EMA/439534/2014
EMEA/H/C/002148

EPAR summary for the public

Eliquis

apixaban

This is a summary of the European public assessment report (EPAR) for Eliquis. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Eliquis.

What is Eliquis?

Eliquis is a medicine that contains the active substance apixaban. It is available as tablets (2.5 mg, 5 mg).

What is Eliquis used for?

Eliquis is used to prevent venous thromboembolism (blood clots in the veins) in adults following a hip or knee replacement operation. It is also used in adults to treat deep vein thrombosis (blood clot in a deep vein, usually in the leg) and pulmonary embolism (clot in a blood vessel supplying the lungs), and to prevent their reoccurrence.

Additionally, Eliquis is used to prevent stroke (caused by blood clots in the brain) and blood clots in other organs in adults with atrial fibrillation (irregular rapid contractions of the upper chambers of the heart). It is used in patients who have one or more risk factors, such as having had a previous stroke, having high blood pressure, diabetes, heart failure or being 75 years old or over.

The medicine can only be obtained with a prescription.

How is Eliquis used?

For patients who have had a hip or knee replacement, treatment with Eliquis should be started 12 to 24 hours after the operation. The recommended dose is one 2.5 mg tablet taken by mouth twice a day, usually for over one month (32 to 38 days) after a hip replacement or for 10 to 14 days after a knee

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replacement. For patients with atrial fibrillation at risk of stroke or blood clots, the recommended dose is 5 mg taken twice a day.

For the treatment of deep vein thrombosis and pulmonary embolism, the recommended dose is 10 mg twice a day for the first week, followed by 5 mg twice a day for at least 3 months. To prevent deep vein thrombosis and pulmonary embolism from reoccurring, the recommended dose is 2.5 mg twice a day. For further information, see the package leaflet.

How does Eliquis work?

Patients undergoing hip or knee replacement surgery, who have had a recent trauma, or are confined to bed are at a high risk of blood clots forming in the veins, which can be dangerous and even fatal if they move to another part of the body such as the lungs. Similarly, patients with atrial fibrillation are at high risk of clots forming in the heart, which can reach the brain where they can cause a stroke.

The active substance in Eliquis, apixaban, is a 'factor Xa inhibitor'. This means that it blocks factor Xa, an enzyme that is involved in the production of thrombin. Thrombin is central to the process of blood clotting. By blocking factor Xa, it reduces the levels of thrombin in the blood, which reduces the risk of blood clots forming in the arteries and veins.

How has Eliquis been studied?

The effectiveness of Eliquis in preventing blood clots in veins following a hip or knee replacement has been investigated in two main studies involving a total of 8,464 patients. The first study was in 5,407 patients who had undergone a hip replacement. The second study was in 3,057 patients who had undergone a knee replacement. In both studies, Eliquis was compared with enoxaparin (another medicine used to prevent blood clots). The medicine's effectiveness was measured by looking at the number of patients who either had problems related to clotting in the veins or who died of any cause during the treatment period.

The effectiveness of Eliquis in preventing strokes and arterial blood clots in patients with atrial fibrillation has been investigated in two main studies: the first (in 18,201 patients) compared Eliquis with another medicine, warfarin, while the second (in 5,598 patients) compared Eliquis with aspirin. The main measures of effectiveness were based on the number of strokes or clotting events that occurred during treatment.

For the treatment of deep vein thrombosis and pulmonary embolism and the prevention of their reoccurrence, Eliquis has been investigated in two main studies: the treatment study included 5,395 patients, and the prevention study included 2,482 patients. In the first study, Eliquis was compared with enoxaparin followed by warfarin; the main measure of effectiveness was based on the number of patients who either had blood clots in the veins of the legs or lungs or died because of this during the treatment period. In the second study, Eliquis was compared with placebo (a dummy treatment) and its effectiveness was measured by looking at the number of patients who either had problems related to clotting in the veins or who died of any cause during treatment.

What benefit has Eliquis shown during the studies?

Eliquis was effective at preventing blood clots in the veins following a hip or knee replacement. In patients undergoing a hip replacement, 1.4% of the patients who completed treatment with Eliquis (27 out of 1,949) had a clotting event or died from any cause, compared with 3.9% (74 out of 1,917) of

the patients taking enoxaparin. In patients undergoing a knee replacement, the corresponding numbers were 15% (147 out of 976) for Eliquis compared with 24% (243 out of 997) for enoxaparin.

Eliquis was also shown to be effective in preventing strokes and arterial blood clots in patients with atrial fibrillation. In the study comparing Eliquis with warfarin, 1.3 % of the patients taking Eliquis had a stroke or clotting event every year compared with 1.6% of the patients taking warfarin. The yearly rates in the second study were 1.6% for patients taking Eliquis and 3.6% for patients taking aspirin.

Eliquis was also effective at treating deep vein thrombosis and pulmonary embolism and preventing their reoccurrence: in the treatment study, 2.3% of patients treated with Eliquis had a clotting event or died, compared with 2.7% of patients treated with enoxaparin plus warfarin, showing that Eliquis was as effective as the comparator treatment. In the prevention study, 2.3% of patients taking Eliquis (2.5 mg twice a day) experienced a clotting event or died, compared with 9.3% of patients taking placebo.

What is the risk associated with Eliquis?

The most frequent side effects with Eliquis (seen in between 1 and 10 patients in 100) are anaemia (low red blood cell counts), haemorrhage (bleeding), haematoma (a collection of blood under the skin), contusion (bruising) and nausea (feeling sick) when Eliquis is used for prevention of venous thromboembolism. When used for the prevention of stroke or systemic embolism the most common are epistaxis (nose bleeds), contusion (bruising), haematuria (blood in urine), haematoma and bleeding, in particular bleeding in the gut, eye, rectum and gums. When Eliquis is used for the treatment of deep vein thrombosis and pulmonary embolism and the prevention of their reoccurrence, the most common side effects are haemorrhage, haematoma, contusion, epistaxis, bleeding in the gut, rectum or gums, and haematuria (blood in the urine).

Eliquis must not be used in patients who are actively bleeding, or who have liver disease which leads to problems with blood clotting and an increased risk of bleeding. The medicine must also not be used in patients with conditions putting them at risk of major bleeding, such as an ulcer in the gut, or in patients being treated with other anticoagulant medicines except in specific circumstances (see summary of product characteristics).

For the full list of all side effects and restrictions with Eliquis, see the package leaflet.

Why has Eliquis been approved?

The CHMP decided that the benefits of Eliquis are greater than its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Eliquis?

A risk management plan has been developed to ensure that Eliquis is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Eliquis, including the appropriate precautions to be followed by healthcare professionals and patients.

In addition, the company that markets Eliquis will provide educational material for healthcare professionals expected to prescribe Eliquis that addresses the risk of bleeding during treatment.

Other information about Eliquis

The European Commission granted a marketing authorisation valid throughout the European Union for Eliquis on 18 May 2011.

The full EPAR for Eliquis can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports. For more information about treatment with Eliquis, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 09-2014.

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Certificate: 08/20/145487
Request: 78481

Certificate of a Medicinal Product[1]
Certificado de Medicamento[1]
Certificat de Médicament[1]

This Certificate conforms to the format recommended by the World Health Organization. (Explanatory notes attached) / El presente certificado se adapta al formato recomendado por la Organización Mundial de la Salud. (Se adjuntan notas explicativas) / Ce Certificat est conforme à la présentation recommandée par l'Organisation Mondiale de la Santé. (Voir notes explicatives ci-jointes)

No. of Certificate / N° de certificado / N° du certificat: ***08/20/145487***

Exporting (Certifying) region / Región exportadora (que certifica) / Région d'exportation (certificateur) :
European Union / Unión Europea / Union Européenne :

Belgium, Bulgaria, Czechia, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, Sweden and United Kingdom.

Bélgica, Bulgaria, Chequia, Dinamarca, Alemania, Estonia, Irlanda, Grecia, España, Francia, Croatie, Italia, Chipre, Letonia, Lituania, Luxemburgo, Hungría, Malta, Paises Bajos, Austria, Polonia, Portugal, Rumanía, Eslovenia, Eslovaquia, Finlandia, Suecia y Reino Unido.

Belgique, Bulgarie, Tchéquie, Danemark, Allemagne, Estonie, Irlande, Grèce, Espagne, France, Croacia, Italie, Chypre, Lettonie, Lituanie, Luxembourg, Hongrie, Malte, Pays-Bas, Autriche, Pologne, Portugal, Roumanie, Slovénie, Slovaquie, Finlande, Suède et Royaume-Uni.

As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period / Depuis le 1er février 2020, le Royaume-Uni n'est plus un État membre de l'UE . Cependant, il continue d'être soumis au droit de l'UE pendant la période transitoire /
A partir del 1 de febrero de 2020, el Reino Unido dejará de ser Estado miembro de la UE. Sin embargo, el Derecho de la UE se seguirá aplicando en el Reino Unido durante el período de transición

Importing (requesting) country / País importador (solicitante) / Pays importateur (sollicitant):

CHILE

1 Name and pharmaceutical form of the product / Nombre y forma farmaceútica del medicamento / Dénomination et forme pharmaceutique du médicament:

Eliquis Film-coated tablet

1.1 Active substance(s)[2] and amount(s) per unit dose or unit volume[3]:
Principio(s) activo(s)[2] y cantidad(es) por unidad de dosis o unidad de volumen[3]:
Substance(s) active(s)[2] et quantité(s) par unité de dose ou unité de volume[3]:

Apixaban; 5 mg; 60 tablets

For complete composition including excipients, see attached. [4]/ Para la composición completa incluidos los excipientes, véase información anexa. [4] / La composition complète du médicament, y compris les excipients, voir annexe. [4]

1.2 Is this product subject to a Community Marketing Authorisation? [5]
¿Está sujeto este medicamento a una autorización de comercialización comunitaria? [5]
Ce médicament fait-il l'objet d'une autorisation communautaire de mise sur le marché ? [5]

yes

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1.3 Is this product actually on the market in the exporting region?
¿Se encuentra este medicamento en el mercado de la región exportadora?
Ce médicament est- il actuellement commercialisé dans la région exportatrice?

yes

2.1 Number in the Community Register of Medicinal Products [7] and date of issue:
Número de autorización de comercialización comunitaria [7] y fecha de emisión:
Numéro au registre communautaire de mise sur le marché [7] et date de délivrance:

EU/1/11/691/009, 19.11.2012

2.2 Community Marketing Authorisation Holder (name and address):
Titular de la autorización de comercialización comunitaria (nombre y dirección):
Titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) :

Bristol-Myers Squibb/Pfizer EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland.

2.3 Status of the Community Marketing Authorisation Holder: [8]
Estatus del titular de la autorización de comercialización comunitaria: [8]
Statut du titulaire de l'autorisation communautaire de mise sur le marché : [8]

c

2.3.1 For categories (b) and (c) the name and address of the manufacturer producing the pharmaceutical form is: [9]
Para las categorías (b) y (c), el nombre y dirección del fabricante que produce la forma farmaceútica es: [9]
Pour les catégories (b) et (c), nom et l'adresse du fabricant de la forme pharmaceutique considérée : [9]

Bristol-Myers Squibb Manufacturing Company, Road 3, km 77.5 Humacao, PR-00791, United States.

2.4 Is the European Public Assessment Report (EPAR) appended? [10]
¿Se adjunta el informe europeo público de evaluación (EPAR)? [10]
Un rapport européen public d'evaluation (EPAR) est-il annexé ? [10]

yes

2.5 Is the attached, officially approved product information included in the Community Marketing Authorisation?[11]
¿Se incluye la información sobre el medicamento adjunto en la autorización de comercialización comunitaria?[11]
L'information sur le médicament, officiellement approuvée, fait elle partie de l'autorisation communautaire de mise sur le marché ? [11]

yes

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2.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address): [12]
Solicitante del Certificado, si es diferente del titular de la autorización de comercialización comunitaria (nombre y dirección): [12]
Demandeur du Certificat, s'il est autre que le titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) : [12]

3. Does the Certifying Authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?
¿La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmaceútica?
L'autorité certificatrice organise-t-elle des inspections périodiques de l'usine de production de la forme pharmaceutique?

yes

If no or not applicable, proceed to question 4 / Si no o no aplicable, pase a la pregunta 4 / Si la réponse est non ou sans objet, passer à la question 4.

3.1 Periodicity of routine inspections: ***Frequency of inspections is determined on risk-based approach.***
Periodicidad de las inspecciones de rutina: ***La frecuencia de las inspecciones esta basada en función del riesgo.***
Périodicité des inspections de routine: ***L'évaluation du risque détermine la fréquence des inspections.***

3.2 Has the manufacture of this type of pharmaceutical form been inspected?
¿Se ha inspeccionado la fabricación de este tipo de forma farmaceútica?
La fabrication de ce type de forme pharmaceutique a-t-elle fait l'objet d'une inspection?

yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? [15]
¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud? [15]
Est-ce que l'établissement pharmaceutique est conforme aux BPF recommandées par l'Organisation Mondiale de la Santé ? [15]

yes

4. Does the information submitted by the applicant satisfy the Certifying Authority on all aspects of the manufacture of the product undertaken by another party? [16]
¿La información presentada por el solicitante satisface a la autoridad de certificación en relación a todos los aspectos de la fabricación del medicamento realizada por terceros? [16]
Les informations fournies par le demandeur satisfont-elles aux exigences des autorités certificatrices sur tous les aspects de la fabrication du médicament pris en charge par une tierce partie ? [16]

yes

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EUROPEAN MEDICINES AGENCY

Certificate: 08/20/145487
Request: 78481

Address of the Certifying Authority / Dirección de la autoridad certificadora / Adresse de l'autorité certificatrice :

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Telephone / Teléfono / Téléphone: ***+31 (0)88 781 6000***
Facsimile / Fax / Télécopie:
E-mail / Correo electrónico/ Courrier électronique: ***certificate@ema.europa.eu***

Name of authorised person / Nombre de la persona autorizada / Nom de la personne autorisée:

Signature / Firma / Signature: Ana Sempere Digitally signed by Ana Sempere Date: 2020.06.10 12:08:02 +02'00'

Stamp and date / Sello y fecha / Tampon et date: ***10.6.2020***

Ministerie van Buitenlandse Zaken

Gezien voor legalisatie van de handtekening
The undersigned legalises the signature

van/of A. Sempere

De minister van Buitenlandse Zaken, voor deze,
For the minister of Foreign Affairs,

19 jun 2020 - S.H. Baidjoe

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(Convention de La Haye du 5 octobre 1961)

1. Country: THE NETHERLANDS
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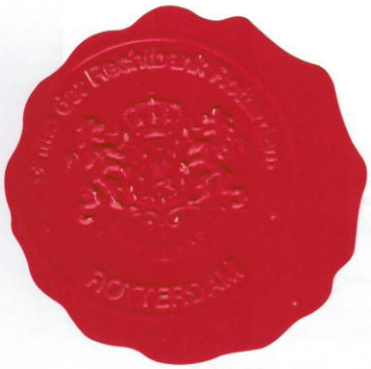
2. has been signed by **S.H. Baidjoe**
3. acting in the capacity of official of the Ministry of Foreign Affairs
4. bears the seal/stamp of aforesaid Ministry

Certified

5. in Rotterdam 6. on 19-06-2020
7. by the registrar of the district court of Rotterdam
8. no. 20 3401

9. Seal/stamp:



10. Signature:

L.B. Rellum