Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Fexofenadine Hydrochloride 120 mg Film-coated tablets
Fexofenadine Hydrochloride 180 mg Film-coated tablets

(fexofenadine hydrochloride)

PL 21880/0258-0260; UK/H/7053/002-003/DC

Medreich plc

LAY SUMMARY

Fexofenadine Hydrochloride 120 mg Film-coated tablets
Fexofenadine Hydrochloride 180 mg Film-coated tablets

(fexofenadine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Fexofenadine hydrochloride 120 mg and 180 mg Film-coated tablets. It explains how these products 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 these products.

These products will be referred to as Fexofenadine Hydrochloride Film-coated tablets in this lay summary for ease of reading.

For practical information about using Fexofenadine Hydrochloride Film-coated tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Fexofenadine Hydrochloride Film-coated tablets and what they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Telfast 120 mg and 180 mg film-coated tablets.

Fexofenadine Hydrochloride Film-coated Tablets are used in adults and adolescents of 12 years and older to relieve the symptoms that occur with hay fever (seasonal allergic rhinitis) such as sneezing, itchy, runny or blocked nose and itchy, red and watery eyes.

How do Fexofenadine Hydrochloride Film-coated tablets work?
Fexofenadine Hydrochloride Film-coated tablets contain fexofenadine hydrochloride, which is an antihistamine.

How are Fexofenadine Hydrochloride Film-coated tablets used?
The pharmaceutical form of these medicines is film-coated tablets and the route of administration is oral (taken by mouth). The patient should take the tablets with water before a meal.

For adults and children aged 12 years and over
The recommended dose is one tablet daily.

Fexofenadine Hydrochloride Film-coated tablets start to relieve the patient’s symptoms within 1 hour and lasts for 24 hours.

For further information on how Fexofenadine Hydrochloride Film-coated tablets are used, refer to the package leaflets and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Fexofenadine Hydrochloride Film-coated tablets have been shown in studies?
Because Fexofenadine Hydrochloride Film-coated tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Fexofenadine Hydrochloride Film-coated tablets?
Because Fexofenadine Hydrochloride Film-coated tablets are generic medicines and are bioequivalent to the reference medicines, the benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflets or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Fexofenadine Hydrochloride Film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Fexofenadine Hydrochloride Film-coated tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Fexofenadine Hydrochloride Film-coated tablets?
A Risk Management Plan (RMP) has been developed to ensure that Fexofenadine Hydrochloride Film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets, 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 and reviewed continuously.

Other information about Fexofenadine Hydrochloride Film-coated tablets
Marketing authorisations for Fexofenadine Hydrochloride Film-coated tablets were granted in the UK on 17 February 2020.

The full PAR for Fexofenadine Hydrochloride Film-coated tablets follows this summary.

This summary was last updated in April 2020.

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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) considered that the applications for Fexofenadine Hydrochloride 120 mg and 180 mg Film-coated tablets (PL 21880/0259-0260; UK/H/7053/002-003/DC) could be approved.

Fexofenadine Hydrochloride Film-coated tablets are approved in adults and children 12 years and older for the following indication:

- the relief of symptoms associated with chronic idiopathic urticaria.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member State (CMS) was Ireland.

Fexofenadine hydrochloride, an active metabolite of terfenadine, is an antihistaminic agent which does not possess significant sedative or antimuscarinic actions. Fexofenadine hydrochloride is used in the symptomatic relief of allergic conditions including seasonal allergic rhinitis and chronic idiopathic urticaria.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of a suitable originator medicinal product, Telfast 120 mg and 180 mg film-coated tablets, that has been licensed within the EU for a suitable time, in line with the legal requirements.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 147) on 20 January 2020. After a subsequent national phase, marketing authorisations were granted in the UK on 17 February 2020.

II QUALITY ASPECTS

II.1 Introduction

These products consist of 120 mg or 180 mg fexofenadine hydrochloride, which are equivalent to 112 mg or 168 mg of fexofenadine, in each film-coated tablet.

In addition to fexofenadine hydrochloride, these products also contain the excipients lactose monohydrate, low-substituted hydroxypropylcellulose, pregelatinised starch, colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium and magnesium stearate in the tablet cores and hypromellose, povidone, titanium dioxide, iron oxide red, iron oxide yellow and Macrogol 400 in the film-coatings.

The finished products are packaged in:

1. aluminium-polyvinylchloride/polyvinylidene chloride blisters, in a pack size of 10 film-coated tablets
2. aluminium/polyvinylchloride/polyethylene/ACLAR blisters, in a pack size of 10 film-coated tablets
3. high density polyethylene bottles, in pack sizes of 500 and 1000 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.

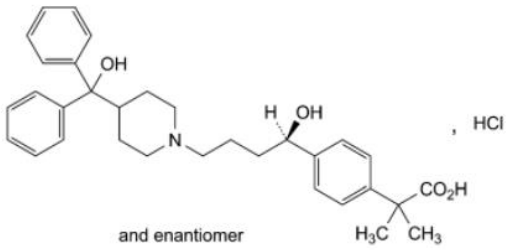
II.2 ACTIVE SUBSTANCE

rINN: **Fexofenadine hydrochloride**

Chemical Name: 2-[4-[(1RS)-1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoic acid hydrochloride

Molecular Formula: $C_{32}H_{40}ClNO_4$

Chemical Structure:



Molecular Weight: 538.1 g/mol

Appearance: White or almost white powder

Solubility: slightly soluble in water, freely soluble in methanol, very slightly soluble in acetone

Fexofenadine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

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

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months, with no special storage conditions, is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of fexofenadine hydrochloride 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.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of fexofenadine hydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following study.

This study was an open label, randomised, two treatment, two sequence, four-period, crossover, replicated, single dose, oral bioequivalence study comparing the test product Fexofenadine hydrochloride 180 mg film-coated tablets versus the reference product Telfast 180 mg tablets in normal, healthy, adult, human subjects under fasted conditions.

Subjects were administered a single dose (1 tablet; 180 mg) of the test or reference product with 240 ml of water, as per the randomisation schedule, following an overnight fast of at least 10 hours. As the study was designed as a fully replicate, cross-over trial, all the subjects were required to receive the test and reference products twice during the entire study.

Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table 1: Pharmacokinetic parameters obtained in the bioequivalence study

Parameters	Geometric least square mean		Relative mean[##]%	90% Confidence Intervals
	Test	Reference		
$C_{max\ (ng/mL)}$	644.63	619.22	104.10	95.36 - 113.66
$AUC_{0\text{-}t\ (ng.h/mL)}$	4349.32	4360.10	99.75	93.03 - 106.96
$AUC_{0\text{-}inf(ng.h/mL)}$	4415.64	4421.75	99.86	93.20 - 107.00

C_{max} maximum plasma concentration
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from zero to t hours
$AUC_{0\text{-}inf}$ area under the plasma concentration-time curve from zero to infinity hours

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength (120 mg) of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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 results show that the PIL 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

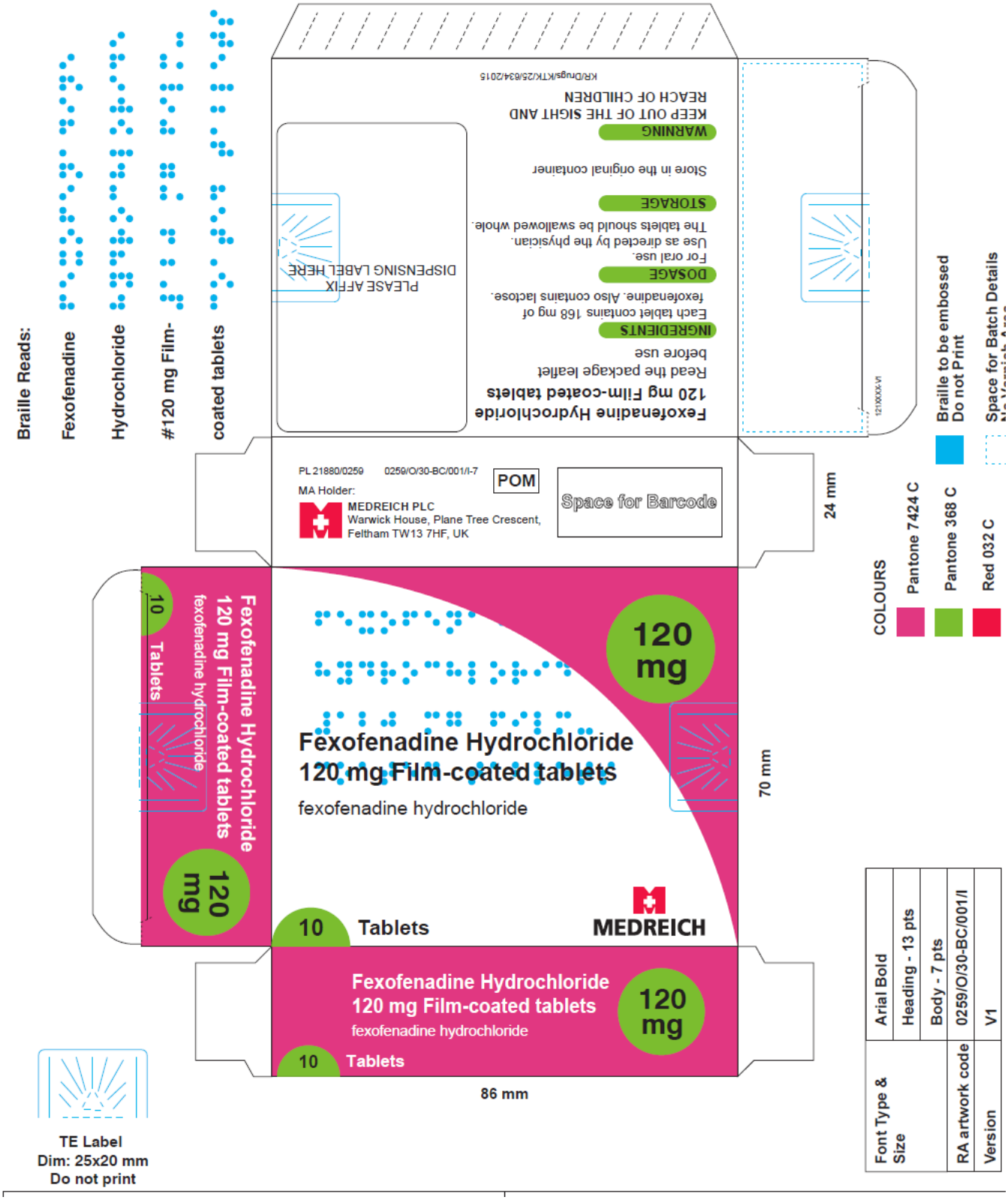
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fexofenadine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

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

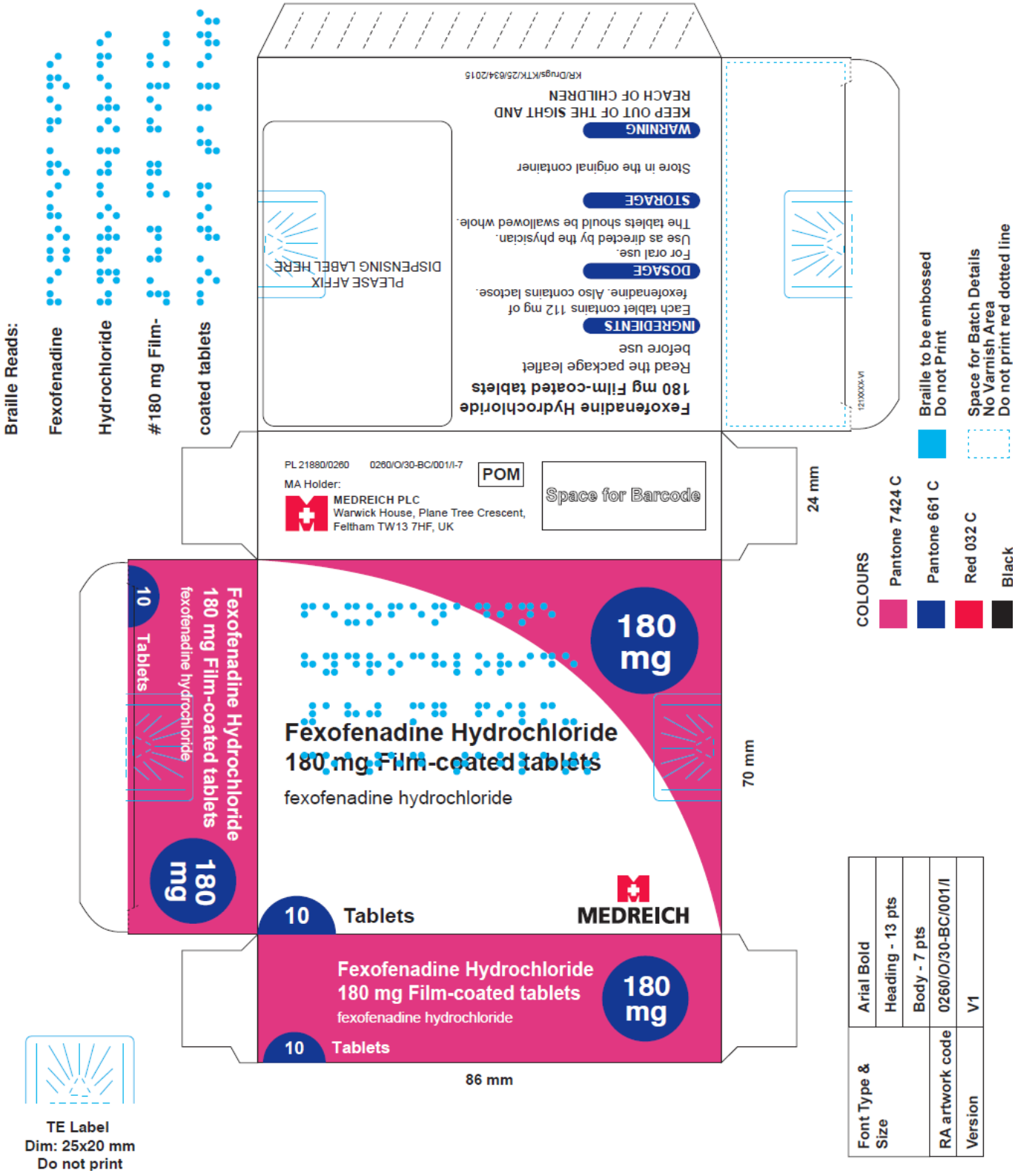
Representative copies of the labels at the time of UK licensing are provided below.

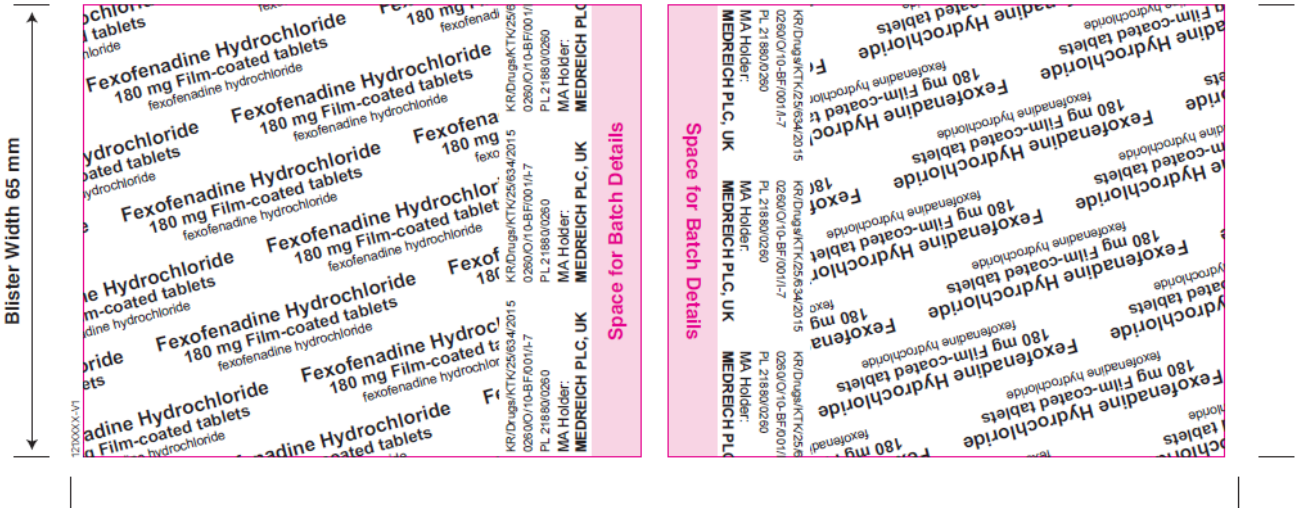
Fexofenadine Hydrochloride120 mg Film-coated tablets




Blister Width 65 mm
Fexofenadine Hydrochloride
120 mg Film-coated tablets
fexofenadine hydrochloride
KR/Drugs/KTK/25/634/2015
0259/O/10-BF/001/I-7
PL 21880/0259
MA Holder:
MEDREICH PLC, UK
Space for Batch Details

Fexofenadine Hydrochloride180 mg Film-coated tablets




Blister Width 65 mm
Fexofenadine Hydrochloride
180 mg Film-coated tablets
fexofenadine hydrochloride
KR/Drugs/KTK/25/634/2015
0260/O/10-BF/001/I-7
PL 21880/0260
MA Holder:
MEDREICH PLC, UK
Space for Batch Details

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisations are recorded in the current SmPCs and/or PILs available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**