COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rivaroxaban Sandoz 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets (rivaroxaban)

NL/H/5327/001-005/DC

Date: 08 September 2022

This module reflects the scientific discussion for the approval of Rivaroxaban Sandoz 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets. The procedure was finalised at 22 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban Sandoz 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets, from Sandoz B.V.

The **2.5 mg** product is indicated:

- co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1 of the SmPC);
- co-administered with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

The **10 mg** product is indicated:

- for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery;
- for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, (see section 4.4 of the SmPC for haemodynamically unstable PE patients).

The **15 mg** product is indicated:

- *in adults for*
    - prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack;
    - treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, (see section 4.4 of the SmPC for haemodynamically unstable PE patients);
- *in the paediatric population for*
    - treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

The **20 mg** product is indicated:

- *in adults for*
    - prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack;

  - treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, (see section 4.4 of the SmPC for haemodynamically unstable PE patients);
- *in the paediatric population for*
  - treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

The **15 mg + 20 mg** product (the *treatment initiation pack*) is indicated:

- for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 of the SmPC for haemodynamically unstable PE patients.)

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets, which have been registered in the EEA by Bayer AG since 30 September 2008 by the centralised procedure EMEA/H/C/000944.

The concerned member states (CMS) involved in this procedure were:

- for the 2.5 mg product: Austria, Belgium, Denmark, Finland, Germany, Hungary, Iceland, Norway, Spain and Sweden;
- for the 10 mg, 15 mg and 20 mg products: Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Iceland, Norway, Spain and Sweden;
- for the 15 mg + 20 mg product: Belgium, Denmark, Finland, Germany, Hungary, Iceland, Norway, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

- Rivaroxaban Sandoz 2.5 mg is a light yellow, round biconvex tablet, debossed with '2.5' on one side and plain on the other side. Each film-coated tablet contains 2.5 mg rivaroxaban.
- Rivaroxaban Sandoz 10 mg is a light red, round biconvex tablet, debossed with '10' on one side and plain on the other side. Each film-coated tablet contains 10 mg rivaroxaban.

- Rivaroxaban Sandoz 15 mg is a red, round biconvex tablet, debossed with '15' on one side and plain on the other side. Each film-coated tablet contains 15 mg rivaroxaban.
- Rivaroxaban Sandoz 20 mg is a brown-red, round biconvex tablet, debossed with '20' on one side and plain on the other side. Each film-coated tablet contains 20 mg rivaroxaban.

The treatment initiation pack (15 mg + 20 mg) contains 15 mg tablets for week 1, 2, and 3 of treatment, and 20 mg tablets for week 4 of treatment. These tablets are identical to the single strength packaged tablets of 15 mg and 20 mg respectively.

The film-coated tablets are packed in Aluminium-PVC/PE/PVdC blisters in cartons or in HDPE bottles with a polypropylene child resistant cap for all strengths.

The excipients are:
Tablet core - sodium lauryl sulphate, lactose, poloxamer, microcrystalline cellulose (E460), croscarmellose sodium, magnesium stearate (E470b) and colloidal anhydrous silica (E551);
Film-coat - hypromellose (E464), titanium dioxide (E171) and macrogol (E1521) for all strengths, plus yellow iron oxide (E172) for the 2.5 mg tablets and red iron oxide (E172) for the 10 mg, 15 mg and 20 mg tablets.

The 2.5 mg and 10 mg tablet cores are dose proportional based upon the 5% rule (see *Biowaiver* under chapter IV.2 Pharmacokinetics). The 15 mg tablet cores are quantitatively proportional to the 20 mg tablet cores.

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellowish powder, non-hygroscopic and practically insoluble in water. Rivaroxaban has one stereogenic centre and is manufactured as the S-enantiomer. The active substance shows polymorphism and is manufactured as the stable polymorphic form I.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP, with additional requirements for particle size and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the reference products, dissolution method development, comparative dissolution studies and formulation optimisation studies. The dissolution method development has been adequately described and the methods are in line with the Ph.Eur. monograph for the 10 mg, 15 mg and 20 mg products. For the 2.5 mg product, a different dissolution method than the method of the Ph.Eur. monograph has been implemented and has been adequately justified.

Bioequivalence studies were performed with the 10 mg and 20 mg products versus the respective reference product strengths. For the 2.5 mg and 15 mg products a biowaiver was granted. The batches used in the bioequivalence studies were manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at three pHs has been successfully studied in support of the bioequivalence studies and biowaivers. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The main steps include mixing, dry granulation, pre-lubrication blending, lubrication, compression, film-coating and packaging. Process validation data on the product have been presented for three full scaled batches for both manufacturing sites in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. requirements. The ready-to-use film-coating materials are controlled according to in-house specifications. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, dimensions, assay, related substances, dissolution, uniformity of dosage units, uniformity of mass and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. All potential sources of nitrosamine impurities currently listed in the EMA Q&A on "Information on nitrosamines for marketing authorisation holders" have been considered in the risk evaluation by the company. No confirmatory testing and/or controls are required. The risk evaluation concerning the presence of nitrosamine impurities is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scaled batches per strength and per manufacturing site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC-Al blisters and HDPE bottles. The batches were evaluated for description, assay, enantiomeric purity, related substances, dissolution and microbial purity. No clear trends or changes were seen at both storage conditions in any of the tested parameters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Because no indication was noted from stability and stress studies that the drug product may be susceptible to deterioration, no in-use stability studies were required for the HDPE bottle packaging. The proposed shelf-life of 3 years without any special storage conditions is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose is the only material of animal origin used in the manufacture of Rivaroxaban film-coated tablets. Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rivaroxaban Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xarelto, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rivaroxaban is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban Sandoz 10 mg and 20 mg film-coated tablets (Sandoz B.V., The Netherlands) are compared with the pharmacokinetic profile of the reference products Xarelto 10 mg and 20 mg film-coated tablets (Bayer AG, Germany), respectively.

The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. The formulas and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

Biowaiver

A biowaiver was applied for strength 2.5 mg and 15 mg. The following general requirements must be met where a waiver for additional strength is claimed: a) the pharmaceutical products are manufactured by the same manufacturing process, b) the qualitative composition of the different strengths is the same, c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule), d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength for which a waiver is considered;

i) the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content;

ii) the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed;

iii) the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths.

The 2.5 and 10 mg tablets are dose proportional based upon the 5% rule and the results obtained for the 10 mg tablet could be extrapolated to the 2.5 mg tablet. To support the biowaiver for the 2.5 mg strength, dissolution data at three pHs have been provided and adequacy of dissolution quality control media has been shown. Comparable composition and dissolution were demonstrated.

The results obtained for the 20 mg tablet could be extrapolated to the 15 mg tablet. The 15 and 20 mg tablet cores are fully dose proportional. To support the biowaiver for the 15 mg strength, dissolution data at three pHs have been provided and adequacy of dissolution quality control media has been shown. Comparable composition and dissolution were demonstrated.

Bioequivalence studies

Study 1 – 10 mg, single-dose under fasting conditions

Design

A single-dose, randomised, two-treatment, two-period, two-sequence crossover bioequivalence study was carried out under fasting conditions in 42 healthy male subjects, aged 18 - 60 years. Each subject received a single dose (10 mg) of both the rivaroxaban formulations. The tablet was orally administered with 240 ml water, after an overnight fast. There were two dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products. According to the SmPC, the 10 mg tablet strength can be taken with or without food. As such, the fasting conditions applied in the study are considered adequate. The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples, long term stability data was shown for rivaroxaban in plasma. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Four subjects were withdrawn from the study. One subject withdrew consent for personal reasons in Period I, two subjects were withdrawn from the study prior dosing in Period II due to a positive screening for drug abuse and one subject was withdrawn from the study prior dosing in Period II due to an adverse event (pyrexia). This resulted in 38 subjects completing the study and being eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban under fasting conditions.

Treatment N=38	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1433 ± 303	1473 ± 310	165 ± 42	2.0 (0.67 – 4.0)	8.5 ± 2.5
Reference	1480 ± 298	1517 ± 304	175 ± 44	2.1 (0.67 – 5.0)	8.6 ± 2.5
***Ratio (90% CI)**	0.97 (0.92 – 1.01)	--	0.95 (0.87 – 1.03)	--	--
CV (%)	11.7	--	21.6	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
* ln-transformed values

Study 2 – 20 mg, single-dose under fed conditions
Design
A single-dose, randomised, two-period, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 20 - 60 years. Each subject received a single dose (20 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 ml water, 30 minutes after intake of a high fat high caloric breakfast (consisting of whole milk, two eggs, potatoes, toast, butter and bacon). There were two dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products. According to the SmPC, the 20 mg

tablet strength should be taken with food. As such, the fed condition applied in the study is considered adequate. The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples, including long term stability shown for rivaroxaban in plasma. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 30 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban under fed conditions.

Treatment N= 30	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	2931 ± 688	2972 ± 688	388 ± 103	4.0 (1.0 – 8.0)	7.3 ± 2.1
Reference	2944 ± 703	2980 ± 705	386 ± 85	2.8 (1.0 – 6.1)	7.6 ± 2.4
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	--	0.99 (0.93 – 1.06)	--	--
CV (%)	10.9	--	15.9	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
***** ln-transformed values

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 for both studies. Based on the submitted bioequivalence studies, the Rivaroxaban Sandoz 10 mg tablet is considered bioequivalent with the Xarelto 10 mg tablet and the Rivaroxaban Sandoz 20 mg tablet is considered bioequivalent with the Xarelto 20 mg tablet.

The results obtained for the 20 mg tablet could be extrapolated to the 15 mg tablet based upon a biowaiver and the results obtained for the 10 mg tablet could be extrapolated to the 2.5 mg tablet based upon a biowaiver as well.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rivaroxaban Sandoz.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal toxicity
Missing information	• Safety in patients with severe renal impairment (creatinine clearance < 30 mL/min) • Remedial procoagulant therapy for excessive haemorrhage • Safety in patients receiving systemic treatment with Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein inhibitors other than azole-antimycotics (e.g. ketoconazole) and Human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir) • Safety in pregnant or breast-feeding women • Safety in patients with atrial fibrillation (AF) secondary to significant valvular heart disease and a prosthetic heart valve • Safety regarding long term therapy with rivaroxaban for treatment of Deep Vein Thrombosis, Pulmonary Embolism, stroke prevention in patients with non-valvular AF (SPAF) and Acute Coronary Syndrome in real-life setting • Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

Additional risk minimisation measures are taken regarding educational material. The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe, dispense or use rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber guide
- Patient alert cards

The MAH must agree with the national competent authority in each Member State on the content and format of the Prescriber Guide together with a communication plan, prior to distribution of the educational pack in their territory. Key safety messages which the Prescriber Guide should contain have been described.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xarelto. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the products are similar to the pharmacokinetic profile of the reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference regarding general safety information to Rivaroxaban Sandoz (NL/H/5039) and for its layout and other content, including specific information on the initiation pack, reference is made to Xarelto (EMEA/H/C/000944). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rivaroxaban Sandoz 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. Xarelto is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivaroxaban Sandoz with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 March 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse