CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zalmeber 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets Chemo Iberica S.A., Spain

telmisartan/hydrochlorothiazide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1994/001-003/DC
Registration number in the Netherlands: RVG 112308, 112310, 112312

11 December 2013

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA07
Route of administration:	oral
Therapeutic indication:	essential hypertension
Prescription status:	prescription only
Date of authorisation in NL:	6 November 2013
Concerned Member States:	Decentralised procedure with DE, IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Zalmeber 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets from Chemo Iberica S.A. The date of authorisation was on 6 November 2013 in the Netherlands.

The product is indicated for treatment of essential hypertension.
The fixed dose combination (telmisartan/hydrochlorothiazide) indicated for treatment of essential hypertension in adults whose blood pressure is not adequately controlled on telmisartan alone.

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

Telmisartan is an orally active angiotensin II receptor antagonist. Angiotensin II has an important role in the renin-angiotensin system by stimulation of the sympathetic activity, arteriolar vasoconstriction and water and salt retention. These effects result in an increase in blood pressure. Treatment with an angiotensin type 2 antagonist blocks this action and is therefore indicated for essential hypertension and renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medical product regimen.
Hydrochlorothiazide is a thiazide diuretic. It affects electrolyte reabsorption mechanisms in the kidney, by inhibition of the Na^+Cl^- symporter. The increased sodium and chloride excretion will result in a decreased plasma volume. The resulting plasma renin activity, aldosterone secretion and urinary potassium excretion is partially mediated by angiotensin II.
The combination of telmisartan and hydrochlorothiazide has an additive effect, reducing the blood pressure more than either medicine alone. By lowering the blood pressure, the risks associated with high blood pressure, such as having a stroke, are reduced.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets, registered since 19 April 2002 by Boehringer Ingelheim through a centralized procedure (MA numbers EU/1/02/213/001-023).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Micardis Plus 80 mg/25 mg tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are telmisartan and hydrochlorothiazide, established active substances that are both described in the European Pharmacopoeia (Ph.Eur.*). Telmisartan is a white or slightly yellowish crystalline powder, which is practically insoluble in water. The polymorphic form of telmisartan is Form A.
Hydrochlorothiazide is a white to almost white crystalline powder, which is very slightly soluble in water. The polymorphic form of hydrochlorothiazide is Form I.

The CEP procedure is used for both active substances. 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 European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Telmisartan
Quality control of drug substance
The MAH has provided a single compiled drug substance specification for telmisartan supplied by both suppliers. The specification is in line with the Ph.Eur. with the additional requirements as stated in the CEPs. The specification is acceptable for both sources in view of the route of synthesis and the various European guidelines. Sufficient batch analysis data have been provided.

Stability of drug substance
For telmisartan of one supplier the re-test period of the substance is 3 years with no specific storage conditions, when stored under the stated conditions. In this case, assessment thereof was part of granting the CEP and has been granted by the EDQM.
For telmisartan of the other supplier, assessment of stability was not part of granting the CEP. Therefore separate stability data have been included by the MAH covering a period of 36 months. Following the current guidelines, on the basis of the submitted real time data a re-test period of 3 years can be granted when stored under the stated conditions.

Hydrochlorothiazide
Quality control of drug substance
The Certificates of Suitability of both suppliers confirm that the drug substance is suitably controlled by the Ph.Eur. Monograph for hydrochlorothiazide. Sufficient batch analysis data have been provided.

Stability of drug substance
For hydrochlorothiazide of one supplier the re-test period of the substance is 5 years if stored at the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

For hydrochlorothiazide of the other supplier, assessment of stability was not part of granting the CEP. Therefore separate stability data have been included by the MAH covering a period of 24 months. Following the current guidelines, on the basis of the submitted real time data a re-test period of 2 years can be granted when stored under the stated conditions.

Medicinal Product

Composition
Zalmeber 40 mg/12.5 mg is a round bilayer tablet with white and yellow color.
Zalmeber 80 mg/12.5 mg is a round bilayer tablet with white and pink color.
Zalmeber 80 mg/25 mg is a round bilayer tablet with white and yellow color.

The tablets are packed in aluminium/aluminium blister packs.

The excipients are: mannitol (E421), povidone K 25 (E1201), crospovidone (E1202), magnesium stearate(E572), meglumine, sodium hydroxide, lactose monohydrate, cellulose microcrystalline (E460), hypromellose (hydroxy-propylmethylcellulose) (E464), sodium starch glycolate Type A, ferric oxide yellow (E 172 – 40/12.5 mg and 80/25 mg), ferric oxide red (E 172 – 80/12.5 mg).

All tablets are bilayer tablets. The 40 mg/12.5 mg and the 80 mg/25 mg strengths are fully dose proportional. The 80 mg/12.5 mg strength differs; for the telmisartan layer it is conform the 80 mg/25 mg strength and for the hydrochlorothiazide layer it is conform the 40 mg/12.5 mg strength. This results in a tablet with a weight in between the two other strengths and distinguishable by the colour (pink).

Pharmaceutical development
The aim of the formulation development was to develop a finished product which is equivalent, and as much similar as possible, to the innovator product Micardis Plus (immediate-release bilayer tablets) which has been authorised by the EMA on 19 April 2002 to Boehringer Ingelheim International GmbH. The development of the product has been described, the choice of excipients is justified and their functions explained. Manufacturing process development has been adequately described. Comparative dissolution data support that the test product is essential similar to the reference product. The bioequivalence study was performed against the German reference product. This is acceptable, as the originator product has been registered through a centralised procedure. The MAH demonstrated comparable dissolution profiles for telmisartan/hydrochlorothiazide tablets 80 mg/25 mg compared to 80 mg/12.5 mg and 40 mg/12.5 mg. The pharmaceutical development of the product been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: wet granulation is used to obtain granulates of the two active substances, after which both granulates are mixed with the rest of excipients separately; final blends of both active substances are compressed to get the bilayer tablets and subsequently these are packaged in Al/Al-blisters. The manufacturing process has been adequately validated.

Control of excipients
The excipients comply with the European Pharmacopoeia, except ferric oxide red and yellow, which comply with USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, water content, identification of both active ingredients, tablet hardness, uniformity of dosage units (content uniformity) of both active ingredients, assay of both active ingredients, dissolution of both active ingredients, related substances and microbial contamination. The release and end-of-shelf-life limits are identical except for the water content. The drug product specification is acceptable. The analytical methods have been adequately described. Validation data have been provided for the water content, dissolution method, impurities method and assay/content uniformity HPLC method. Batch analysis data have been provided for four pilot-scale batches per tablet strength. Compliance with the proposed release requirements is demonstrated. Batch analysis results of

commercial-scale batches are not provided. The MAH has declared that they will be available upon request.

Stability of drug product
Stability data on four pilot-scale batches of the 40/12.5 mg and 80/25 mg tablets and three pilot-scale batches of the 80/12.5 mg tablets have been provided. These were stored at 25°C/60% RH (12 months), 30°C/65% RH (12 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 Al/Al blisters. Despite some variability in the results for assay, no trends or changes were seen in any of the tested parameters. A photostability study has not been performed.
On the basis of the currently available data the proposed shelf-life of 24 months with storage condition 'Store in the original package (sealed blister) in order to protect from moisture and light' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used in the manufacture of telmisartan/hydrochlorothiazide tablets are of animal or human origin, except for lactose monohydrate. A declaration has been provided in section stating that this excipient has been prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01 rev 2. BSE statements are presented in this section as well. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Micardis Plus, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of telmisartan or hydrochlorothiazide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Telmisartan and hydrochlorothiazide are well-known active substances 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 a bioequivalence study in which the pharmacokinetic profile of the test product Zalmeber 80/25 mg (Chemo Iberica S.A., Spain) is compared with the pharmacokinetic profile of the reference product Micardis Plus 80/25 mg tablets (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study is justified, as it has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, four-period, two sequence, two-treatment, replicate, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male volunteers (non-smoking, age 19-52 years, with a BMI from 19.3 to 30.0 kg/m2). Each subject received a dose (80/25 mg) of one of the 2

telmisartan/hydrochlorothiazide formulations. The subjects fasted from 10 hours prior to drug administration and until 4 hours following drug administration. The tablet was orally administered with 240 ml water. Subjects were randomly assigned to one of the two dosing sequences TRTR or RTRT (T=test, R=reference). The treatment periods were separated by a wash-out period of 14 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 14, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The sampling schedule is sufficient to characterize the C_{max} of both analytes adequately and sufficiently long to characterise the absorption and elimination of telmisartan and hydrochlorothiazide appropriately. The replicate design is adequate to justify widening of the acceptance criteria for the C_{max} of telmisartan. Within-Subject-within-Reference CV% (38.49%) is larger than 30%. Therefore the MAH applied a wider bioequivalence acceptance range of 75.39 - 132.64%, which is in accordance with the guidelines.

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

Results
Forty subjects completed all four periods of the study. Two subjects discontinued during the study: one subject was dismissed due to weakness and vomiting in period 1 and the other subject withdrew consent during period 2. Since this subject completed period 1 and period 2 of the study, he was included in the analysis. Therefore forty-one subjects are included in the pharmacokinetic and statistical analysis.

Table 1. Telmisartan primary pharmacokinetic parameters, A = test, B = reference

Parameter	TRT	Means Arithmetic	Means CV%	Means Geometric	Contrast	Ratio	90% CI lower	90% CI upper	intra-sub CV(%)
Based on Measured Data									
AUC_{0-72} (ngh/mL)	A1	1865.61	82	1441.71	A vs. B	98.15	94.33	102.12	A: 15
	A2	1886.87	80						
	B1	1907.53	82	1468.90					B: 16
	B2	1895.53	76						
C_{max} (ng/mL)	A1	307.36	96	238.85	A vs. B	89.66	82.39	97.58	A: 27
	A2	313.96	90						
	B1	348.27	82	266.39					B:37
	B2	323.14	83						

Analyte: (A1 & B1: n = 41 / A2 & B2: n = 40 (Replicate Measures)) *ln-transformed *values*

For the test formulation the t_{max} was 2.21 ± 0.62 hours and for the reference formulation the t_{max} was 1.03 ± 0.48 hours.

Table 2. Results for hydrochlorothiazide

Treatment	AUC_{0-t} ng/ml/h	AUC_{0-inf} ng/ml/h	C_{max} ng/ml	$\frac{AUC_{0-t}}{AUC_{0-inf}}$ %	t_{max} h	t_{half} h	K_{el} l/h
Test	1120 ± 198	1150 ± 198	173 ± 38	97	1.50 ± 0.47	9.83 ± 0.97	0.07
Reference	1152 ± 205	1181 ± 216	185 ± 40	98	1.42 ± 0.41	9.60 ± 0.94	0.07

Table 3. Hydrochlorothiazide primary pharmacokinetic parameters, A = test, B = reference

Parameter	TRT	Means			Contrast	Ratio	90% CI		intra-sub
		Arithmetic	CV%	Geometric			lower	upper	CV(%)
Based on Measured Data									
AUC_{0-t} (ngh/mL)	A1	1125.778	18	1100.984	A vs. B	97.20	95.37	99.07	A: 8
	A2	1113.842	17						
	B1	1150.885	17	1132.663					B: 7
	B2	1153.749	19						
C_{max} (ng/mL)	A1	172.759	24	168.800	A vs. B	93.36	89.64	97.24	A: 17
	A2	174.100	20						
	B1	184.341	21	180.806					B:15
	B2	186.225	22						

Analyte: (A1 & B1: n = 41 / A2 & B2: n =40 (Replicate Measures))

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 80% – 125%. Based on the pharmacokinetic parameters of telmisartan/HCTZ under fasted conditions, it can be concluded that Zalmeber 80/25 mg and Micardis Plus 80/25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
Subjects were administered a single dose of the study medications 14 days apart, in four study periods. There were 65 adverse events involving 18 subjects in the study of which 63 were of mild intensity and two were of severe intensity. No serious adverse events were reported during the conduct of this study.

Telmisartan and hydrochlorothiazide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of telmisartan or hydrochlorothiazide. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
According to the CPMP guideline “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process
- The pharmacokinetics has been shown to be linear over the therapeutic range
- The qualitative composition of the different strengths is the same.
- The tablet formulation is a bi-layer tablet, the layers have the same qualitative and quantitative composition.
- The composition of the strengths is quantitatively proportional.
- The dissolution profiles should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study

The biowaiver for Micardis Plus 40 mg/12.5 mg and 80 mg/12.5 mg tablets can be granted. All requirements as outlined in the guideline on the investigation of bioequivalence were met.

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).

Risk management plan

The combination of telmisartan and hydrochlorothiazide was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of telmisartan and hydrochlorothiazide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The proposed SPC is considered acceptable. Besides the chemical-pharmaceutical information, the SPC is completely in line with that of the centrally approved innovator product Micardis Plus EU/1/02/213.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. Inclusion and exclusion criteria were well described. The target groups, who were considered to be potential users of telmisartan/hydrochlorothiazide, were people over 18 years of age. The interviewed population is acceptable.

The developed questionnaire contained 16 questions specific to Telmisartan/hydrochlorothiazide tablets and 3 questions specific to the format of the PIL. Prior to formulating the questions, the test administrator identified all the key safety messages in the PIL and then designed questions around those issues that would ensure a patient's comprehension and ability to act upon.

A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. The data showed that all questions met the passing criteria in the first and second round. Based on quantitative and qualitative results from testing, no edits were suggested to the PIL.

There were sufficient questions about the critical sections, and the areas concerning traceability, comprehensibility and applicability were sufficiently covered. The study report is detailed in describing the subjects, the study protocol, analysis of results.

The results of the test were satisfactory. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zalmeber 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets. Micardis Plus 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Zalmeber 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 July 2013. Zalmeber 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg, tablets were authorised in the Netherlands on 6 November 2013.

The date for the first renewal will be: 12 July 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform stability studies under proposed storage conditions on the first three industrial-scale production batches.
- The MAH committed to perform validation of manufacturing process on the first three industrial-scale production batches.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached