CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard Elpen Pharmaceutical Co. Inc., Greece

temozolomide

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/1666/001-006/DC
Registration number in the Netherlands: RVG 106603, 106604, 106607-106610

22 November 2010

Pharmacotherapeutic group:	antineoplastic and immunomodulating agents; other alkylating agents
ATC code:	L01AX03
Route of administration:	oral
Therapeutic indication:	newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment in adults; malignant glioma showing recurrence or progression after standard therapy in children from the age of three years, adolescents and adult patients.
Prescription status:	prescription only
Date of authorisation in NL:	4 November 2010
Concerned Member States:	Decentralised procedure with EL
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 Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard from Elpen Pharmaceutical Co. Inc. The date of authorisation was on 4 November 2010 in the Netherlands.

The product is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

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

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules, hard which have been registered through centralised procedure EU/1/98/096/001-008 by Schering Plough Europe since 26 January 1999. Further information can be found in the EPAR of Temodal (http://www.emea.europa.eu/htms/human/epar/).

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 20 mg and 250 mg product is compared with the pharmacokinetic profile of the reference products Temodal 20 mg and 250 mg capsules, hard, registered in the EU. 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. These generic products can be used instead of its reference product.

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

Scientific advice was given to the MAH on 14 June 2006 with regard to the possibility of obtaining a biowaiver for the product.
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 these product types 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 substance
The active substance is temozolomide, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to light tan/light pink powder, which is slightly soluble in water and methanol, and practically insoluble in ethanol. The active substance is not chiral. Temozolomide shows polymorphism. Only one form is used in the product at issue.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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.

Manufacturing process
The manufacturing process of the drug substance consists of two main steps. Sufficient information on the starting materials and synthesis has been provided.

Quality control of drug substance
The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. The control of the drug substance performed by the manufacturer has been satisfactorily described. Batch analysis data from three batches of drug substance have been provided, demonstrating compliance with the specification.

Stability of drug substance
Drug substance batches have been stored for up to 24 months at long term stability conditions, and up to 6 months at accelerated conditions. Based on the stability data presented, the proposed a retest period of 3 years is deemed acceptable.

** 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
Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules have a white opaque body and cap with two stripes on the cap. These stripes are green, orange, pink, blue, red and black, respectively, as well as the ink imprint *T 5 mg, T 20 mg, T 100 mg, T 140 mg, T 180 mg or T250 mg* on the body.

The hard capsules are packed in amber glass bottles with white polypropylene child-resistant screw cap equipped with an induction seal of polyethylene.

The excipients are:

Capsule content - anhydrous lactose, sodium starch glycolate Type A, colloidal anhydrous silica, tartaric acid, stearic acid
Capsule shell - gelatin, titanium dioxide (E171)
Printing ink - 5 mg: shellac, propylene glycol, titanium dioxide (E171), yellow iron oxide (E172), indigo carmine aluminium lake (E132)
20 mg: shellac, propylene glycol, titanium dioxide (E171), sunset yellow aluminium lake (E110)
100 mg: shellac, propylene glycol, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172)
140 mg: shellac, propylene glycol, indigo carmine aluminium lake (E132)
180 mg: shellac, propylene glycol, red iron oxide (E172)
250 mg: shellac, propylene glycol, black iron oxide (E172).

The ratio between amounts of active substance and excipients is the same within the strength range from 100 mg to 250 mg, these capsules are therefore dose proportional. The 5 mg and 20 mg strengths are not dose proportional compared to the higher strengths; the amount of active substance is low (5%) and the amount of excipients of the 5 mg strength is similar to that of the 20 mg strength except a small increase in lactose to compensate for the lower amount of active substance.

Pharmaceutical development
The pharmaceutical development is adequately described in accordance with the relevant European guidelines. The choice of manufacturing process and excipients has been adequately justified. The primary packaging material was chosen in view of the requirements for packaging of hard capsules. The choice is supported by the results of the stability studies on the finished product packed in glass bottles.
Dissolution studies of the innovator product demonstrated that more than 85% of the drug was released in 15 minutes in three different media. The *in vitro* dissolution profile of the product at issue was shown to be similar for the different tablet strengths. The 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strengths versus the 250 mg strength were observed to be similar. In all media more than 85% was released after 15 minutes. The pharmaceutical development has been adequately performed.

Manufacturing process
A straight-forward manufacturing process is used, including defined mixing sequences and filling into pre-printed capsules. The manufacturing process is regarded as a non-complex method. Results from the process validation studies confirm that the process is under control and ensures both batch-to-batch reproducibility and compliance with the product specification. Process validation has been performed at the maximum proposed batch size of the powder blends. The manufacturing process has been adequately validated.

Control of excipients
All of the excipients of the capsule fill and the gelatine of the hard capsules comply with the monographs of the current Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specification includes tests for appearance, identification, assay, related substances, uniformity of dosage units, dissolution, water content and microbial limits. The tests and limits in the specification are considered appropriate to control the quality of the finished product. Method descriptions and reports on analytical validations are provided.
Batch analysis results have been provided on two batches of each strength, demonstrating compliance with the proposed specifications.

Stability of drug product
Stability data have been provided on production-scale batches of each strength, stored at long-term storage conditions for 24 months and at accelerated conditions for 6 months.
For all strengths an increase at accelerated conditions for the main degradation product was observed. No significant changes of other relevant parameters have been observed at any storage condition. A photostability study has been performed on one batch of each strength. Since the product concerns a

toxic drug product, it is considered acceptable that the capsules were not directly exposed to the photolytic conditions, *i.e.* out of the original packaging. The photostability data for all the primary packaged dosages demonstrated that the chosen packaging configuration protects the product from light.
Based on the stability data presented, the proposed shelf-life of 2 years could be granted. The applicable storage condition is 'Store in the original package. Keep the bottles tightly closed in order to protect from moisture'.

Several post-approval commitments have been made with regard to the finished product; these can be found on page 9 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All raw materials used in the product are of vegetable origin/have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

II.2 Non-clinical aspects

This product is a generic formulation of Temodal, 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 temozolomide 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

Temozolomide is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test products Ridoca 250 mg (test 1) and 20 mg (test 2) hard capsules (Elpen Pharmaceutical Co. Inc, Greece) is compared with the pharmacokinetic profile of the reference products Temodal 250 mg (reference 1) and 20 mg (reference 2) hard capsules (Schering-Plough Ltd, Germany).

The choice of the reference product
It is considered to be unnecessary to demonstrate that the dissolution profiles in the various European countries are identical, because the innovator's product is registered by means of a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-centre, crossover, controlled bioequivalence study was carried out under fasted conditions in 29 cancer patients (18 males/11 females), aged 21-69 years. A bioequivalence study in patients is considered acceptable since temozolomide is a cytotoxic substance and is not suitable for administration in healthy volunteers.
Planned chemotherapy consisted of 4 up to 6 treatment cycles of temozolomide. One treatment cycle comprised of: 200 mg/m^2 temozolomide orally per day for 5 consecutive days/cycles (aiming at obtaining a final dose of 1000 mg/m^2 in 5 days), followed by a 23 days treatment interruption (in total one cycle lasts 28 days). Temozolomide was administered in a dose of 200 mg/m^2 for 5 consecutive days at a 4 weeks interval as multiple of 250 mg or 20 mg hard capsules in cycles 1, 3, 4 to 6. No blood sampling for pharmacokinetic profiling was performed during these treatment cycles.

Only in cycle 2 blood sampling for pharmacokinetic evaluation was performed. During treatment cycle 2 each subject received 1 capsule of either test 1 or reference 1 (250 mg) in a randomised fashion at days 1 and 2 of the cycle, and varying doses of test 2 or reference 2 (20 mg) in a randomised fashion at days 3 and 4 of the cycle. Actual doses provided using the 20 mg capsules ranged from 340-660 mg (17-33 x 20 mg capsules), each patient received the same dose on days 3 and 4. Blood samples for pharmacokinetic evaluation were collected was done during these days. At day 5 of cycle 2 the patients received a combination of test 1 (250 mg) and test 2 (20 mg) products in order to obtain a total dose of 1000 mg/m^2 in 5 days. For this bioequivalence assessment only Cycle 2 is considered. Safety parameters collected during cycle 1 and 2 are presented.

In this study there is a washout period of less than one day, since equal doses were administered at subsequent days. However, considering the very short $t_{1/2}$ of temozolomide (approximately 2-3 hours in this study) this is considered acceptable. This is supported by the fact that no carry-over is detected in any patient.
The drug was administered with 240 ml of water, after an overnight fast of 10 hours. The patients kept a standing position during treatment intake.
During the pharmacokinetic determination days (days 1 to 4 of the second treatment cycle) venous blood samples were taken at the following time points: before temozolomide administration (time 0) at 10 minutes, 20 minutes, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post-dose.

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
Twenty seven patients were evaluable for pharmacokinetic profiling. Two subjects dropped out: one subject due to death (not related to medication) and another due to haematological toxicity resulting in non-compliance to inclusion criteria for the next cycle.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of temozolomide under fasted conditions – 250 mg capsule, (test 1/ reference 1)

Treatment N=27	**AUC_{0-t}** microg.h/ml	**$AUC_{0-\infty}$** microg.h/ml	**C_{max}** microg/ml	**t_{max}** h	**$t_{1/2}$** h
Test 1	22.8 ± 5.9	23.5 ± 5.7	7.1± 2.7	1.0 (0.33-6.0)	2.1± 0.5
Reference 1	22.7 ± 5.3	23.3 ± 5.3	7.3 ± 2.1	0.75 (0.17-6.0)	2.1± 0.3
***Ratio (90% CI)**	1.00 (0.96-1.04)	1.00 (0.97-1.04)	0.94 (0.85-1.04)	--	--
CV (%)	8.7	6.9	21.0	--	--

$AUC_{0-\infty}$ 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 temozolomide under fasted conditions – 20 mg capsule, (test 2/

reference 2) *NB. actual dose given ranged from 340-660 mg (17-33 x 20 mg capsule), each patient received the same dose of test and reference*.

Treatment N=27	AUC_{0-t} microg.h/ml	$AUC_{0-\infty}$ microg.h/ml	C_{max} microg/ml	t_{max} h	$t_{1/2}$ h
Test 1	41.0 ± 6.3	41.7 ± 6.3	14.1 ± 3.0	0.5 (0.17-1.33)	1.9 ± 0.17
Reference 1	40.1 ± 5.0	40.6 ± 5.1	13.8 ± 3.5	0.75 (0.33-3.0)	1.9 ± 0.15
***Ratio (90% CI)**	1.02 (1.00-1.04)	1.02 (1.00-1.04)	1.03 (0.94-1.13)	-	-
CV (%)	4.7	4.7	19.1	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

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 0.80-1.25. Based on the pharmacokinetic parameters of temozolomide under fasted conditions, it can be concluded that Ridoca 250 mg and 20 mg are bioequivalent with Temodal 250 and 20 mg hard capsules with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Administration of Temozolomide with food results in a 33 % decrease in C_{max} and a 9% decrease in AUC. As it cannot be excluded that the change in C_{max} is clinically significant, temozolomide should be administered without food. 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.

Extrapolation to different strengths
The 100 mg, 140 mg and 180 mg strengths are dose-proportional to the 250 mg. Since all other requirements are also fulfilled, data obtained for the 250 mg strength can be extrapolated to these strengths. The 5 mg strength is not dose proportional but amount of active substance is low (5%) and the ratio between excipients is similar to that of the 20 mg strength. Dissolution was demonstrated to be rapid and complete for all strengths. Considering the fact that temozolomide is a BCS class I drug, absorption is not expected to be affected by the quantitative difference in excipients. Therefore, a waiver was also granted for the 5 mg strength.

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).

Safety
Sixty-five non-serious adverse events of mild and moderate intensity occurred in 27 subjects in the present study until the end of the second cycle.
Besides these non-serious events, one serious adverse event occurred. One subject died as a result of progression of the underlying disease with metastases in the brain and cerebral oedema. Death was not related to the study medication.
The other study procedures required by the protocol and accordingly applied to the participant volunteers (e.g. venipuncture) were very well tolerated by the participant subjects.

Risk management plan

Temozolomide was first approved in 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of temozolomide 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 has been adapted to the latest version of the Temodal SPC. All sections have been revised as requested during the decentralised procedure.

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 3 participants, followed by two rounds with 10 participants each. Participants were a total of 9 males and 11 females, aged 22 to 47 years and with varying educational background. The subjects were asked 14 questions related to safety and compliance issues, such as indication, dosage, warnings and side effects plus 3 additional questions regarding the general design and layout of the leaflet. The questions were open and randomly ordered. The most important aspects of the leaflet are covered by the test, and the questionnaire is considered acceptable. Amendments were made between the pilot study and the first test round. Minor changes in the mock-up layout of the PIL were made; subheadings were added or changed in section 2 and 3. Also, 2 questions in the User test questionnaire were rephrased and one question was omitted.

Both the first and the second test round met the success criteria of 90 % of the subjects being able to locate the requested information, and of those, 90 % being able to give the correct answer, to indicate that they understood the information presented.

The general impression of the PIL (content, language and layout) was mostly positive. In conclusion, the user test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules, hard. Temodal 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, package leaflet and labelling are in the agreed templates and are in agreement with the reference's product information.

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 Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 24 September 2010. Ridoca 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules, hard were authorised in the Netherlands on 4 November 2010.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from September 2010 to September 2013.

The date for the first renewal will be: 24 September 2015.

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

Quality - active substance
- The MAH committed to add one batch to the long-term stability program each year.

Quality - medicinal product
- The MAH committed to continue the ongoing long-term stability study (25°C±2°C/60%±5%RH) up to 36 months.
- The MAH committed to place additional production-scale batches on stability.
- The MAH committed to evaluate the limits for total impurities when more data are available.
- The MAH committed to perform hold-time stability testing over 12 weeks on one batch of 5 mg capsules and one batch of 250 mg capsules.
- The MAH committed to perform in-use stability testing for a period of 3 weeks.

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
MTIC	Monomethyl Triazenoimidazole Carboxamide
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
RT	Radiotherapy
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