COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Metformine HCl 1000 mg Focus, prolonged-release tablets

(metformin hydrochloride)

NL Licence RVG 123374

Date: 5 November 2020

This module reflects the scientific discussion for the approval of Metformine HCl 1000 mg Focus, prolonged-release tablets. The marketing authorisation was granted on 3 June 2020. 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
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Metformine HCl 1000 mg Focus, prolonged-release tablets from Focus Care Pharmaceuticals B.V.

The product is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control.
Metformine HCl 1000 mg may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.

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

This national procedure concerns a hybrid application. The innovator product Glucophage 500 mg, film-coated tablets was first authorised in France on 19 March 1953. Compared to the reference medicinal product, the drug product applied for has a different pharmaceutical form (prolonged-release tablet instead of immediate release film-coated tablet) and has a different strength (1000 mg instead of 500 mg). In the Netherlands, the reference product Glucophage is no longer registered.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Metformine HCl 1000 mg Focus 1000 mg is an off-white coloured, oval, biconvex, film coated tablet with score line on one side and plain on other side. This score line is non-functional and not intended to subdivide the tablets into equal halves.

And contains as active substance 1000 mg of metformin hydrochloride, equivalent to 780 mg metformin base.

The prolonged-release tablets are packed in PVC/PVDC aluminium blisters.

The excipients are:
Tablet core – stearic acid (E570), shellac (E904), povidone K30 (E1201), silicon dioxide (E551), magnesium stearate (E470b)
Film-coating – hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), propylene glycol (E1520), macrogol 6000, talc (E553b)

II.2 Drug Substance

The active substance is metformin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder, which is freely soluble in water. Known polymorphic forms are form A and form B. Form B is a metastable form and converts to form A on standing. The drug substance is manufactured as form A.

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 in line with the Ph.Eur. monograph, with additional requirements for particle size, residual solvents and extraneous matter. The drug substance specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided on several batches, including at least three of commercial scale.

Stability of drug substance
The active substance is stable for 5 years 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 development of the product has been described, the choice of excipients is justified and their functions explained. The choice of the excipients was based on a novel approach of hot melt technology. Stearic acid acts as a release retardant in the formulation. The manner in which prolonged release is achieved (matrix type) and release mechanism (pore diffusion and erosion) is sufficiently described. The system format is a non-disintegrating unit. The main development studies were the characterization of the reference product, formulation optimization (optimizing the levels of stearic acid, shellac and povidone), dissolution method

development, alcohol interaction studies and performance of comparative dissolution studies at 3 pHs in support of the bioequivalence study. The choices of the packaging and manufacturing process are justified.
The tablets contain a score line, but the tablets cannot be broken by hand due to their hardness. The MAH has shown that unintended breaking using a tablet splitter does not affect the dissolution profile. The product information clearly states that the score line is not functional and the tablets should be swallowed whole. The non-functional score line can therefore be accepted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are hot melt granulation, dry mixing, wet granulation, blending, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for at least three pilot scaled and three full scaled batches from both manufacturing sites.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average mass, uniformity of dosage units, dissolution, related substances, assay, residual isopropyl alcohol and microbiological quality. The release and shelf-life requirements are identical. The specification is acceptable. Analytical methods have been adequately described and validated.
Batch analytical data from the proposed production sites have been provided on at least three pilot scaled and three full scaled batches per site, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on six pilot scaled and three full scaled batches from one manufacturing site and on three pilot scaled and three full scaled batches from the other manufacturing site that were stored at 25°C/60% RH (36-60 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/PVdC-Al blisters. Except for a slight decrease in dissolution in the three pilot scaled batches from the first manufacturing site. No changes or trends were seen in any of the tested parameters at both storage conditions in any of the other batches. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. The product was shown to be photostable in its primary packaging.
The proposed shelf-life of 36 months is justified. The storage conditions are ‘Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage condition.‘

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Metformine HCl 1000 mg Focus, prolonged-release tablets 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 Metformine HCl 1000 mg Focus 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 hybrid formulation of Glucophage 500 mg, film-coated tablets, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metformin HCl 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 MEB agreed that no further clinical studies are required.

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

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Metformine HCl 1000 mg Focus, prolonged-release tablets (Focus Care Pharmaceuticals B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Glucophage 1000 mg prolonged-release tablets (Merck Sanites, UK), under fasted and fed conditions.

The choice of the reference product in the bioequivalence study has been justified. The reference product Glucophage 1000 mg prolonged-release tablets is not available on the Dutch market anymore. The study reference batch sourced from the UK can be considered a representative batch. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. Bioequivalence was declared by the MAH in case the 90% CI were within 0.80 – 1.25 for AUC_{0-t} and C_{max}. Next to AUC_{0-t}, AUC_{0-inf} and C_{max}, also partial AUCs have been calculated over 0-12h and 12-36h. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
Partial AUCs have been provided to support the waiver for a multiple dose study. For such a waiver, the MAH should show that there is no significant accumulation at steady state and should show that the shape of the C-t curves between test and reference are comparable.

Bioequivalence studies
Bioequivalence study I – fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 20-43 years. Each subject received a single dose (1000 mg) of one of the 2 metformin HCl formulations. The tablet was orally administered with 150 ml of 20% w/v aqueous glucose solution after an overnight fast. In addition, 150 ml of 20% w/v aqueous glucose solution was provided at 1, 2, 3 and 4h post dosing in each period. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 18, 20, 24 and 36 hours after administration of the products.

A single-dose, crossover study under fasting to assess bioequivalence for metformin is acceptable. A glucose solution was given during administration of the tablet and during the study period. In addition, glucose solution was given whenever glucose values were found to be < 70 mg/dl, to prevent hypoglycaemic symptoms, which is acceptable.

Results

Four subjects were withdrawn:

- One subject vomited after dosing in Period I.
- One subject had fever before dosing in Period I.
- One subject did not report to the facility before dosing in Period II.
- One subject tested positive on benzodiazepine in urine before dosing in Period II.

The remaining 56 subjects completed the and were eligible for pharmacokinetic analysis.

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

Treatment N=56	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	AUC_{0-12} (ng.h/ml)	AUC_{12-36} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	11257 ± 4157	11614 ± 4212	8959 ± 2476	2509 ± 2085	1388 ± 317	4.0 (2.0 - 4.5)	5.3 ± 2.3
Reference	10533 ± 4532	10834 ± 4522	8001 ± 2477	2719 ± 2266	1213 ± 285	4.0 (2.0 - 6.0)	4.7 ± 1.6
***Ratio (90% CI)**	1.09 (1.02 - 1.17)	1.09 (1.02 - 1.17)	1.13 (1.08 - 1.18)	0.98 (0.82 - 1.17)	1.15 (1.09 - 1.20)	--	--
CV (%)	21.9	21.4	15.0	59.4	26.1	--	--

$AUC_{0-\infty}$	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*

Bioequivalence study II – fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 54 healthy male subjects, aged 19-43 years. Each subject received a single dose (1000 mg) of one of the 2 metformin HCl formulations. The tablet was orally administered 30 min after start of intake of a high fat, high caloric breakfast. The tablets were taken with 150 ml of 20% w/v aqueous glucose solution. In addition, 150 ml of 20% w/v aqueous glucose solution was provided at 1, 2, 3 and 4h post dosing in each period. There were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 18, 20, 24 and 36 hours after administration of the products.

A single dose, crossover study under fed conditions to assess bioequivalence for metformin is acceptable. As in the fasted study, glucose solution was given to prevent hypoglycaemic symptoms, which is acceptable.

Results
The following subjects withdrawn:

- Four subjects did not report to the facility before dosing in Period II.
- One subject tested positive on THC in urine before dosing in Period II.
- One subject did not report to the facility before dosing in Period II.
- One subject was withdrawn in Period II due to an AE (emesis).

The remaining 48 subjects completed the and were eligible for pharmacokinetic analysis.

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

Treatment N=56	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	AUC_{0-12} (ng.h/ml)	AUC_{12-36} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	13525 ± 2992	14065 ± 2723	1022 ± 204	8365 ± 1648	5481 ± 1633	5.0 (3.0 - 10.0)	4.7 ± 1.1
Reference	13334 ± 2775	13772 ± 2646	986 ± 181	8091 ± 1609	5521 ± 1792	6.25 (4.0 - 12.0)	4.6 ± 1.3
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	1.02 (0.98 - 1.06)	1.03 (0.99 - 1.08)	1.01 (0.92 - 1.11)	1.03 (0.99 - 1.08)	--	--
CV (%)	11.6	10.7	12.0	28.2	13.2	--	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of metformin, the reference and test formulation are considered bioequivalent with respect to the extent and rate of absorption under fasting and fed conditions. The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-inf} and C_{max} were inside the normal range of acceptability (0.80 – 1.25).

The shape of the C-t curves between the test and reference formulation are considered comparable, as bioequivalence was also proven for AUC_{0-12h} and AUC_{12-36h} in both studies.

No significant accumulation is expected at steady state, as the $AUC_{0-\tau}$ for Test and Reference is more than 90% of AUC_{0-inf}. Based on these data the waiver for the multiple dose study is considered acceptable.

The MEB has been assured that the bioequivalence studies have 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 Pharmacodynamics

The main effects of metformin involve suppression of hepatic glucose output, increased peripheral glucose utilisation, reduced fatty acid utilisation and increased glucose turnover, particularly in the splanchnic bed. In addition, metformin alters glucose handling by erythrocytes and reduces hypertriglyceridaemia.

IV.4 Clinical efficacy

The MAH provided several studies examining the efficacy of metformin immediate-release formulations as monotherapy or in combination with other antidiabetic agents. The efficacy, dose-response relationships and safety of an extended-release formulation of metformin were evaluated in the five studies. An overview of these clinical studies are presented in the table below.

Table 3. Studies focusing on extended-release metformin

Study, Author, Year	Trial Design, No. of Subjects, Duration	Patient Population	Intervention and Control	End Point Results (Primary End Point)	Strengths and Limitations
Fujioka 2005	Two double-blind, randomized, placebo-controlled studies; Protocol 1). N = 1240, 24 weeks;	Patients with inadequate glycaemic control despite diet and exercise	Protocol 1). Intervention: metformin XR 1000mg OD Control: placebo	Protocol 1). Reduction HbA1C vs. placebo: -0.7% at 12 weeks -0.8% at 24 weeks ($p<0.001$ for each).	Strengths: double-blind placebo-controlled design, duration of follow-up. Limitation: no comparison of

	Protocol 2). N = 742 patients, 16 weeks		Protocol 2). Intervention: metformin XR 500mg OD, 1000mg OD, 1500mg OD, 2000mg OD. 1000mg BD (Glucophage® XR) Control: placebo	Protocol 2). A clear dose–response relationship was evident at doses up to 1500 mg. Reduction HbA1C vs. placebo: -0.6% (500mg OD), -0.7% (1000mg OD), -1.0% (1500mg OD) -1.0% (2000 mg OD) The efficacy of metformin XR 2000mg OD and 1000mg BD were similar (Reduction HbA1C vs. placebo: -1.0% and -1.2%, respectively). Metformin XR was well tolerated; gastrointestinal side effects were more common with metformin XR vs. placebo, but few patients withdrew for this reason (1.3% vs. 1.3% in Protocol 1 and 1.6% vs. 0.9% in Protocol 2).	metformin XR to metformin IR
Schwartz 2006	A double-blind, randomized study; N = 750, 24 weeks;	Newly diagnosed DM2 patients, treated with diet and exercise only, or patients previously treated with oral diabetic medication	Intervention: metformin XR (1500mg OD, 1500mg BD, 2000mg OD Control: metformin IR 1000mg BD	Mean difference in HbA1C: metformin XR 1500mg (-0.73 OD and -0.74% BD) vs. metformin IR (-0.70%). Overall incidence of AEs: similar for all treatment groups, fewer patients in the metformin XR groups discontinued treatment due to nausea	Strengths: double-blind placebo-controlled design, direct comparison of metformin XR with metformin IR
Hsieh 2007	Prospective, randomized, double-blind study; N = 55, 12 weeks;	DM2 patients that had been first diagnosed with DM2 after 30	Intervention: metformin XR 1000mg OD Control: metformin IR 500mg.	Mean difference in HbA1C and fasting plasma glucose : significant decrease (P<0.001) in each group. Changes in metabolic	Strengths: double-blind placebo-controlled design, direct comparison of metformin XR

		years of age.	During a 2 week titration interval metformin was increased to a maximal dosage of 2000mg OD	parameters were similar except that a decreased TC was observed in the metformin IR	with metformin IR Limitations: small sample size
Levy 2010	Open-label, prospective study; N = 61, 24 weeks	DM2 patients currently treated with metformin	Intervention: switched to metformin XR 500mg and titrated to a maximal dosage of 2000mg OD	The metformin daily dose at baseline and following titration of metformin XR was 1861 +/- 711mg and 1500 +/- 402 mg per day (p=0.004) respectively. On completion of six months on metformin XR, a total of 27 patients (77.1%) were asymptomatic, with the remainder reporting symptoms of diarrhoea (n=5), nausea (n=2) and epigastric pain Ghost tablets were reported in the faeces by the majority of the patients (54.1%).	Strengths: data on dose titration Limitations: open label design, small sample size, no control group
Lewin 2007	A multicenter, double-blind, randomized, controlled study; N = 741, 24 weeks	DM2 patients who were either drug naive or previously treated with oral diabetic medication and who had not achieved glycaemic control.	Intervention: metformin XR (1500 mg OD, 1000 mg BD, or 2000 mg OD) plus sulfonylurea Control: sulfonylurea monotherapy	Mean difference HbA1C: Intervention -0.74% [95% CI -0.85% to -0.64%]; FPG: -12.9 [95% -17.1 to -8.7] mg/dL) vs. control group (HbA1c, 0.08% [95% -0.08% to 0.25%]; FPG, 15.5 [95% 8.2 to 22.8] mg/dL; P < 0.001). A modest rise in plasma triglycerides was seen in the intervention group (140.2 +/- 74.8 vs. 202.9 +/-102.2 p=0.01).	Strengths: double-blind randomized design Limitations: no control group of patients using metformin IR.

IV.5 Clinical safety

Metformin
Data has been presented based on information in the SmPC of Glucophage 500mg film-coated tablets. Safety information based on publications has also been presented and is in alignment with other registered SmPCs in the Netherlands.

Extended-release formulation
Blonde et al (2004)[1] reviewed 471 patient charts and collected data from adult patients with type 2 diabetes started on metformin XR or switched from immediate-release metformin to metformin-XR within the previous 2 years. Patients switched from immediate release metformin to extended-release metformin experienced fewer gastro-intestinal adverse effects on comparable doses of metformin XR.

IV.6 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 Metformine HCl 1000 mg Focus.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	Lactic acidosis (occurring with or without renal failure/ impairment and/or concomitant use with iodinated contrast media)
Important potential risks	Leukocytoclastic vasculitis
Missing information	Use in pregnancy and lactation

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

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

[1] Blonde, Lawrence & Dailey, George & Jabbour, Serge & Reasner, Charles & Mills, Donna. (2004). Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: Results of a retrospective cohort study. Current medical research and opinion. 20. 565-72.

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 to the successfully user tested PL of Glucient SR 1000 mg prolonged-release tablets (NL/H/4819/001). 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

Metformine HCl 1000 mg Focus, prolonged-release tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Glucophage 500 mg, film-coated tablets. Glucophage 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this medicine with the reference product, and has therefore granted a marketing authorisation. Metformine HCl 1000 mg Focus was authorised in the Netherlands on 3 June 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse