Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Terbinafine 250mg Tablets

terbinafine hydrochloride

PL 30684/0356

DAWA Limited

LAY SUMMARY

Terbinafine 250mg Tablets
terbinafine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Terbinafine 250mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Terbinafine tablets in this lay summary for ease of reading.

For practical information about using Terbinafine tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Terbinafine tablets and what are they used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Lamisil Tablets 250mg.

Terbinafine tablets are used to treat a number of fungal infections of the skin and nails.

How does Terbinafine tablets work?
Terbinafine, the active ingredient in Terbinafine tablets, is an antifungal medicine. It works by killing the fungus that is causing the infection.

How is Terbinafine tablets used?
The pharmaceutical form of this medicine is tablets and the route of administration is by mouth (oral use).

The tablets should be swallowed whole with a glass of water.

The usual dose for adults, including the elderly, is one tablet (250 mg) once a day.

- for skin infections the patient should continue taking the tablets for 2 to 6 weeks
- for nail infections the treatment usually lasts for between 6 weeks and 3 months, although some patients with toenail infections may need to be treated for 6 months or longer.
- If the patient's kidneys are not working very well, their doctor may reduce the dose of Terbinafine tablets they take.

For further information on how Terbinafine tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine 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 Terbinafine tablets have been shown in studies?
Because Terbinafine tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Terbinafine tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Terbinafine tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Terbinafine tablets approved?
It was concluded that Terbinafine tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 Terbinafine tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Terbinafine tablets. The RMP details the important risks of Terbinafine tablets, how these risks can be minimised, any uncertainties about Terbinafine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Terbinafine tablets:

Summary of safety concerns	
Important identified risks	• Allergic recations
Important potential risks	• Use during pregnancy
Missing information	• Use in paediatric pupulation

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Terbinafine tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Terbinafine tablets

A marketing authorisation for Terbinafine tablets was granted in the United Kingdom (UK) on 31 August 2022.

The full PAR for Terbinafine tablets follows this summary.

This summary was last updated in March 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare product Regulatory Agency (MHRA) considered that the application for Terbinafine 250mg Tablets (PL 30684/0356) could be approved.

The product is approved for the following indications:
Fungal infections of the skin and nails caused by *Trichophyton (eg. T. rubrum, T.mentagrophytes, T. verrucosum, T.violaceum), Microsporum canis and Epidermophyton floccosum.*

1. Oral terbinafine is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.
2. Oral terbinafine is indicated in the treatment of onychomycosis.

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species. Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system. When given orally, the drug concentrates in skin at levels associated with fungicidal activity.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Lamisil Tablets 250mg that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. 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 this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

A marketing authorisation for Terbinafine tablets was granted in the United Kingdom (UK) on 31 August 2022.

II QUALITY ASPECTS

II.1 Introduction

The active substance is terbinafine as terbinafine hydrochloride. Each tablet contains 250mg of the active substance. The other ingredients are microcrystalline cellulose, sodium starch glycollate, anhydrous colloidal silica, ferric oxide E172, hypromellose, and magnesium stearate.

Terbinafine tablets are packed in packs of 14, 28, 42 and 56 tablets in Al/PVC/PVDC foil blisters. Not all pack sizes are marketed.

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

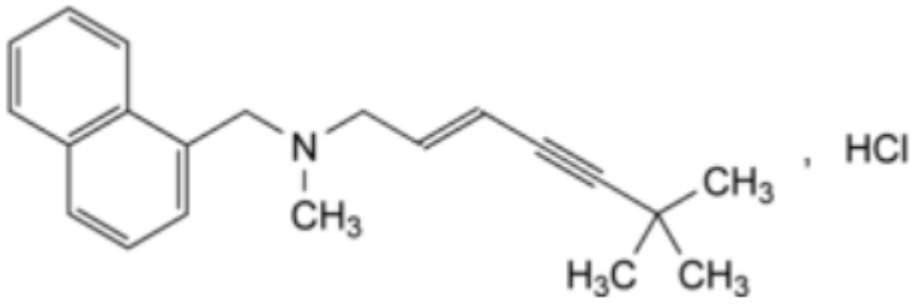
II.2 ACTIVE SUBSTANCE

rINN: Terbinafine Hydrochloride

Chemical Name: (2*E*)-*N*,6,6-Trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride.

Molecular Formula: $C_{21}H_{26}ClN$

Chemical Structure:



Molecular Weight: 327.9

Appearance: White or almost white powder.

Solubility: Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone.

Terbinafine 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 PRODUCT

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 product.

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.

No excipients of animal or human origin are used in the final product.

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

Satisfactory batch formulation data have been provided for the manufacture of the product, 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 at release and shelf-life 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 36 months without 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 a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of terbinafine hydrochloride is 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 this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version(s) of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of terbinafine hydrochloride is well-known. With the exception of data from a 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 bioequivalence study (954/06).

A randomised, open label, two treatment, two period, two sequence , single dose, crossover bioequivalence study of Terbinafine Hydrochloride 250mg Tablets (test product) versus Lamisil 250mg Tablets (reference product) in healthy human adult male subjects under fasting conditions.

After an overnight fast, a single dose of either the test or reference product was administered to subjects in each study period. Blood samples were taken pre-dose and up to 72.00 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Pharmacokinetic Parameter	Ratio (%)	90% Confidence Intervals (%)
C_{max}	1.02	0.93 to 1.12
AUC_{0-t}	1.00	0.95 to 1.07
$AUC_{0-\infty}$	1.00	0.94 to 1.06

In accordance with the regulatory requirements, 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.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted for this application 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 this application.

. There were nine adverse events in the study, of which eight were considered to be unrelated to the study products. One adverse event was considered to be related to the reference product. Six adverse events were mild in intensity, two were moderate in intensity and one was considered to be severe in intensity. There was one serious adverse event in the study. In terms of the subject who experienced a serious adverse event, this subject went on to report no clinical complaints toward the end of the study. The adverse events reported did not give rise to concerns

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, 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 a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Terbinafine 250 mg, tablets (PL 30684/0225; Dawa Limited). The bridging report submitted by the applicant is acceptable.

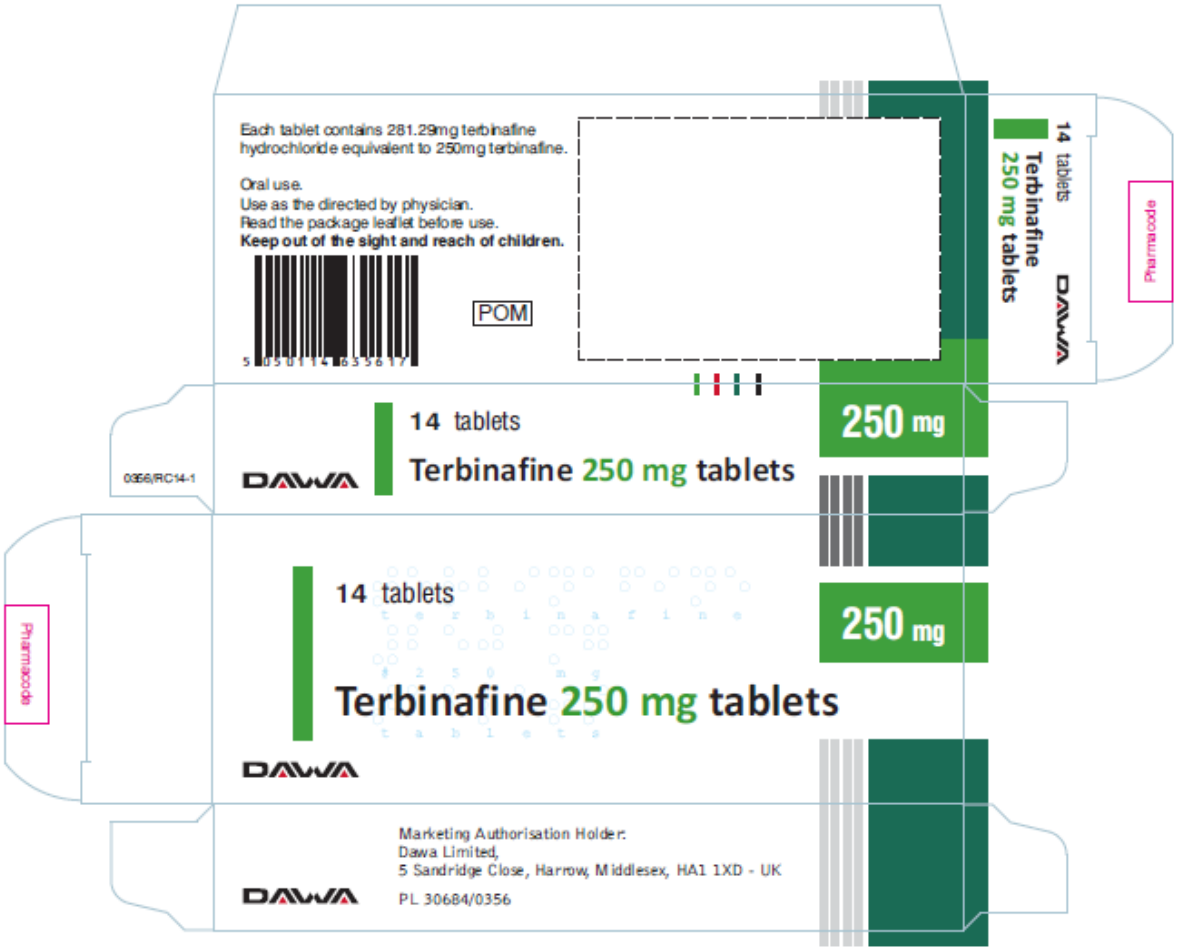
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

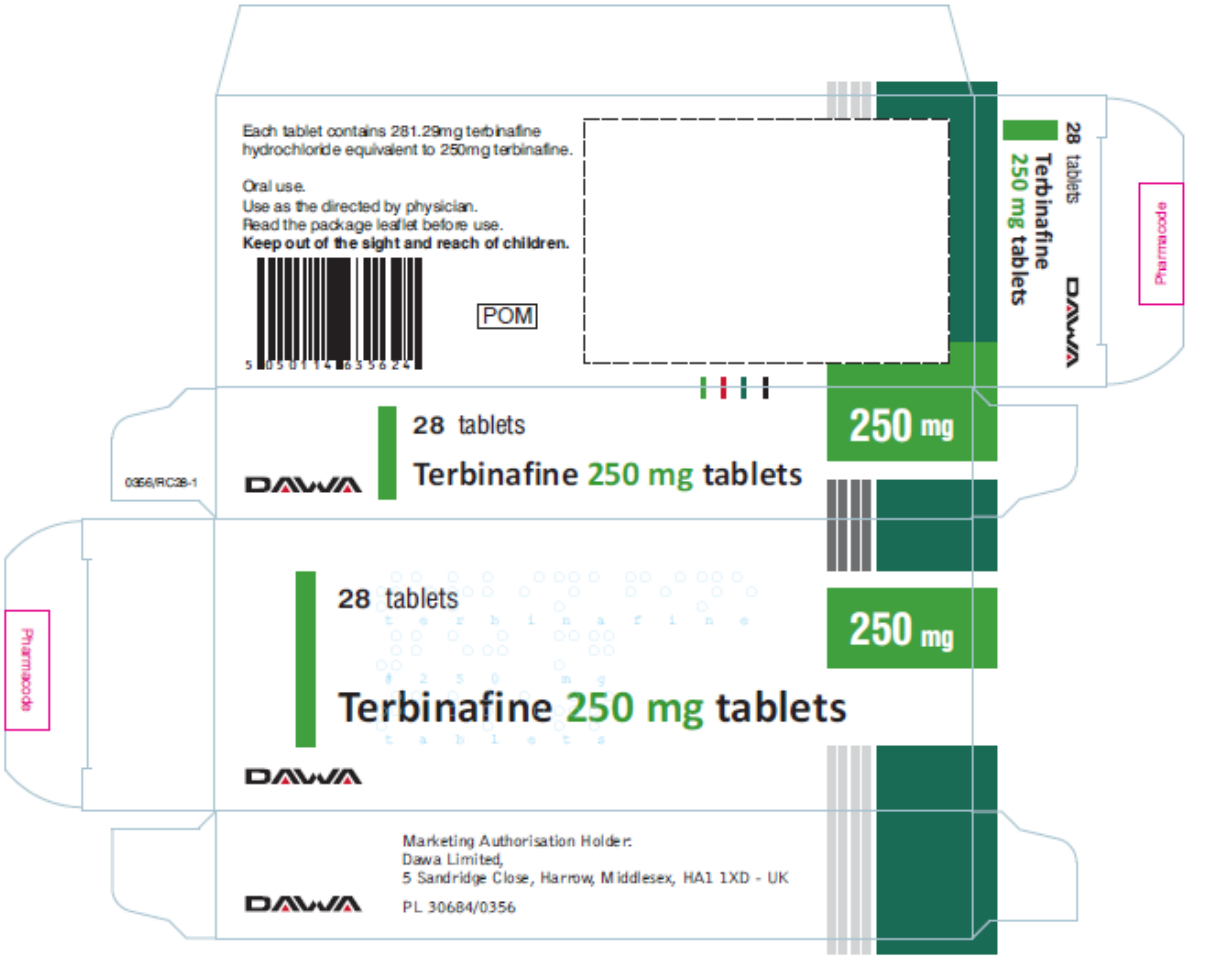
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with terbinafine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

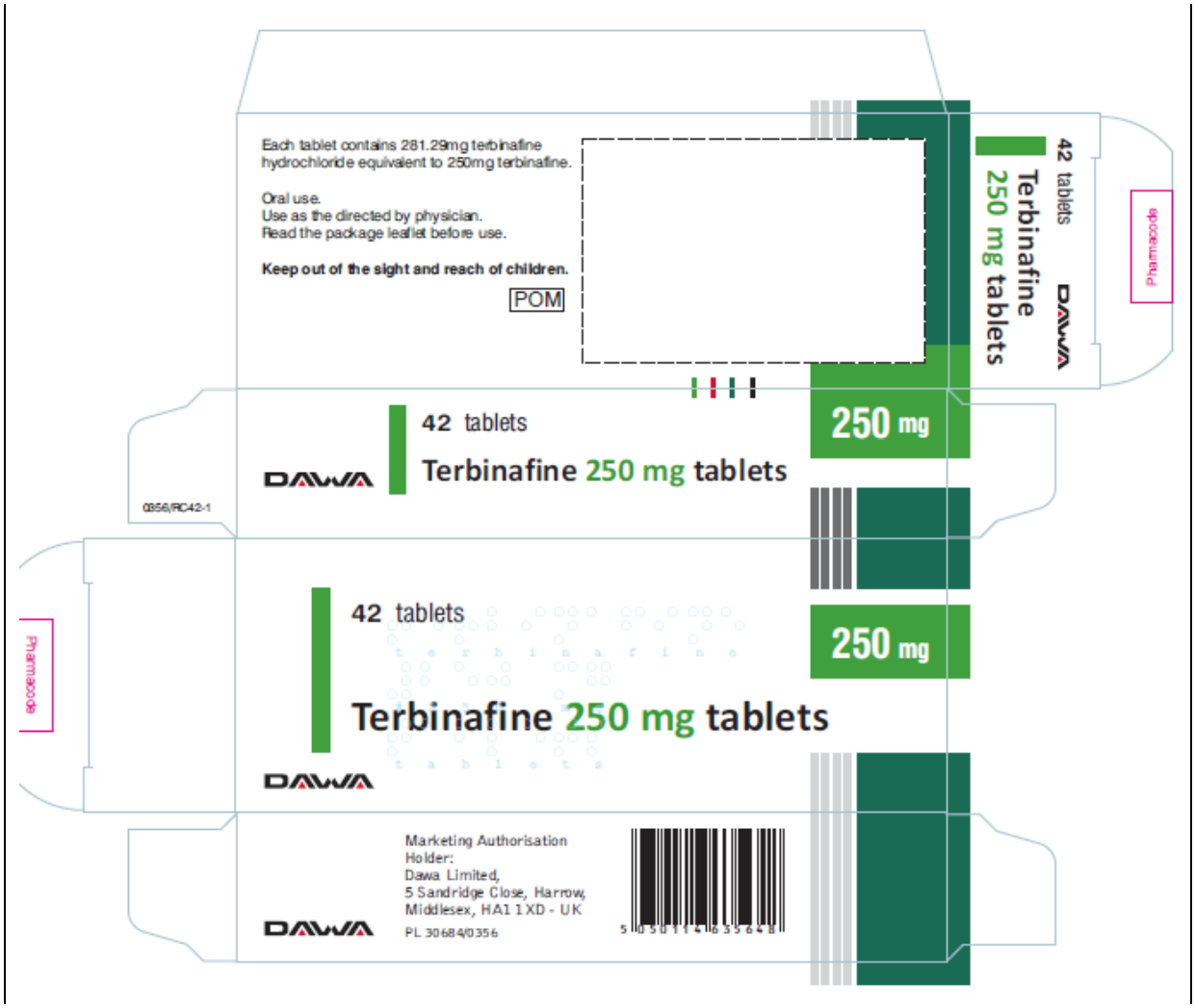
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

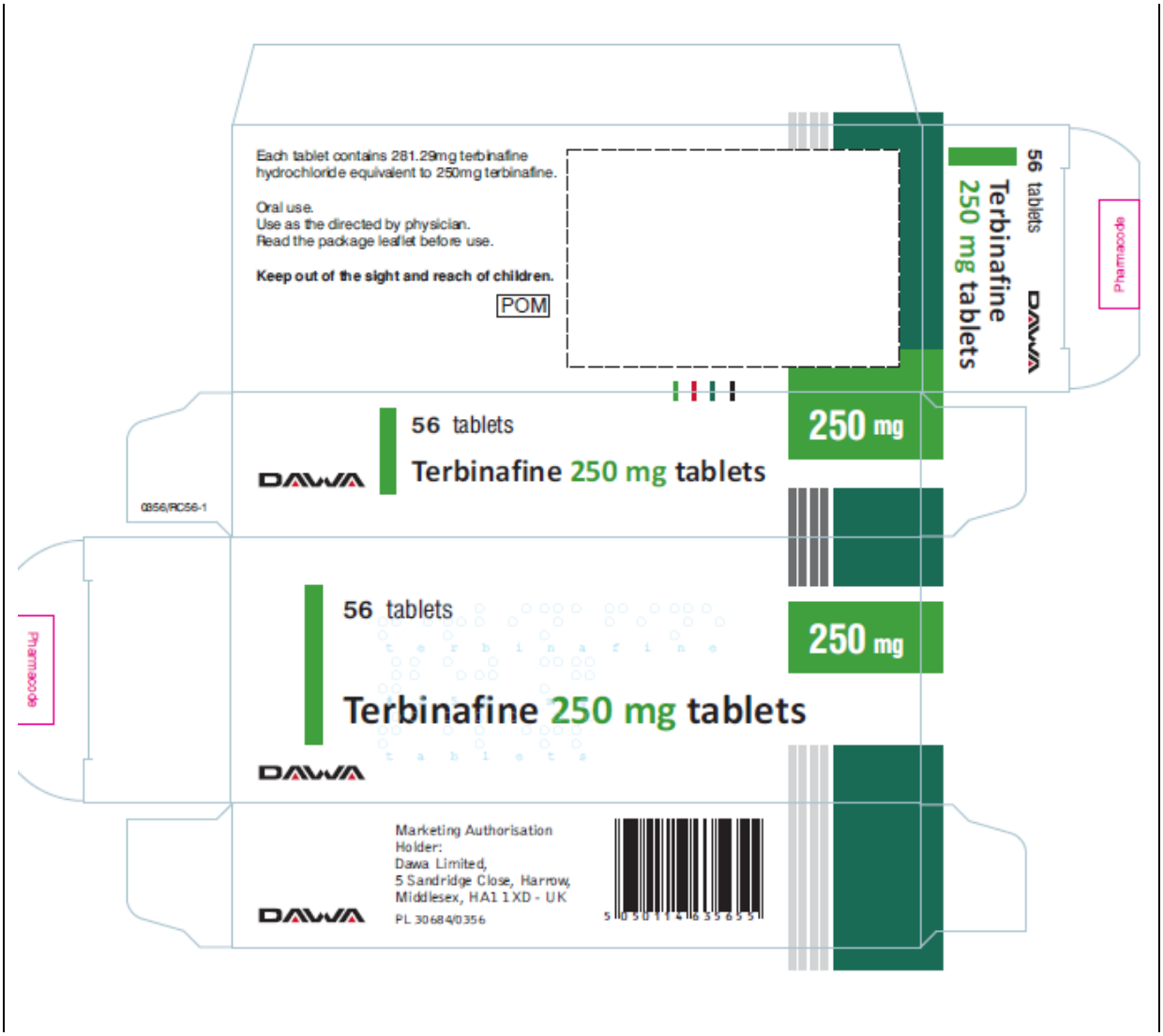
In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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




Each tablet contains 281.29mg terbinafine hydrochloride equivalent to 250mg terbinafine.
Oral use.
Use as the directed by physician.
Read the package leaflet before use.
Keep out of the sight and reach of children.
POM
28 tablets
Terbinafine 250 mg tablets
DAWA
Pharmacode
0356/RC28-1
250 mg
Marketing Authorisation Holder:
Dawa Limited,
5 Sandridge Close, Harrow, Middlesex, HA1 1XD - UK
PL 30684/0356


Each tablet contains 281.29mg terbinafine hydrochloride equivalent to 250mg terbinafine.
Oral use.
Use as the directed by physician.
Read the package leaflet before use.
Keep out of the sight and reach of children.
POM
42 tablets
Terbinafine 250 mg tablets
DAWA
Pharmacode
250 mg
0356/RC42-1
Marketing Authorisation Holder:
Dawa Limited,
5 Sandridge Close, Harrow,
Middlesex, HA1 1XD - UK
PL 30684/0356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Oral use.
Use as the directed by physician.
Read the package leaflet before use.
Keep out of the sight and reach of children.
POM
56 tablets
Terbinafine 250 mg tablets
DAWA
Pharmacode
250 mg
0356/RC56-1
Marketing Authorisation Holder:
Dawa Limited,
5 Sandridge Close, Harrow,
Middlesex, HA1 1XD - UK
PL 30684/0356

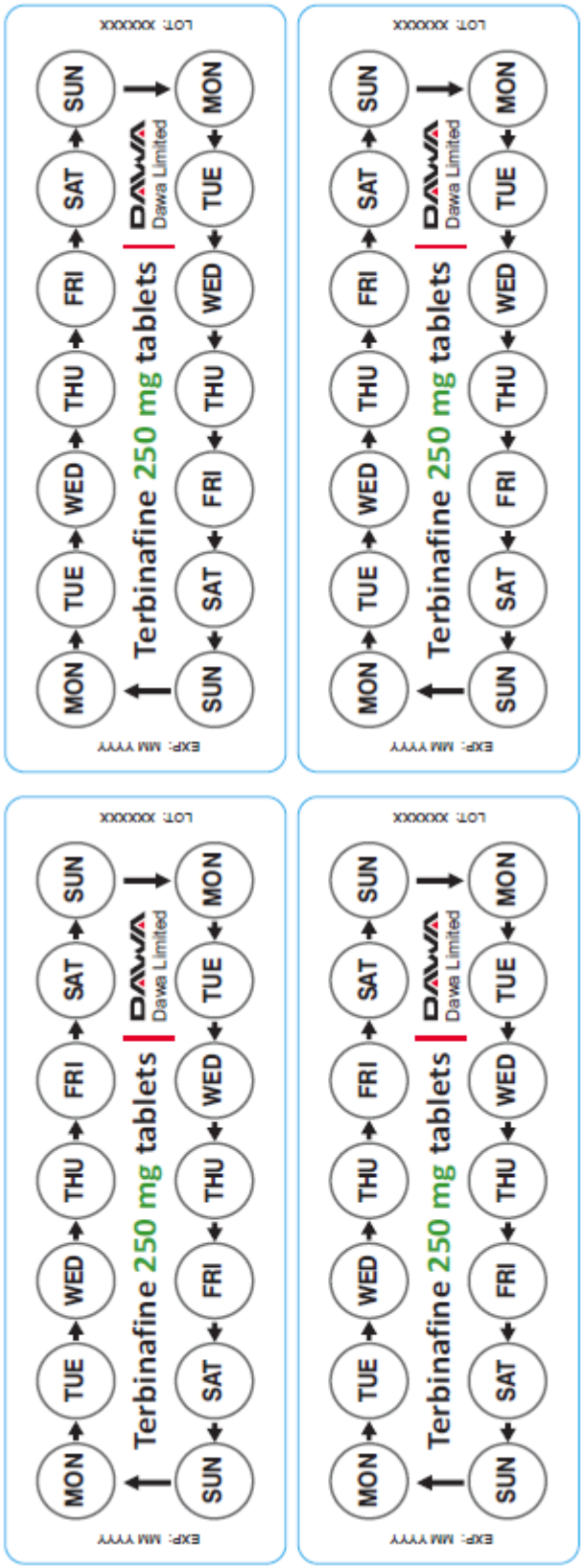
LOT: xxxxxx
MON TUE WED THU FRI SAT SUN
Terbinafine 250 mg tablets
DAWA Dawa Limited
SUN MON TUE WED THU FRI SAT
EXP: MM YYYY

TABLE OF CONTENT OF THE PAR UPDATE

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 authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

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