) blister packs containing, 20, 30, 60 and 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

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:	$C_{19}H_{24}F_6N_2O_5$
Molecular weight:	474.4 g/mol
Appearance:	White or almost white crystalline powder, very hygroscopic in nature.
Solubility:	Soluble in water and in anhydrous ethanol. It is freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid.

The drug substance is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, tablet containing 50 mg and 100 mg flecainide acetate per tablet that are generic versions of the reference products Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference product, similarity has been confirmed between Flecainide acetate Tablets and the reference product Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Limited)

All excipients comply with their respective European Pharmacopeia monographs.
Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

None of the excipients used contain material of 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).

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, together with an appropriate account of the manufacturing process. Process validation data on pilot scale batches have been provided. The results are satisfactory. The MAH has committed to perform process validation on future commercial scale batch sizes and a satisfactory validation protocol has been provided.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years. Th medicinal products do not require any special storage condition

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of flecainide 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 this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

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

III.4 Toxicology

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

Impurities

The levels of residual solvents within the drug substance meet their respective limits as set out in ICH Q3C (R6), and are therefore acceptable from a toxicological perspective.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Flecainide acetate Tablets are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of flecainide are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of flecainide.

Based on the results of the bioequivalence study, Flecainide acetate tablets can be considered bioequivalent to the reference product, Tambocor 50 mg and 100 mg Tablets (Meda Pharmaceuticals Limited BV).

IV.2 Pharmacokinetics

In support of these applications, the following bioequivalence study was submitted:

STUDY

An open label, randomised, two treatment, two period, two sequence, cross-over, single-dose, crossover bioequivalence study of Flecainide acetate tablets 100 mg (Test) of Tillomed Laboratories Limited, versus the reference product (Reference); Tambocor 100 mg Tablets (Meda Pharmaceuticals Limited) in healthy, adult, human subjects under fasting conditions.

Subjects were randomised to receive a single oral dose (1 x 100 mg tablet) of either the test (T) or the reference (R) product with 240 mL ± 2 mL of water at ambient temperature under fasting condition in each study period. Blood samples were collected for plasma levels pre-dose and up to and including 72 hours after the drug administration in each period. The washout period between treatment phases was 14 days.
The main pharmacokinetic results are presented below:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	2911.8645	3131.996	153.1009	2.714
Reference	2920.9578	3131.683	148.9212	2.760
***Ratio (90% CI)**	99.69 (96.68, 102.79)		102.81 (98.96, 106.80)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

The extrapolated AUC was not higher than 20% in any subject.

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for flecainide acetate 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**). Thus, the data support the claim that the applicant's test product; Flecainide acetate 100 mg Tablets(Tillomed Laboratories Limited), and the reference product Tambocor 100 mg Tablets (Meda Pharma BV) are bioequivalent.

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 pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety

With the exception of the safety data collected during the bioequivalence study, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed in the bioequivalence study.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL), which is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

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.

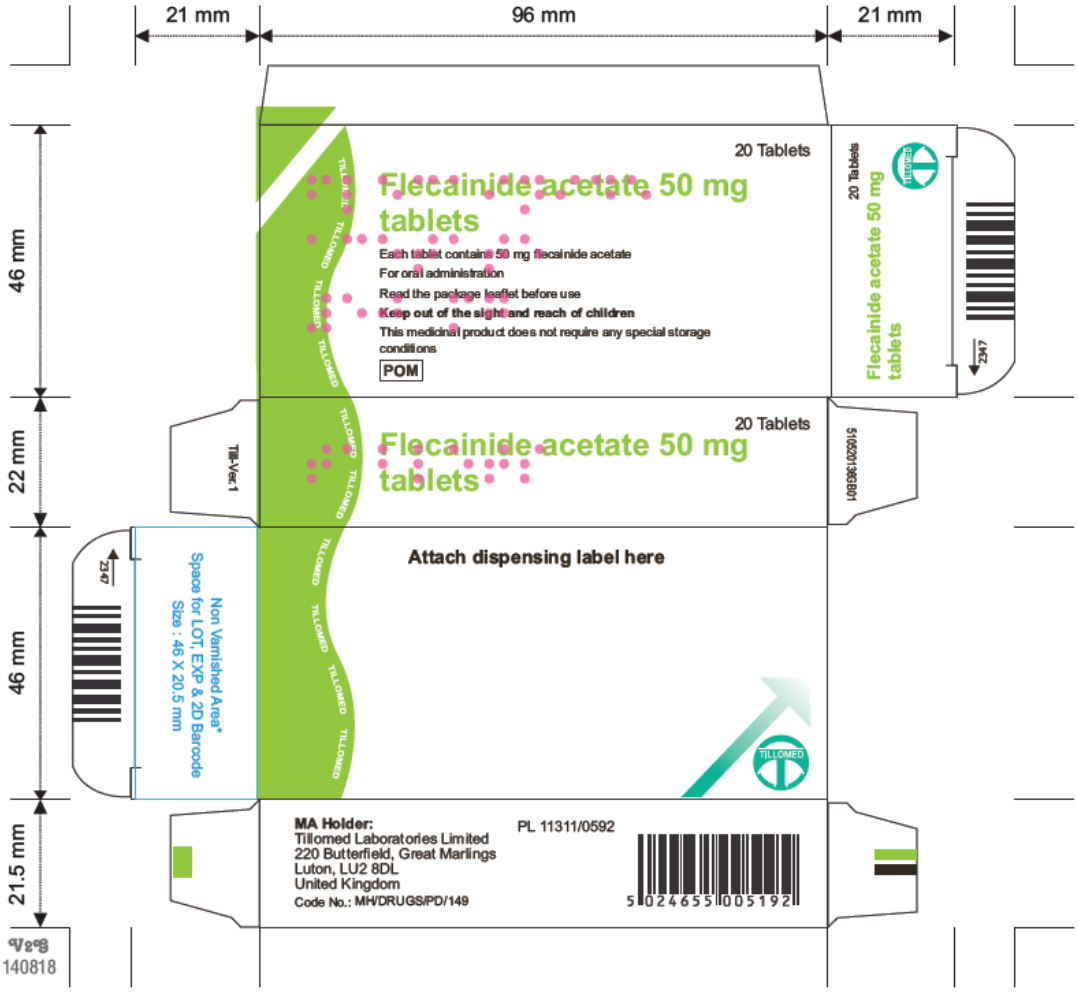
VI Overall conclusion, benefit/risk assessment and recommendation

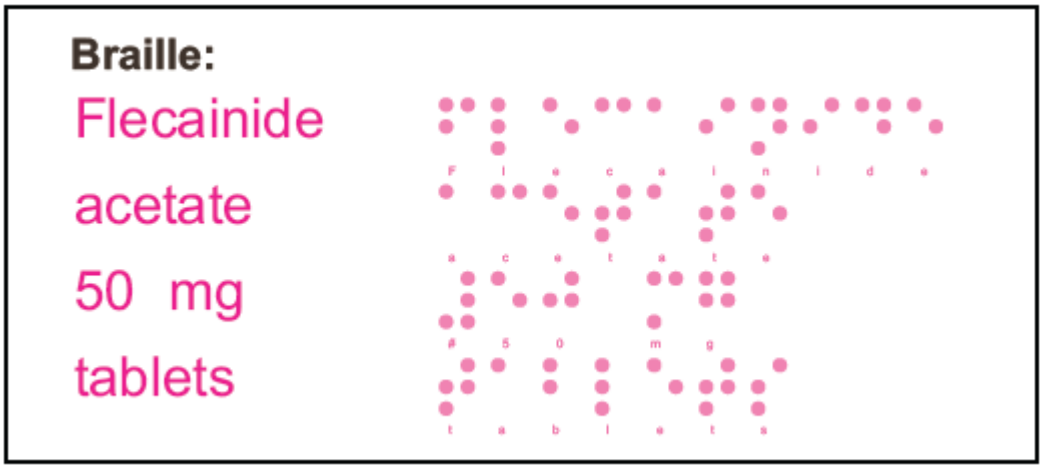
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with flecainide acetate is considered to have demonstrated the therapeutic value of the compound. The results of the clinical study confirm that the product is bioequivalent to the reference product and its benefit-risk is, therefore, considered to be positive.

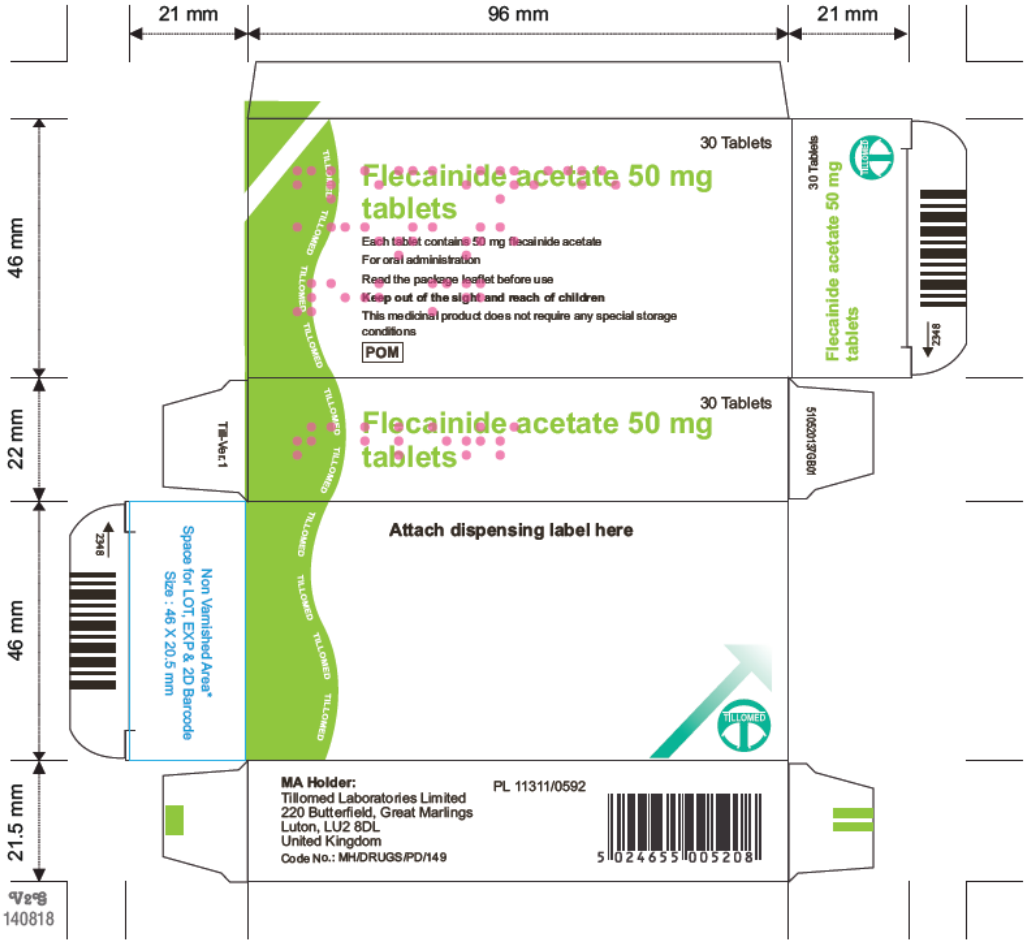
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The MAH has submitted the following approved labelling these products which are presented below:







Braille:

Flecainide acetate 50 mg tablets

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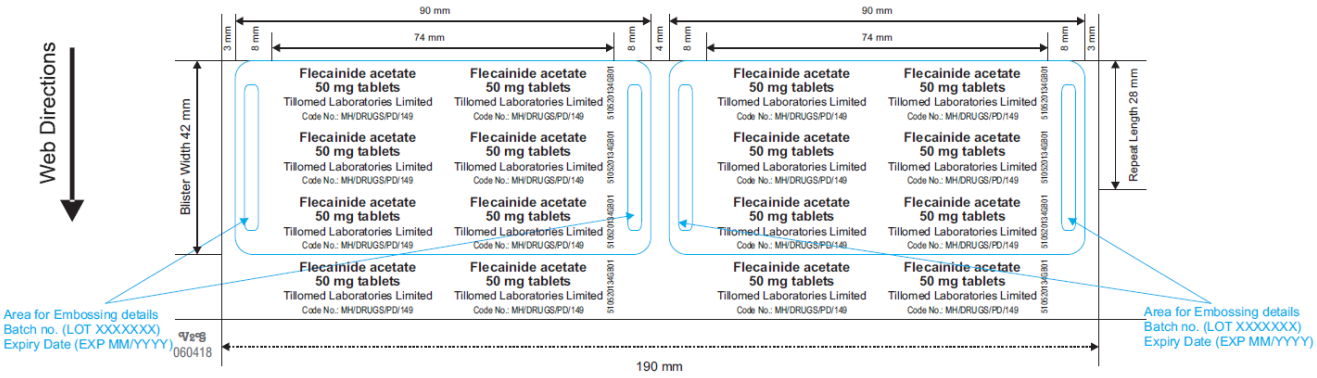
Flecainide acetate 50 mg tablets

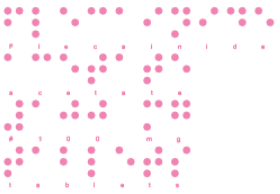


Braille:

Flecainide acetate 100 mg tablets

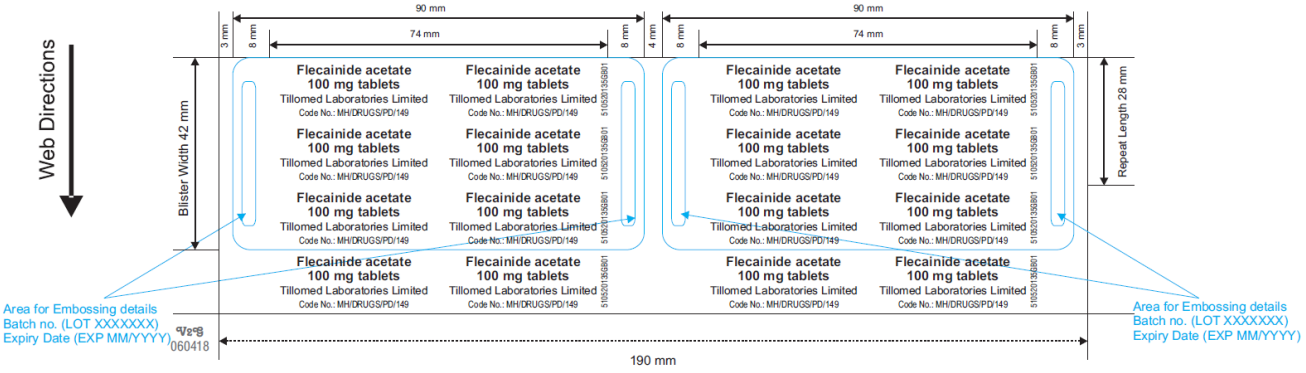
Braille:

Flecainide
acetate
100 mg
tablets



Braille:

Flecainide acetate 100 mg tablets


Web Directions
90 mm
74 mm
3 mm
8 mm
4 mm
Blister Width 42 mm
Repeat Length 28 mm
Flecainide acetate
100 mg tablets
Tillomed Laboratories Limited
Code No.: MH/DRUGS/PD/149
Area for Embossing details
Batch no. (LOT XXXXXXX)
Expiry Date (EXP MM/YYYY)
060418
190 mm

Annex 1

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)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)