CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Risperidon Aurobindo 0.5/1/2/3/4/6 mg film-coated tablets Aurobindo Pharma Limited, UK

risperidone

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/1957/001-006/MR
Registration number in the Netherlands: RVG 33495-33500

14 September 2010

Pharmacotherapeutic group:	other antipsychotics
ATC code:	N05AX08
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episodes associated with bipolar disorders; persistent aggression in patients with moderate to severe Alzheimer's dementia; persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria.
Prescription status:	prescription only
Date of first authorisation in NL:	21 February 2008
Concerned Member States:	Mutual recognition procedure with DE, IT, PT, and UK
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 Risperidon Aurobindo 0.5 mg,1 mg, 2 mg, 3 mg, 4 mg, and 6 mg film-coated tablets, from Aurobindo Pharma Limited. The date of authorisation was on 27 August 2009 in the Netherlands. The product is indicated for:

- treatment of schizophrenia
- treatment of moderate to severe manic episodes associated with bipolar disorders.
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others
- short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment

Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

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

Risperidon Aurobindo contains the active ingredient risperidone, which is an atypical antipsychotic that combines the known antipsychotic effects of dopamine antagonism, seen in classical antipsychotic, with serotonin antagonism.
Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone also binds to $alpha_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and $alpha_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Risperdal 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 6 mg tablets (NL license RVG 22714, 16096, 16097, 16098, 16099 and 19585) which have been registered in the Netherlands by Janssen-Cilag B.V. since 1999 (0.5 mg) 1994 (1 mg, 2 mg, 3 mg, 4 mg) and 1998 (6 mg, marketing authorization withdrawn on 31 December 1998 for commercial reasons) (original product). The data-protection period is determined by the reference product Risperdal, authorised since 1992 in the UK. In addition, reference is made to Risperdal authorisations in the individual member states (reference product).

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Risperdal 2 mg tablets, registered in the UK. 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 generic medicinal products.

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 substance
The active substance is risperidone, an established active substance described in the Ph. Eur.*. The active substance is practically insoluble in water, sparingly soluble in ethanol 96% and freely soluble in methylene chloride. It shows polymorphism. 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 suitablity 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
This is covered by the Certificate of Suitability.

Quality control of drug substance
The drug substance specification is in line with the Certificate of Suitability. The specifications of the Ph. Eur. have been adopted, together with the additional test and requirement from the CEP, an additional requirement for benzene NMT 0.6 ppm and additional tests and requirements for heavy metals, particle size distribution and microbial quality. The specification is acceptable in view of the Certificate of Suitability and the various European guidelines. Results of batch analysis have been provided of several batches including three commercial batches tested by the drug product manufacturer on compliance with the current drug substance specifications. All results comply.

Stability of drug substance
The active substance is stable for 24 months, without specific storage conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur., USP, BP 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
Risperidon Aurobindo 0.5 mg are green, biconvex, capsule-shaped, film-coated tablets inscribed with *'A'* on one side and *'50'* on the other side. Scored between *'5'* and *'0'*. The tablet can be divided into equal halves.
Risperidon Aurobindo 1 mg are white, biconvex, capsule-shaped, film-coated tablets inscribed with *'A'* on one side and *'51'* on the other side. Scored between *'5'* and *'1'*. The tablet can be divided into equal halves.
Risperidon Aurobindo 2 mg are light orange, biconvex, capsule-shaped, film-coated tablets inscribed with *'A'* on one side and *'52'* on the other side. Scored between *'5'* and *'2'*. The tablet can be divided into equal halves.
Risperidon Aurobindo 3 mg are yellow, biconvex, capsule-shaped, film-coated tablets inscribed with *'A'* on one side and *'53'* on the other side. Scored between *'5'* and *'3'*. The tablet can be divided into equal halves.
Risperidon Aurobindo 4 mg are green, biconvex, capsule-shaped, film-coated tablets inscribed with *'A'* on one side and *'54'* on the other side. Scored between *'5'* and *'4'*. The tablet can be divided into equal halves.
Risperidon Aurobindo 6 mg are green, biconvex, tablets inscribed with *'A'* on one side and *'55'* on the other side.

At the time of writing there was a mistake in the SPC regarding the composition of the Risperidon Aurobindo 6 mg tablets (colour and shape). The MAH committed to correct this by means of a post-approval type IA variation.

The excipients are:
Tablet Core – lactose monohydrate, cellulose, microcrystalline (E 460), colloidal anhydrous silica, magnesium stearate (E470b).
Film coating:
0.5 mg and 4 mg film-coated tablets:
Opadry green 03B51373 containing: hypromellose (E464), titanium dioxide (E171),macrogol (PEG 400), quinoline yellow (E104), indigotine (E132).

1 mg and 6 mg film-coated tablets:
Opadry white Y-1-7000 containing:
hypromellose (E464)
titanium dioxide (E171)
macrogol (PEG 400)

2 mg film-coated tablets:
Opadry orange 03B53576 containing:
hypromellose (E464)
titanium dioxide (E171)
macrogol (PEG 400)
yellow iron oxide (E172)
red iron oxide (E172)
black iron oxide (E172)

3 mg film-coated tablets:
Opadry yellow 03B52852 containing:
hypromellose (E464)
titanium dioxide (E171)
macrogol (PEG 400)
quinoline yellow iron oxide (E172) (E104)

The excipients and packaging are usual for this type of dosage form.

The quantitative composition is dose proportional for the 1 mg, 2 mg, 3 mg and 4 mg tablets whereas the 0.5 mg and 1 mg tablets and the 4 mg and 6 mg tablets are manufactured as similar formulations with a small difference in the contents of lactose to compensate the difference in active substance.

The film-coated tablets are packed in Clear PVC/PE/PVDC/Aluminium foil blister packs and white opaque round HDPE bottles closed with white opaque polypropylene closure.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Particle size distribution and polymorphic form of the active substance have been defined. The composition is based on the composition and dissolution of the reference product. Compatibility with the excipients has been demonstrated. The products used in the bioequivalence study are acceptable. A waiver for other strengths has been justified acceptably from chemical-pharmaceutical point of view. The pharmaceutical development of the product has been adequately performed. Adequate breakability has been demonstrated.

Manufacturing process
The process is a straight-forward wet granulation process. The components of the tablet core are sieved and blended. Wet granulation (using water) is applied to obtain granules. After adding magnesium stearate the granules are compressed into tablets. The tablets are then coated.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for small blend batches.

Container closure system
The drug product is packaged in blister packs consisting of clear PVC (250µm) / PE (25 µm) / PVDC and aluminium foil with a heat seal lacquer coating or in white opaque HDPE container with white opaque polypropylene closure. It is declared that the components comply with the Ph. Eur. requirements and applicable European Directives.

Excipients
The excipients comply with Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification active substance and colorant, average weight, uniformity of dosage units by content uniformity, water content, dissolution, assay active substance, degradation products, and microbial purity. Release specifications for impurity C and Total impurities are tighter than the shelf-life specification. Adequate validations have been provided. Results of batch analysis have been provided of two batches of all strengths from the proposed production site. These batches were manufactured from smaller proposed blend batch sizes. As these blend sizes are the currently approved batch sizes, the provided data are sufficient. The results demonstrate compliance to the set specifications.

Breakability
The tablet strengths 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg bear a score line. Results are included of testing subdivision of tablets (breakability study results), two batches per strength, at the end of the current shelf-life of 24 months stored in blister. The results demonstrate compliance with the Ph. Eur. requirement of the Monograph Tablets. As no change in water content is observed in the stability studies for both the blister and HDPE tablet container packaging, it is acceptable that these results are extrapolated to the HDPE tablet container and the whole shelf-life.

Overages
An overage is used for the manufacture of the coating suspensions.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth.The microbial contamination test as per the requirements of European Pharmacopoeia was carried

out on the submission batches of risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg tablets. The results comply with the requirements of Ph.Eur 5.1.4 (category 3).

Stability tests on the finished product
Stability data on the product has been provided for two small batches of all strengths packed in both the blister- and tablet container packaging and covering 24 months storage at 25°C/60%RH and 6 months at 40°C/75%RH. Batches packed in blister were also stored for 12 months at 30°C/70%RH. The conditions used in the stability studies are according to the ICH stability guideline. For the products packed in the clear PVC/PE/PVdC-Aluminium foil blister, the data obtained from samples stored at 30°C/70% RH show that the levels of impurity K and L increase considerably in the 0.5 mg strength batches during 12 months storage. The 1 mg strength shows increase in these levels as well but less pronounced. At accelerated conditions, it is observed that out of specification results are observed for impurities K and L for strengths 0.5 mg and 1 mg. For the product packed in the HDPE tablet container also an increase in impurity L is observed at accelerated conditions, yet remain with the shelf life specification of NMT 0.5%. The tablets were found to be photo stable. The results support the proposed shelf-life of 24 months when stored not above 25°C for both the blister- and tablet container packaging.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Risperdal, 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 risperidone 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Risperidon Aurobindo 2 mg film-coated tablets (Aurobindo Pharma Limited, UK) is compared with the pharmacokinetic profile of the reference product Risperdal 2 mg tablets (Janssen-Cilag, UK).

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.

Study design
A single-dose, randomised, two-treatment, two-sequence, two-period, cross-over bioequivalence study was carried out under fasted conditions in 34 healthy male volunteers, aged 18-40 years. Each subject received a single dose (2 mg) of one of the 2 risperidone formulations. The tablet was orally administered

with 240 ml water after a 10 hour fasting period. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 48, 72, and 96 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Risperidone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of risperidone. 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*.

Results
Six subjects were withdrawn from the study because of fever (Period II), and one subject was withdrawn because of fever and cough in Period II. Another subject was withdrawn because of drug abuse, (vomiting before drug administration in Period II), and one subject was withdrawn because of a fracture.
Twenty-five subjects were eligible for pharmacokinetic analysis. Although the MAH stated that the subject with the fracture was withdrawn, this subject was included in the statistical analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	****$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	86.1 ± 61.3	84.5 ± 59.9	15.7 ± 6.8	1.0 (0.75 – 2.50)	5.9 ± 4.2
Reference	92.5 ± 81.9	91.6 ± 82.3	16.9 ± 6.5	1.0 (0.75 – 3.50)	5.5 ± 3.8
***Ratio (90% CI)**	0.96 (0.86 - 1.07)	0.96 (0.86 - 1.07)	0.92 (0.83 - 1.02)	---	---
CV (%)	21.9	21.7	20.5	---	---
$AUC_{0-\infty}$ 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*
*** AUC0-inf was based upon data of 24 subjects, as for one subject (no. 2) the elimination phase of the curve could not be accurately determined (coefficient of correlation < 0.8).*

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 risperidone under fasted conditions, it can be concluded that Risperidon Aurobindo 2 mg film-coated tablets and Risperdal 2 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results to the other strengths
The 1, 3 and 4 mg tablets are dose-proportional with the 2 mg tablet. The 6 mg tablet has the same qualitative composition as the 4 mg tablet and the 0.5 mg tablet has the same qualitative composition as the 1.0 mg tablet. For all concerned strenghts, the relative amount of active substance is less than 5% and

the ratio between the amounts of excipients is similar. Dissolution profiles are comparable as well. Therefore, it is acceptable to extrapolate the results obtained for the 2 mg tablet to the 0.5, 1, 3, 4 and 6 mg tablets.

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

Risperidone was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of risperidone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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 SPCs have been brought in line with the SPC of the innovator product Risperdal, which was harmonised during the referral procedure EMEA/H/A-30/911. In addition, the SPCs have been updated with the core wording of the relation between antipsychotics and venous thromboembolism (VTE), which has been agreed upon in the PhVWP.
The MAH committed to correct a mistake in the SPC (shape and colour of 6 mg tablets) by means of a post-approval type IA variation.

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 MAH stated that Risperidon Aurobindo filmcoated tablets are duplicates of Risperidone Aurobindo filmcoated tablets and that the product formula, the proposed SPC and the medical and technical text in the product information are therefore identical.
Furthermore, the applicant states that the proposed PIL for the MRP is identical to the PIL already approved during a national procedure in The Netherlands.

The proposed PIL of Risperidon Aurobindo 0,5, 1, 2, 3, 4 and 6 mg film-coated tablets is in line with the approved text of the innovator Risperdal after the article 30 procedure EMEA/H/A-30/911. The member states consider the justification for the absence of a readability test for Risperidone Aurobindo 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 6 mg filmcoated tablets acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risperidon Aurobindo 0.5/1/2/3/4/6 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Risperdal 0.5/1/2/3/4/6 mg tablets. Risperdal 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. Risperidon Aurobindo 0.5/1/2/3/4/6 mg film-coated tablets were authorised in the Netherlands on 27 August 2009.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Risperidon Aurobindo 0.5/1/2/3/4/6 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 7 June 2010.

The EHBD will be followed for PSUR submissions. This means the first PSUR will be submitted in July 2012 (DLP = May 2012). Afterwards the PSUR cycle is 3 years.

The date for the first renewal will be: January 2013.

There were no post-approval commitments made during the procedure.

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