CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg, film-coated tablets HCS bvba, Belgium

losartan potassium / 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/1930/001/DC
Registration number in the Netherlands: RVG 106577

14 March 2011

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA01
Route of administration:	oral
Therapeutic indication:	essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.
Prescription status:	prescription only
Date of authorisation in NL:	7 March 2011
Concerned Member States:	Decentralised procedure with CZ, EL, ES, FR, HU, PL, SI, SK
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 Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg, film-coated tablets from HCS bvba. The date of authorisation was on 7 March 2011 in the Netherlands. The product is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

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

Losartan
Losartan is a synthetic oral angiotensin-II receptor (type *AT1*) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the *AT1* receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. Losartan selectively blocks the *AT1* receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis. Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects. Both Losartan and its principal active metabolite have a far greater affinity for the *AT1*-receptor than for the *AT2*-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

HCTZ
Hydrochlorothiazide is a thiazide diuretic which acts as by inhibiting fluid-expelling and blood pressure-lowering agent which increase the tubular re-absorption of sodium in the cortical diluting segment. It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

The components of losartan potassium/HCTZ tablets have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components.
Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Cozaar Plus 100 mg/12.5 mg (NL license RVG 32433), which has been registered in the Netherlands by Merck, Sharpe & Dome B.V. since 9 August 2006. In addition, reference is made to the innovator product Cozaar Comp 100mg/25 mg film-coated tablets, authorised since 1996 in Denmark (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In Spain and Poland the 100/12.5 mg formulation has not been authorised. In these countries the application is made according to art. 10(3) of Dir. 2001/83/EC, hybrid application, based on the reference medicinal product Hyzaar Forte 100/25 mg film-coated tablets registered in Spain and Poland.

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 Lorzaar Plus 100 mg/12.5 mg film-coated tablets, registered in Germany. 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 a paediatric development programme is not required for generics.

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 substance losartan potassium is a well-known substance, which is described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to almost white crystalline powder, which is freely soluble in water and soluble in ethanol and methanol. Different polymorphic forms are known.
The active substance hydrochlorothiazide is described in the Ph.Eur. It is a white to almost white crystalline powder, which is very slightly soluble in water, soluble in acetone and sparingly soluble in alcohol.

The Active Substance Master File (ASMF) procedure is used for the active substance losartan potassium. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the active substance hydrochlorothiazide. 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 new 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
The manufacture of losartan potassium consists of two main steps: synthesis of losartan and formation of the potassium salt. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material and solvents. For hydrochlorothiazide, assessment of the manufacturing process was part of the CEP approval.

Quality control of drug substance

The drug substances specifications are in line with resp. the DMF and the CEP. For both substances the specifications are acceptable in view of the route of synthesis and the various European guidelines, except for some solvents.
Batch analytical data demonstrating compliance with the drug substance specifications have been provided.

Stability of drug substance
Losartan potassium
Stability data on the active substance have been provided for three full-scale batches stored at 25 °C/60% RH (60 months) and 40 °C/75% RH (6 months). Moreover, stability data for three pilot-scale batches, stored at 25 °C/60% RH (60 months) and 40 °C/75% RH (6 months), have been provided. The batches were stored in the proposed commercial packaging.
No trends or out of specifications have been observed. The proposed re-test period of 4 years without special storage conditions is justified.

Hydrohclorothiazide
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**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.*

Medicinal Product

Composition
Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg is a white, oval, biconvex, film-coated tablet.

The film-coated tablets are packed in Al/PVC/PVDC blisters.

The excipients are:
Tablet core - pregelatinised maize starch, microcrystalline cellulose, lactose monohydrate, magnesium stearate.
Film-coating - hypromellose, macrogol 4000, talc, titanium dioxide (E171).

Pharmaceutical development
The development of the product has been described, the choice of excipients is acceptable. The wet granulating process, with water as granulating liquid, was chosen on the basis of data that were obtained in different experiments. The packaging and manufacturing process are justified.
Dissolution rates of losartan potassium and hydrochlorothiazide from the 100/12.5 mg tablets used in the bioequivalence were compared to the innovator product. The profiles were comparable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of sieving, mixing, granulation and drying steps, folllowed by compresion. A coating suspension is prepared and the cores are coated by continuous spraying of the coating suspension. After spraying, the film-coated tablets are kept rotating and dried. The film coated tablets are packed.
The manufacturing process has been sufficiently validated. The product is manufactured using conventional manufacturing techniques. Validation on production scale batches will be performed post-approval.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification of losartan, hydrochlorothiazide and titanium dioxide, uniformity of dosage units (content uniformity), dissolution of losartan potassium and hydrochlorothiazide, assay of losartan potassium and hydrochlorothiazide, related substances, water, hardness and microbiological purity. The release and shelf-life limits are identical, except for one hydrochlorothiazide impurity and total impurities. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided on three pilot-scale batches, stored at 25 °C/60% RH (24 months), 30 °C/60% or 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, except for the intermediate conditions for two of the pilot-scale batches. This was deemed acceptable. The batches were stored in the proposed Al/PVC-PVDC blister packaging.
Out-of-specification results were observed when the product was stored at accelerated and intermediate conditions: impurity levels were above the limits.
Photostability results have been provided on losartan potassium/HCTZ 50/12.5 mg and 100/25 mg products. The results show that the products are not light sensitive. Considering the similarity of the composition, the results also apply to the 100/12.5 mg product.
The granted shelf life, packaging material and storage conditions are: 24 months in PVC/PVDC-Alu blisters, when stored below 25 °C and in the original blister in order to protect from moisture.
The MAH committed to continue the stability testing on three pilot-scale batches at long-term, intermediate and accelerated conditions until the end of shelf-life. Three additional production-scale batches will be placed on stability testing.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only excipient of animal origin. A statement was provided, declaring that the milk is sourced from healthy animals in the same condition as the milk collected for human consumption.

II.2 Non-clinical aspects

This product is a generic formulation of Cozaar Plus 100 mg/12.5 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 losartan and 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

Losartan potassium and hydrochlorthiazide are a well-known active substances with established efficacy and tolerability. The use of the combination is also well established.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg (HCS bvba) is compared with the pharmacokinetic profile of the reference product Lorzaar plus forte 100 mg/12.5 mg (MSD, Germany).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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. Each subject received a single dose (100/12.5 mg) of one of the 2 losartan potassium/hydrochlorothiazide formulations. The tablet was orally administered under fasted conditions with 240 ml water. There were 2 dosing periods, separated by a washout period of 1 week.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products for determination of losartan and losartan carboxylic acid levels. For determination of hydrochlorothiazide levels blood samples were taken pre-dose and at 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 and 36 hours.

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
One subject was withdrawn from the study due to protocol violation. Fifty-nine volunteers completed the study and were included in the pharmacokinetic analysis.

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

Treatment N=59	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	733 ± 273	753 ±276	461 ± 239	1.33 (0.5-4.0)	2.1 ± 0.6
Reference	761 ± 276	783 ±280	482 ± 323	1.33 (0.5-4.0)	2.3 ± 0.9
***Ratio (90% CI)**	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.95 (0.86-1.05)	--	--
CV (%)	11	11	34	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

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

Treatment N=59	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3967 ± 1326	4049 ± 1330	695 ± 262	2.5 (1.67-6.0)	6.6 ± 1.5
Reference	4131 ± 1417	4212 ± 1426	715 ± 276	2.5 (1.67-6.0)	7.0 ± 1.5

***Ratio (90% CI)**	0.97 (0.94-0.99)	0.97 (0.95-0.99)	0.98 (0.94-1.02)	-	-
CV (%)	8	7	14	-	-
$AUC_{0-\infty}$ 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					

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=59	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	462 ± 94	509 ± 95	74 ± 19	2.0 (1.33-5.0)	9.5 ± 1.9
Reference	458 ± 110	505 ± 113	72 ± 19	2.0 (1.33-5.0)	9.3 ± 1.7
***Ratio (90% CI)**	1.02 (0.98-1.06)	1.01 (0.98-1.05)	1.03 (0.97-1.10)	--	--
CV (%)	12	10	20	--	--
$AUC_{0-\infty}$ 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					

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of losartan, losartan carboxylic acid and hydrochlorothiazide are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of losartan, losartan carboxy acid and hydrochlorothiazide under fasted conditions, it can be concluded that Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg and Lorzaar plus forte 100 mg/12.5 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Losartan and hydrochlorothiazide may be administered with or without food. From the literature it is known that food does not interact with the absorption of losartan and 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.

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 losartan potassium/hydrochlorothiazide was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile 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 SPC is in line with the product information of the innovator product, agreed during a Art 30 procedure. The SPC was updated in accordance with the latest PhVWP recommendations on pregnancy and lactation.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report was submitted. Results of User Testing on readability of Losartan/Hydrochlorothiazide KRKA tablets were submitted in the registration procedure CZ/H/0101/01/MR. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

Two documents comparing the differences between the two leaflets with differences highlighted and summarised have been submitted as well as the complete readability testing report of Losartan/Hydrochlorothiazide KRKA tablets.

The bridging is justified on the following grounds:
- Both products contain the same active ingredients, losartan potassium and hydrochlorothiazide.
- Both products are licensed for the same indication.
- Both products have the same route of administration.
- The precautions before taking the two products are similar.
- The instructions for taking the products are the same.
- The expected side effects of the two products are the similar.
- The package leaflets have common design and layout.

Besides, the PL for current product was also harmonized with PLL for Cozaar Comp film-coated tablets published as originators Article 30 - 'harmonisation' referral on 25/09/2008 and therefore, actually bridging for lay-out aspects should have been sufficient.

It is concluded that the proposed leaflet is legible, clear and easy to use and does not require additional readability testing. 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.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Cozaar Plus 100 mg/12.5 mg. Cozaar 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 Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on December 2010. Kaliumlosartan/hydrochlorothiazide HCS 100/12.5 mg, film-coated tablets was authorised in the Netherlands on 7 March 2011.

A European harmonised birth date has been allocated (15 February 1995) and subsequently the first data lock point for losartan-hydrochlorothiazide is February 2013. The first PSUR will cover the period from December 2010 to February 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 October 2013.

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

Quality - medicinal product

- The MAH committed to perform validation of the manufacturing process for the 100 mg + 12.5 mg strength on three production-scale batches.
- The MAH committed to continue the stability testing on three pilot-scale batches at long-term, intermediate and accelerated conditions until the end of shelf-life. Three additional production-scale batches will be placed on stability testing.

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
HCTZ	Hydrochlorothiazide
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
PhVWP	Pharmacovigilance Working Party
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