23 February 2017
EMA/158410/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Roteas

International non-proprietary name: edoxaban

Procedure No. EMEA/H/C/004339/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
AF	Atrial fibrillation
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic obstructive pulmonary disease
eCTD	Electronic Common Technical Document
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
eg	*exampli gratia* (for example)
FXa	Factor Xa
ie	*id est* (that is)
INR	International normalised ratio
LMWH	Low molecular weight heparin
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MI	Myocardial infarction
NA	Not applicable
NVAF	Non-valvular atrial fibrillation
PE	Pulmonary embolism
PI	Product information
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SC	Subcutaneous
SE	Systemic embolism
SEE	Systemic embolic event
SmPC	Summary of Product Characteristics
TIA	Transient ischemic attack
UFH	Unfractionated heparin
UK	United Kingdom
USA	United States of America
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Daiichi Sankyo Europe GmbH submitted on 10 August 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Roteas, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 November 2015.

The applicant applied for the following indications:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information quality, non-clinical and clinical data with a letter from Daiichi Sankyo Europe GmbH allowing the cross reference to relevant quality, non-clinical and/or clinical data.

The applicant has addressed the request to provide the EC agreement for the duplicate Marketing authorisation application (MAA) required by Article 82(1) of the regulation, by providing the EC letter of acceptance, dated 23 January 2017.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

This application is submitted as a multiple of Lixiana, authorised on 19 June 2015 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Martina Weise

- The application was received by the EMA on 10 August 2016.
- The procedure started on 12 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 October 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 October 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 November 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 10 November 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 January 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 February 2017.
- During the meeting on 23 February 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Roteas on 23 February 2017.

2. Scientific discussion

2.1. Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended. The marketing authorisation holder (MAH) of the reference product, Lixiana, has provided consent to allow access to Module 2 to Module 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved.

The reference product, Lixiana had been submitted as a full application under Art 8(3) of Directive 2001/83/EC. As a consequence, the quality, safety and efficacy of Roteas are identical to the up to date quality, safety and efficacy profile of Lixiana.

2.1.1. Disease or condition

Atrial fibrillation (AF) represents the most common sustained cardiac rhythm disorder. AF, particularly when it is persistent/permanent, predisposes patients to the development of atrial thrombi, which may embolize to the systemic circulation.

Vitamin K antagonists ([VKAs]; coumarins, like warfarin and acenocoumarol) have been the only oral anticoagulants available over the last 60 years. These agents are effective to prevent stroke in patients with

AF, but their management remains problematic due to their narrow therapeutic index and variability in drug exposure, necessitating routine coagulation monitoring, clinical surveillance, and continuous patient education[1]. Such monitoring is inconvenient for patients and medical staff, and costly for healthcare payers. As a result, approximately only half of eligible patients with AF receive oral anticoagulation with VKA.

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading mortality cause due to circulatory diseases, only behind of myocardial infarction and stroke.

Current guidelines recommend treating patients with acute VTE with an oral VKA for at least 3 months[2]. As VKA have a slow onset of action, overlapping with a parenteral anticoagulant [e.g.: low molecular weight heparin (LMWH) or unfractionated heparin (UFH)] is needed for the initial 5–10 days of acute VTE, until appropriate anticoagulation with VKA is achieved [i.e.: international normalized ratio (INR) between 2.0 and 3.0]. LMWH are effective and safe also for the long-term treatment of VTE. However, they still require daily parenteral subcutaneous (SC) administration, which may be problematic for many patients. On the other hand, the VKA have several limitations, as mentioned in previous paragraph.

Direct oral anticoagulants (DOACs) are currently available in the European Union (EU) and other regions for several indications, including prevention of stroke/systemic embolic events (SEE) in nonvalvular atrial fibrillation (NVAF) and/or treatment of VTE: the direct thrombin inhibitor dabigatran (as etexilate) and the direct factor Xa inhibitors rivaroxaban and apixaban. The pivotal studies conducted with the DOACs in prevention of stroke/SEE in NVAF or treatment of VTE were mainly large non-inferiority event-driven clinical trials recruiting heterogeneous populations in different geographic regions and with different quality of oral anticoagulation with warfarin. The potential influence of differences in clinical, geographic factors and quality of oral anticoagulation across studies on the relative efficacy and safety of the DOACs, as well as the clinical relevance of these differences, may be significant, particularly in NVAF indication[3].

2.1.2. Epidemiology and risk factors

AF affects approximately 4.5 million adults in the EU and about 2.3 million adults in the United States of America (USA). Over the past three decades, the incidence of AF has been increasing. The variability and uncertainty about the incidence and prevalence of AF is in part related to case definitions and/or inclusion of different types of AF (permanent, paroxysmal, related to other particular underlying pathologies). Older studies tended to include only patients with permanent AF. The lifetime risk of developing AF is about 25% among those who have reached the age of 40 years. Prevalence of AF has increased over time and is projected to increase further in the next 50 years. In a recent pooled analysis of published studies, AF prevalence was estimated at 2.8%. The incidence and prevalence of AF increase with age. Using data from 4 large prospective population-based studies (USA, Australia, European studies) and the USA census data, the median age of patients with AF is estimated to be about 75 years, and an estimated 70% of patients fall between the ages of 65 to 85 years. In international (UK, Iceland, France, and Sweden) large population studies, prevalence was higher in men than in women. In a recent pooled analysis of published studies, AF prevalence was estimated at 3.3% in men and 2.4% in women. In a prospective cohort study in USA, the risk of AF was 45% lower in Blacks compared to Whites. In a cross-sectional study (in UK), the prevalence of AF was 1.4% in African-Caribbeans and 0.7 % in South Asians.

[1] Ansell J, et al. Chest. 2008;133:160S-198S.
[2] Kearon C, et al. Chest. 2012;141(2 Suppl):e419S-e494S.
[3] Gómez-Outes A, et al. Thrombosis. 2013:640723.

The following risk factors for AF have been identified: increasing age, hypertension, symptomatic heart failure, cardiomyopathy, valvular heart disease, atrial septal defect, other congenital heart defects, coronary heart disease, hyperthyroidism, obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), sleep apnoea, chronic renal disease.

AF is an important marker of future morbidity with major consequences for the healthcare delivery systems and imposes substantial burden on increased morbidity and mortality-associated therapeutic interventions. Patients were hospitalized more frequently, for longer durations with more visits to specialists as opposed to general physicians. Death rates are doubled by AF, independently of other known predictors of mortality. Only antithrombotic treatment has been shown to reduce AF-related deaths. In an international study (Observational Euro Heart Survey (n = 3182)) with one year follow-up, all-cause mortality was 5.3% (3.5% for paroxysymal AF, 3.0% for persistent AF and 8.2% for permanent AF). The mean age of the patients with paroxysymal AF, persistent AF and permanent AF at baseline were 64, 66 and 71 years, respectively.

There are several known risk factors that can be attributed to the development of AF and constitute important comorbidities for AF. Concomitant medical conditions play a role in the perpetuation of AF. The prevalence of these comorbidities is much higher in patients with AF than in patients without. AF is an independent risk factor for stroke which increases a patient's risk of stroke 4- to 5- fold.

DVT and PE are considered to be manifestations of a single pathophysiological process collectively referred to as **VTE**. DVT and PE often present together, share the same risk factors, and are associated with high morbidity that may progress to a fatal outcome if left untreated. VTE is the third most common cardiovascular illness after acute coronary syndrome and stroke. The reported incidence of VTE vary widely due to differences in the study populations, the coding or classification of the diagnoses and the settings under which VTE are diagnosed (eg, hospital, outpatient clinics etc.) and study methodologies. Many of the large epidemiology studies on VTE in European countries reported the cumulative incidence or incidence rate of VTE rather than prevalence data. The incidence of VTE steadily increases with age, and particularly after age 40 years. No consistent differences in the incidence of VTE among men and women have been observed. Risk of recurrence may be higher in men than in women. A few studies showed 2-4 fold lower risk of VTE in Asian and Hispanic population than in Caucasians.

The following temporary risk factors for VTE have been identified: surgery, trauma, pregnancy and post-partum period, prolonged immobilization and use of female hormones. Other risk factors include age, cancer and chemotherapy, cardiovascular diseases such as myocardial infarction (MI), congestive heart failure (CHF), COPD, obesity, cigarette smoking, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, thrombophilia.

Studies in Europe report that the total number of symptomatic VTE events per annum across the 6 countries was estimated to be 761697 nonfatal VTE events and 399808 associated complications. Early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease. Survival after PE is much worse than after DVT alone.

Compared with the AF population, patients presenting with VTE arise from diverse populations. Patients with short-term increased risk of thromboembolic events (such as preoperatively or during significant periods of immobilization) will have different concomitant medications from patients with chronic comorbid conditions. For patients with chronic comorbid conditions, complex polypharmacy is frequent and complicates individual patient management. Patients with COPD, renal disease and impairment with consequent anaemia, lead to potentially complex multifactorial ongoing treatment.

Comorbidities that the AF population and the VTE population have in common are stroke/TIA, coronary artery disease/MI, CHF, hypertension, diabetes mellitus, malignancy, COPD, and renal failure, albeit their incidence, prevalence and mortality/morbidity typically differ. Malignancy is an associated risk factor for VTE but not for AF.

About the product

Edoxaban is an orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa). Factor Xa plays a pivotal role in the coagulation cascade because it sits at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is exerting anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.

At the time of submission of the current application, edoxaban was approved in Japan, Switzerland, European Union, Hong Kong, Korea, and Turkey for prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF) as well as the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE.

In the United States and Taiwan, edoxaban was approved for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF), for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

In Japan, edoxaban was also approved for VTE prophylaxis following orthopedic surgery.

The CHMP granted the positive opinion for Roteas, for the following indications:

- *Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).*

- *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).*

For *the prevention of stroke and systemic embolism*, the recommended dose is 60 mg Roteas once daily. For *the treatment of VTE including DVT and PE*, *and prevention of recurrent VTE*, the recommended dose is 60 mg Roteas once daily following initial use of heparin. For NVAF and VTE the recommended dose is 30 mg Roteas once daily in patients with one or more of the following clinical factors: a) moderate or severe renal impairment (creatinine clearance: 15-50 ml/min); b) low body weight ≤60 kg; c) concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporine, dronedarone, erythromycin, ketoconazole, quinidine, or verapamil.

2.2. Quality aspects

Since this application is an informed consent of the Lixiana, the quality data in support of the Roteas application are identical to the up-to-date quality data of the Lixiana dossier, which has been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

2.3.1. Introduction

Roteas is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Module 4 of Roteas dossier cross-refers to the up-to-date module 4 of Lixiana which has been assessed and approved (including all post-marketing procedures). No additional non-clinical data have been submitted.

2.3.2. Ecotoxicity/environmental risk assessment

Roteas is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Module 1.6 of Roteas dossier cross-refers to the up-to-date Module 1.6 of Lixiana authorised previously. This was considered acceptable.

2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no new issues related to the non-clinical data. All the non-clinical data have been assessed in the application for reference medicinal product, Lixiana and adequately reflected in the Product Information (PI).

2.4. Clinical aspects

2.4.1. Introduction

Roteas is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Module 5 of Roteas dossier cross-refers to the up-to-date module 5 of the dossier of Lixiana. No additional clinical data have been submitted.

2.4.2. Conclusions on the clinical aspects

In this informed consent application, there are no new issues related to the clinical data. All the clinical data have been assessed within Lixiana application and adequately reflected in the PI.

2.5. Risk Management Plan

The MAH has submitted a risk management plan (RMP) dated January 2017 based on originator licence Lixiana RMP Version number 6.0, which is the currently approved version. The MAH has addressed the request to confirm that the safety specification in the proposed RMP is in line with that of the last approved RMP for Lixiana and to ensure that the corrected invented name (Roteas) is presented throughout the proposed RMP.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7. New Active Substance

The CHMP, based on the available data, considers that edoxaban is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Edoxaban is contained in Lixiana, which was authorised in the European Union on 19 June 2015.

2.8. Product information

Roteas is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. PI of the present dossier cross-refers to the up-to-date PI of Lixiana, which has been assessed and authorised, with the logical changes in the medicinal product specific data (i.e.: invented name). The PI for Roteas 15 mg, 30 mg and 60 mg film-coated tablets is therefore identical to the one of Lixiana 15 mg, 30 mg and 60 mg film-coated tablets, with the only exception of the invented name of the medicinal product.

The (invented) name of the medicinal product followed by its strength expressed in Braille format is included in the proposed labelling and mock-ups for the cartons.

The applicant has addressed the request to confirm that the Patient information leaflet for Roteas will be identical in design and layout to the one of Lixiana.

2.8.1. User consultation

The applicant has submitted a document justifying that as Roteas is an informed consent application, the User Testing performed for Lixiana that has been reviewed in the original MAA is relevant for the current initial MAA. There are no significant changes for the proposed patient leaflet. Therefore, the company´s justification to not undertake further consultation with target patient groups is considered acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Roteas is included in the additional monitoring list as it contains an active substance (edoxaban) which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

This Marketing Authorisation application for Roteas has been submitted by Daiichi Sankyo Europe GmbH as an informed consent application in accordance with Article 10(c) of Directive 2011/83/EC, as amended.

As a consequence, quality, safety and efficacy of the Roteas medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Lixiana. The application for Roteas concerns the identical strengths to those approved for Lixiana and consists of only Module 1. Information on the scientific discussion can be found in Lixiana European Public Assessment Report (EPAR) published on the EMA website.

Consequentially, and in line with the assessment of data undertaken in the framework of the Lixiana initial marketing authorisation application as well as within all post-authorisation procedures, the CHMP considers that the benefit/risk balance for Roteas is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Roteas is favourable in the following indications:

- *Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).*

- *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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 European Medicines Agency;
- 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

Prior to launch of Roteas in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at mitigating the risk of serious bleeds or haemorrhage in patients treated with Roteas by ensuring prescriber awareness and providing guidance on appropriate patient selection, correct dosing as well as management of the risk.
The programme is also aimed at ensuring that the healthcare professionals who intend to prescribe Roteas are aware of the Patient alert card and that the card is to be given to and reviewed with all patients treated with Roteas.

The MAH shall ensure that in each Member State where Roteas is marketed, all healthcare professionals who are expected to use Roteas are provided with the following educational material:

- The Summary of Product Characteristics
- Prescriber Guide for healthcare professionals
- Patient alert card

The Prescriber Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the risk of bleeding
- Details of the population potentially at higher risk of bleeding
- Contraindications
- Recommendations for dose adjustment in at risk populations, including patients with renal or hepatic impairment, low body weight and concomitant use of some P-gp inhibitors
- Guidance on switching from or to Roteas treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- Use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
  - The signs or symptoms of bleeding and when to seek attention from a healthcare provider
  - Importance of treatment compliance
  - Necessity to carry the Patient alert card with them at all times

- The need to inform Health Care Professionals that they are taking Roteas if they need to have any surgery or invasive procedure

The Patient alert card should contain the following key safety messages:

- The signs or symptoms of bleeding and when to seek attention
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Roteas if they need to have any surgery or invasive procedure

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.