Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Apixaban 2.5 mg film-coated tablets
Apixaban 5 mg film-coated tablets
(apixaban)

PL 00289/2534-2535

Teva UK Limited

LAY SUMMARY

Apixaban 2.5 mg film-coated tablets
Apixaban 5 mg film-coated tablets
(apixaban)

This is a summary of the Public Assessment Report (PAR) for Apixaban 2.5 mg and 5 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 Apixaban Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Apixaban Film-coated Tablets, patients should read the Patient Information Leaflets (PILs) or contact their doctor or pharmacist.

What are Apixaban Film-coated Tablets and what are they used for?
These products have been authorised by MHRA for the United Kingdom (UK). This procedure takes into account the outcome of decentralised (DC) procedures in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 08 February 2021 (MT/H/0468/001-002/DC). This is known as the MR/DC Reliance Procedure.

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 United Kingdom (UK) called Eliquis 2.5 mg and 5 mg film coated tablets.

Apixaban 2.5 mg Film-coated Tablets are used in adults:
- to prevent blood clots (deep vein thrombosis [DVT]) from forming after hip or knee replacement operations. After an operation to the hip or knee a person may be at a higher risk of developing blood clots in the leg veins. This can cause the legs to swell, with or without pain. If a blood clot travels from the leg to the lungs, it can block blood flow causing breathlessness, with or without chest pain. This condition (pulmonary embolism) can be life-threatening and requires immediate medical attention.

Apixaban 2.5 mg and 5 mg Film-coated Tablets are used in adults:
- to prevent a blood clot from forming in the heart in patients with an irregular heart beat (atrial fibrillation) and at least one additional risk factor. Blood clots may break off and travel to the brain and lead to a stroke or to other organs and prevent normal blood flow to that organ (also known as a systemic embolism). A stroke can be life-threatening and requires immediate medical attention.
- to treat blood clots in the veins of the legs (deep vein thrombosis) and in the blood vessels of the lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of the legs and/or lungs.

How do Apixaban Film-coated Tablets work?
Apixaban Film-coated Tablets contain the active substance apixaban, which belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming by blocking Factor Xa, which is an important component of blood clotting.

How are Apixaban Film-coated Tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (taken by mouth).

Dose
The patient should swallow the tablet with a drink of water. Apixaban Film-coated Tablets can be taken with or without food. The patient should try to take the tablets at the same times every day to have the best treatment effect.

If the patient has difficulty swallowing the tablet whole, they should talk to their doctor about other ways to take Apixaban Film-coated Tablets. The tablet may be crushed and mixed with water, or 5% glucose in water, or apple juice or apple puree, immediately before taking it.

Instructions for crushing:
- Crush the tablets with a pestle and mortar.
- Transfer all the powder carefully into a suitable container then mix the powder with a little e.g. 30 ml (2 tablespoons), water or one of the other liquids mentioned above to make a mixture.
- Swallow the mixture.
- Rinse the pestle and mortar used for crushing the tablet and the container with a little water or one of the other liquids (e.g. 30 ml), and swallow the rinse.

If necessary, the patient's doctor may also give the patient the crushed Apixaban Film-coated Tablets mixed in 60 ml of water or 5% glucose in water, through a nasogastric tube.

Take Apixaban 2.5 mg Film-coated Tablets as recommended for the following:
<u>To prevent blood clots from forming after hip or knee replacement operations</u>
The recommended dose is **one tablet** of Apixaban **2.5 mg** twice a day.
For example, one in the morning and one in the evening.
The patient should take the first tablet 12 to 24 hours after their operation.

If the patient has had a major **hip** operation they will usually take the tablets for 32 to 38 days.

If the patient has had a major **knee** operation they will usually take the tablets for 10 to 14 days.

Take Apixaban Film-coated Tablets as recommended for the following:
<u>To prevent a blood clot from forming in the heart in patients with an irregular heart beat and at least one additional risk factor</u>
The recommended dose is one tablet of Apixaban **5 mg** twice a day.

The recommended dose is one tablet of Apixaban **2.5 mg** twice a day if:
- the patient has severely **reduced kidney function**
- **two or more of the following apply to the patient**:
- the patient's blood test results suggest poor kidney function (value of serum creatinine is 1.5 mg/dL (133 micromole/L) or greater)
- the patient is 80 years old or older
- the patient's weight is 60 kg or lower.

The recommended dose is one tablet twice a day, for example, one in the morning and one in the evening. The patient's doctor will decide for how long the patient must continue treatment.

To treat blood clots in the veins of the legs and blood clots in the blood vessels of the lungs
The recommended dose is **two tablets** of Apixaban **5 mg** twice a day for the first 7 days, for example, two in the morning and two in the evening.

After 7 days the recommended dose is **one tablet** of Apixaban **5 mg** twice a day, for example, one in the morning and one in the evening.

For preventing blood clots from re-occurring following completion of 6 months of treatment
The recommended dose is **one tablet** of Apixaban **2.5 mg** twice a day for example, one in the morning and one in the evening.

The patient's doctor will decide for how long the patient must continue treatment.

The doctor might change their patient's anticoagulant treatment as follows:
- Changing from Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets to anticoagulant medicines
Stop taking Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets.

Start treatment with the anticoagulant medicines (for example heparin) at the time the patient would have taken the next tablet.

- Changing from anticoagulant medicines to Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets
Stop taking the anticoagulant medicines. Start treatment with Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets at the time the patient would have had the next dose of anticoagulant medicine, then continue as normal.

- Changing from treatment with anticoagulant containing vitamin K antagonist (e.g. warfarin) to Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets
Stop taking the medicine containing a vitamin K antagonist. The patient's doctor needs to do blood-measurements and instruct the patient when to start taking Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets.

- Changing from Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets to anticoagulant treatment containing vitamin K antagonist (e.g. warfarin)
If the doctor tells their patient that they have to start taking the medicine containing a vitamin K antagonist, the patient should continue to take Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated for at least 2 days after their first dose of the medicine containing a vitamin K antagonist. The patient's doctor needs to do blood-measurements and instruct their patient when to stop taking Apixaban 2.5 mg Film-coated Tablets or Apixaban 5 mg Film-coated Tablets.

Patients undergoing cardioversion
If the patient's abnormal heartbeat needs to be restored to normal by a procedure called cardioversion, the patient should take Apixaban Film-coated Tablets at the times their doctor tells them, to prevent blood clots in blood vessels in their brain and other blood vessels in the body.

For further information on how Apixaban Film-coated Tablets are used, refer to the PILs and Summaries of Product Characteristics (SmPCs) 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 Apixaban Film-coated Tablets have been shown in studies?
As Apixaban 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 Apixaban Film-coated Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PILs 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 PILs that comes with these medicines. Patients can also report suspected side effects themselves, or a report can be made on behalf of the patient by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

As Apixaban Film-coated Tablets are generic medicines, their possible side effects are considered to be the same as for the reference medicines.

Why were Apixaban Film-coated Tablets approved?
The MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

Apixaban Film-coated Tablets have been authorised with the condition to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Apixaban Film-coated Tablets?"

What measures are being taken to ensure the safe and effective use of Apixaban Film-coated Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Apixaban Film-coated Tablets. The RMP details the important risks of Apixaban Film-coated Tablets, how these risks can be minimised, any uncertainties about Apixaban Film-coated Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Apixaban Film-coated Tablets:

Summary of safety concerns	
Important identified risks	- Bleeding
Important potential risks	- Liver Injury - Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	- Use in patients with severe renal impairment

The information included in the SmPCs and the PILs 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 Apixaban Film-coated Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Apixaban Film-coated Tablets product information, to ensure the safe and effective use of Apixaban Film-coated Tablets, additional risk minimisation activities are proposed for the safety concern 'Important identified risks: Bleeding' in the form of the provision of a prescriber guide and patient alert card.

A RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Apixaban Film-coated Tablets
Marketing Authorisations were granted in the UK on 23 February 2022.

The full PAR for Apixaban Film-coated Tablets follows this summary.

This summary was last updated in April 2022.

TABLE OF CONTENTS

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 Apixaban 2.5 mg and 5 mg Film-coated Tablets (PL 00289/2534-2535) could be approved.

The products are approved for the following indications:

Apixaban 2.5 mg film-coated tablets

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Apixaban 2.5 mg and 5 mg film-coated tablets

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

The active substance, apixaban, is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

These products have been authorised by Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK). This procedure takes into account the outcome of decentralised (DC) procedures in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 08 February 2021 (MT/H/0468/001-002/DC).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted during the DC procedures, please refer to the Reference Member State (RMS) Public Assessment Report, available on the RMS regulatory agency website or on the Heads of Medicines Agencies website.

These applications were approved under Regulation 51B of the Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Eliquis 2.5 mg and 5 mg film-coated tablets that have been licensed within the UK for a suitable time, in line with the legal requirements.

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.

Marketing Authorisations were granted on 23 February 2022.

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PILs are in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of Marketing Authorisations are recommended.

IV. NON-CLINICAL ASPECTS

The MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations are recommended.

V. CLINICAL ASPECTS

The MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of Marketing Authorisations are recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

Full colour mock-ups of the Patient Information Leaflets (PILs) have been provided with the applications, in accordance with legal requirements.

The PILs have 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:

1. Eliquis 2.5 mg and 5 mg film coated tablets (Bristol-Myers Squibb/Pfizer EEIG; EMEA/H/C/002148), with regard to content, key messages and safe use.
2. Succinato de Solifenacina Combino (PT/H/0547/001-002/DC), with regard to design and layout.

The bridging report submitted by the MAH is acceptable.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

Apixaban Film-coated Tablets have been authorised with the condition to provide additional measures to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

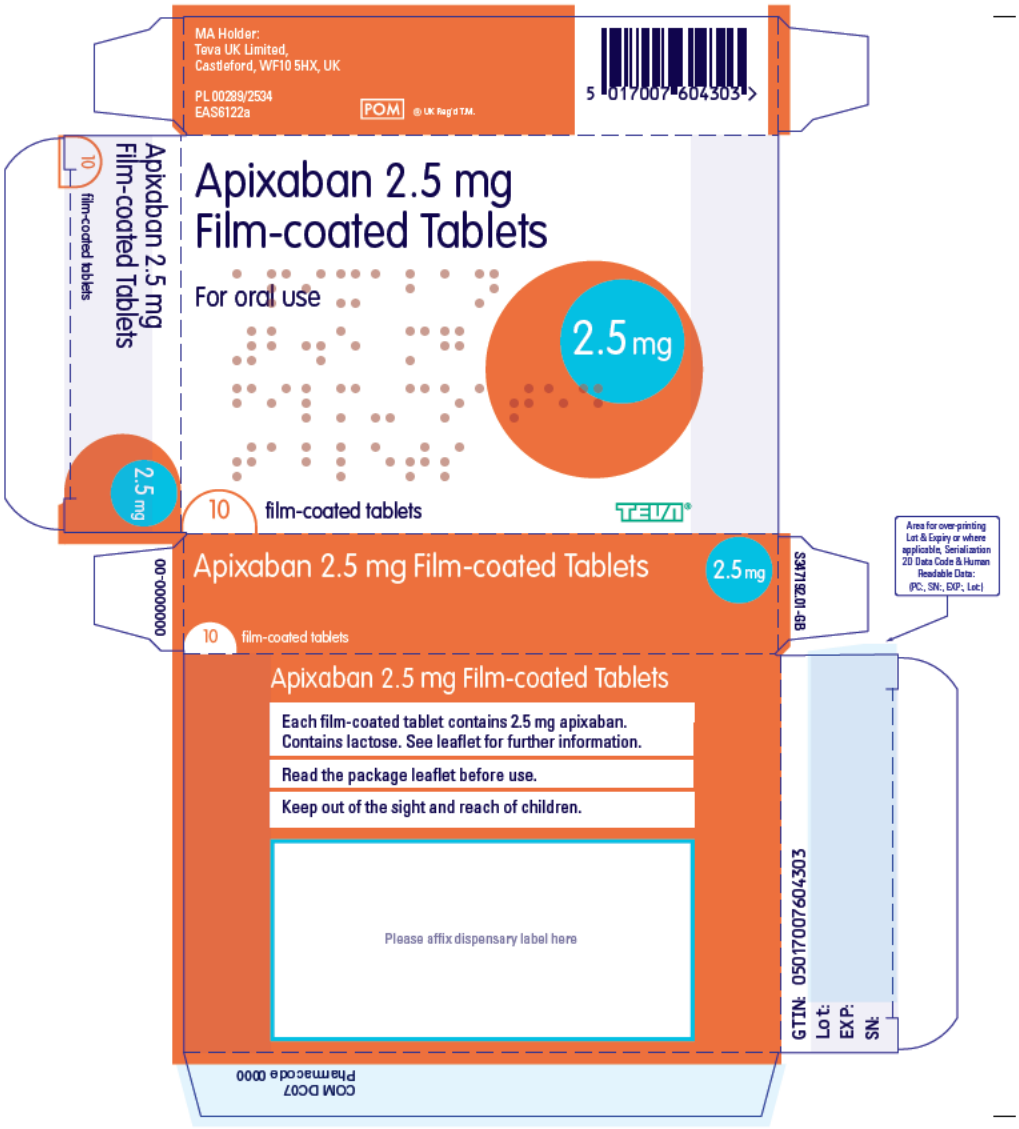
Description	Due date
Physician educational pack and patient alert card	22/07/27

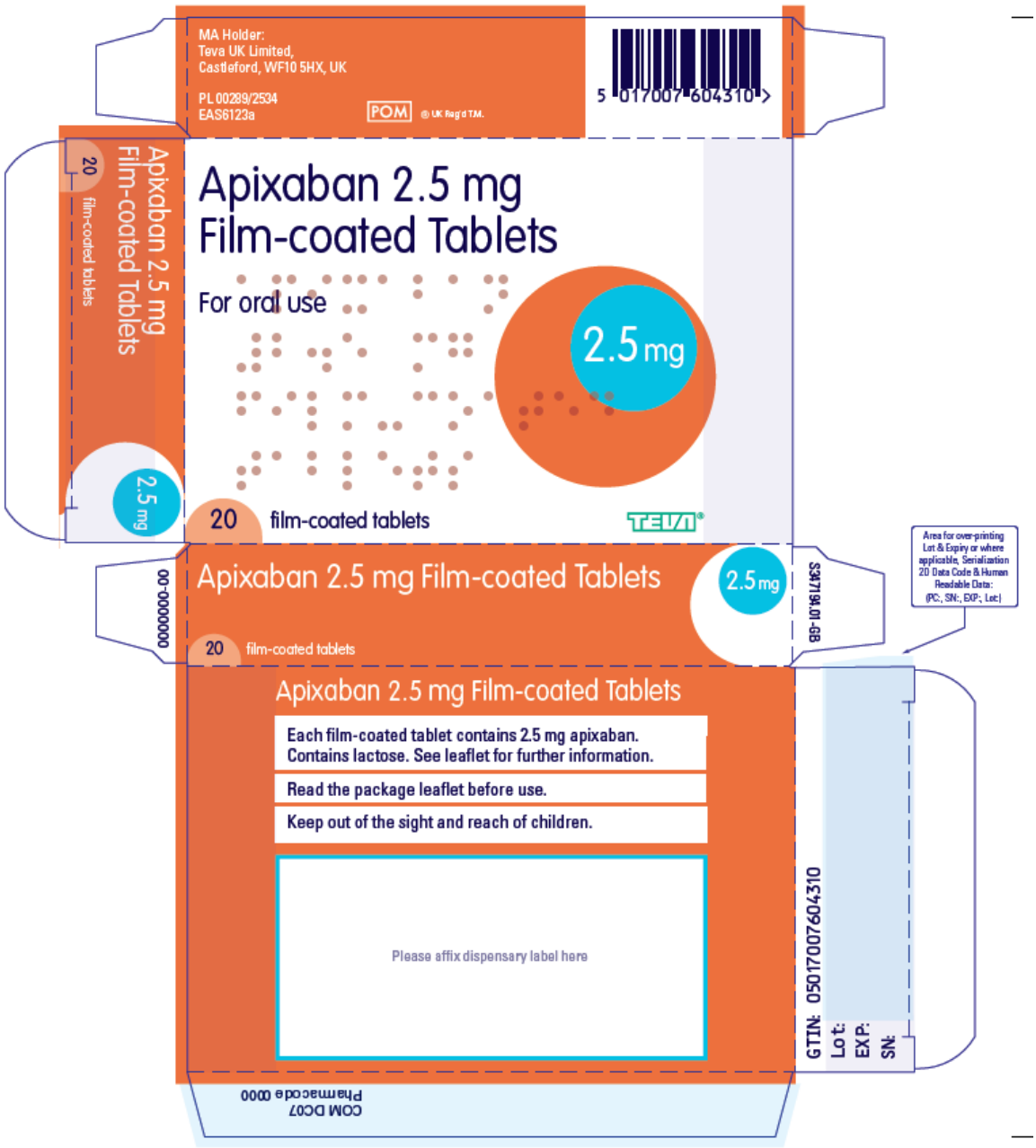
The SmPCs, PILs and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

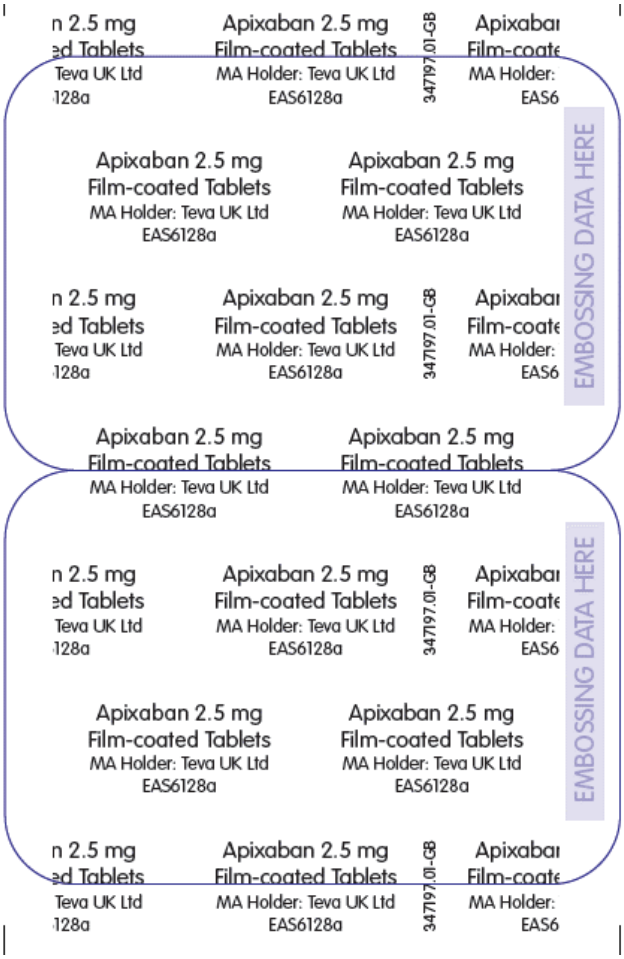
Representative copies of the labels at the time of UK licensing are provided below.

Apixaban 2.5 mg Film-coated Tablets




MA Holder:
Teva UK Limited,
Castleford, WF10 5HX, UK
PL 00289/2534
EAS6123a
POM
5 017007 604310
Apixaban 2.5 mg
Film-coated Tablets
For oral use
2.5 mg
20 film-coated tablets
TEVA
Apixaban 2.5 mg Film-coated Tablets
20 film-coated tablets
2.5 mg
SN:
00-0000000
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC:, SN:, EXP:, Lot:)
Apixaban 2.5 mg Film-coated Tablets
Each film-coated tablet contains 2.5 mg apixaban.
Contains lactose. See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Please affix dispensary label here
GTIN: 05017007604310
Lot:
EXP:
SN:
COM DC07
Pharmacode 0000


MA Holder:
Teva UK Limited,
Castleford, WF10 5HX, UK
PL 00289/2534
EAS6124a
POM
5 017007 604327
Apixaban 2.5 mg
Film-coated Tablets
For oral use
2.5 mg
60 film-coated tablets
Apixaban 2.5 mg
Film-coated Tablets
2.5 mg
60 film-coated tablets
Apixaban 2.5 mg Film-coated Tablets
Each film-coated tablet contains 2.5 mg apixaban.
Contains lactose. See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Please affix dispensary label here
Area for over-printing Lot & Expiry or where applicable, Serialisation 2D Data Code & Human Readable Data: (PC., SN:, EXP., Lot:)
GTIN: 05017007604327
Lot:
EXP:
SN:


Apixaban 2.5 mg
Film-coated Tablets
MA Holder: Teva UK Ltd
EAS6128a
347197.01-GB
EMBOSSING DATA HERE
Each blister will be embossed with the batch number and expiry date.

TEVA UK LIMITED
EAS6137a
347198.01-GB

Apixaban 2.5 mg Film-coated Tablets

Patient Alert Card

Carry this card with you at all times

Show this card to your pharmacist, dentist and any other healthcare professionals that treat you.

I am under anticoagulation treatment with Apixaban 2.5 mg Film-coated Tablets to prevent blood clots

Please complete this section or ask your doctor to do it

Name:
Birth Date:
Indication:
Dose: mg twice daily
Doctor's Name:
Doctor's telephone:

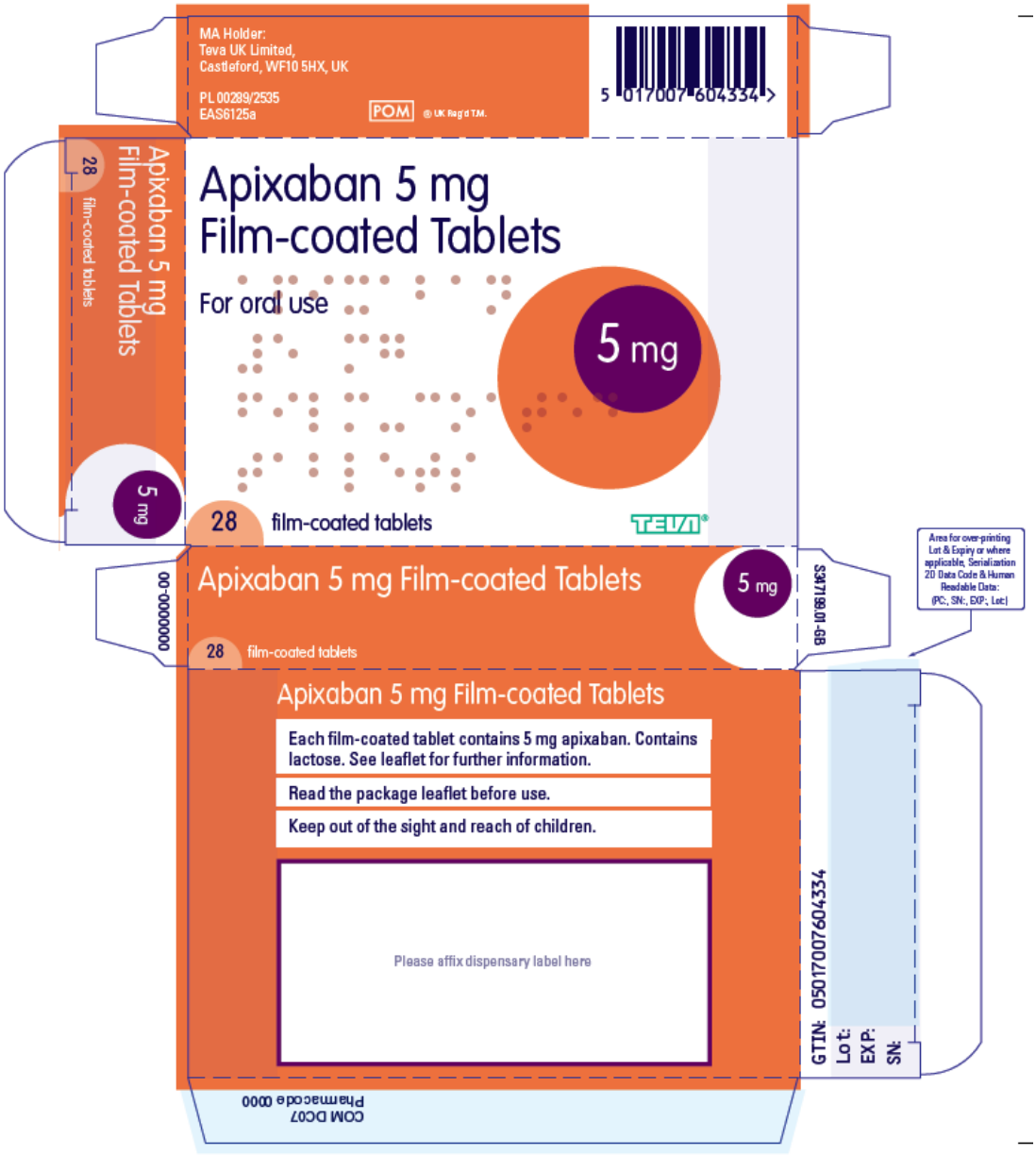
Information for patients

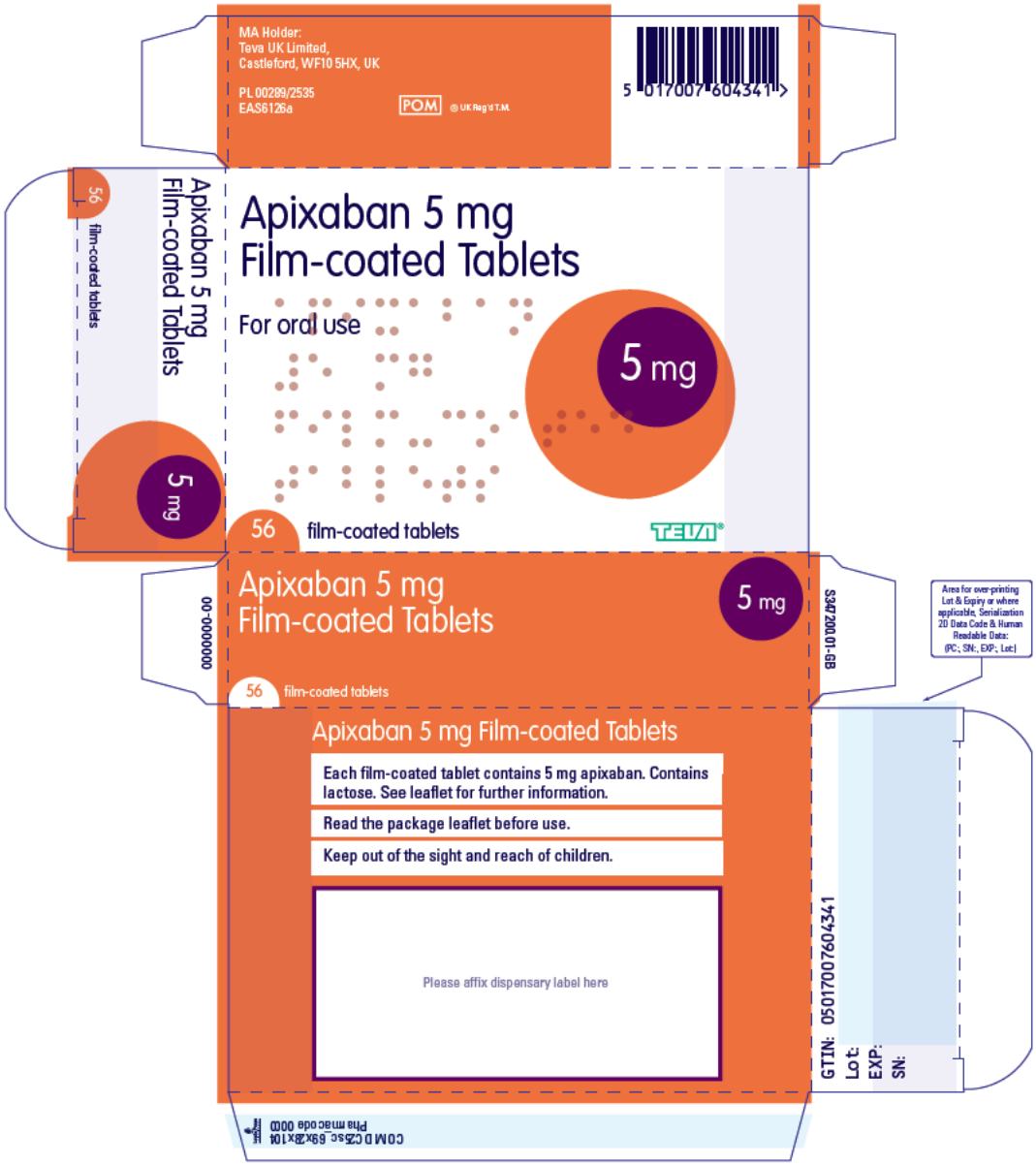
- Take Apixaban 2.5 mg Film-coated Tablets regularly as instructed. If you miss a dose, take it as soon as you remember and continue to follow your dosing schedule.
- Do not stop taking Apixaban 2.5 mg Film-coated Tablets without talking to your doctor, as you are at risk of suffering from a stroke or other complications.
- Apixaban 2.5 mg Film-coated Tablets helps to thin your blood. However, this may increase your risk of bleeding.
- Signs and symptoms of bleeding include bruising or bleeding under the skin, tar-coloured stools, blood in urine, nose-bleed, dizziness, tiredness, paleness or weakness, sudden severe headache, coughing up blood or vomiting blood.
- If the bleeding does not stop on its own, **seek medical attention immediately.**
- If you need surgery, inform your doctor that you are taking Apixaban 2.5 mg Film-coated Tablets.

Information for healthcare professionals

- Apixaban 2.5 mg Film-coated Tablets is an oral anticoagulant acting by direct selective inhibition of factor Xa.
- Apixaban 2.5 mg Film-coated Tablets may increase the risk of bleeding. In case of major bleeding events, it should be stopped immediately.
- Treatment with Apixaban 2.5 mg Film-coated Tablets does not require routine monitoring of exposure. A calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations, e.g., overdose and emergency surgery (prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) clotting tests are not recommended) - see SmPC.
- An agent to reverse the anti-factor Xa activity of apixaban is available.

Apixaban 5 mg Film-coated Tablets




MA Holder:
Teva UK Limited,
Castleford, WF10 5HX, UK
PL 00289/2535
EAS6126a
POM
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Apixaban 5 mg
Film-coated Tablets
For oral use
5 mg
56
film-coated tablets
TEVA
Apixaban 5 mg
Film-coated Tablets
5 mg
56 film-coated tablets
Apixaban 5 mg Film-coated Tablets
Each film-coated tablet contains 5 mg apixaban. Contains lactose. See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Please affix dispensary label here
GTIN: 05017007604341
Lot:
EXP:
SN:
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC; SN:; EXP:; Lot:)
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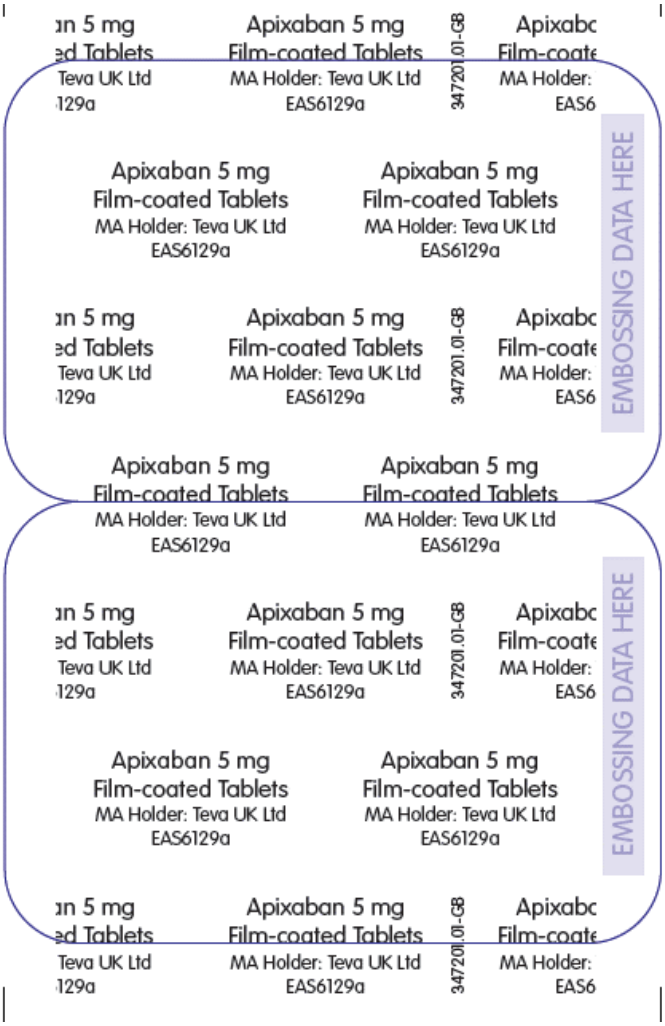

Each blister will be embossed with the batch number and expiry date.

TEVA UK LIMITED
EAS6138a
347203.01-GB

Apixaban 5 mg Film-coated Tablets

Patient Alert Card

Carry this card with you at all times

Show this card to your pharmacist, dentist and any other healthcare professionals that treat you.

I am under anticoagulation treatment with Apixaban 5 mg Film-coated Tablets to prevent blood clots

Please complete this section or ask your doctor to do it

Name:
Birth Date:
Indication:
Dose: mg twice daily
Doctor's Name:
Doctor's telephone:

Information for patients

- Take Apixaban 5 mg Film-coated Tablets regularly as instructed. If you miss a dose, take it as soon as you remember and continue to follow your dosing schedule.
- Do not stop taking Apixaban 5 mg Film-coated Tablets without talking to your doctor, as you are at risk of suffering from a stroke or other complications.
- Apixaban 5 mg Film-coated Tablets helps to thin your blood. However, this may increase your risk of bleeding.
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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**