CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cisplatine 0,5 mg/ml PCH, concentrate for solution for infusion
Cisplatine 1 mg/ml PCH, concentrate for solution for infusion
Pharmachemie B.V., the Netherlands

cisplatin

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/1251/001-002/DC
Registration number in the Netherlands: RVG 101429, 101430

7 September 2009

Pharmacotherapeutic group:	other antineoplastic agents, platinum compounds
ATC code:	L01XA01
Route of administration:	intravenous use
Therapeutic indication:	advanced or metastasised testicular, ovarian, bladder cancer, squamous cell carcinoma of the head and neck, (non-)small cell lung carcinoma, cervical carcinoma
Prescription status:	prescription only
Date of authorisation in NL:	16 January 2009
Concerned Member States:	Decentralised procedure with AT, BE, CY, CZ, DE, EE, EL, ES, FR, IE, IT, LT, LU, LV, MT, PL, RO, SI, UK (PT and SK only 1 mg/ml)
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 Cisplatine 0,5 mg/ml PCH, concentrate for solution for infusion and Cisplatine 1 mg/ml PCH, concentrate for solution for infusion from Pharmachemie B.V.. The date of authorisation was on 16 January 2009 in the Netherlands.

The product is indicated for the treatment of:

- advanced or metastasised testicular cancer
- advanced or metastasised ovarian cancer
- advanced or metastasised bladder carcinoma
- advanced or metastasised squamous cell carcinoma of the head and neck
- advanced or metastasised non-small cell lung carcinoma
- advanced or metastasised small cell lung carcinoma

Cisplatin is indicated in combination with radiotherapy in the treatment of cervical carcinoma.
Cisplatin can be used as monotherapy and in combination therapy.

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

Cisplatin is an inorganic compound which contains a heavy metal [cis-diamminedichloridoplatinum(II)]. It inhibits DNA-synthesis by the formation of DNA cross-links. Protein and RNA synthesis are inhibited to a lesser extent.
Although the most important mechanism of action seems to be inhibition of DNA synthesis, other mechanisms can also contribute to the antineoplastic activity of cisplatin, including the increase of tumour immunogenicity. The oncolytic properties of cisplatin are comparable to the alkylating agents. Cisplatin also has immunosuppressive, radiosensitising, and antibacterial properties. Cisplatin seems to be cell-cycle non-specific. The cytotoxic action of cisplatin is caused by binding to all DNA-bases, with a preference for the N-7 position of guanine and adenosine.

This decentralised procedure concerns a generic application claiming essential similarity with the historical reference product Platinol, (NL RVG 09987) which was registered in the Netherlands by Bristol-Myers Squibb B.V. in 1982 (original product), and withdrawn in December 2000. Other identical products are on the market.

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

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

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. As Cisplatine 0,5 mg/ml PCH and Cisplatine 1 mg/ml PCH are products in aqueous solution for parenteral use, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product is essentially similar to its reference product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

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

General information
The active substance is cisplatin, an established active substance described in the European, United States and British Pharmacopoeia. (Ph.Eur., USP, BP*) The active substance is slightly soluble in water.

For one of the suppliers, 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/EMEA 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.

For the other two suppliers, the CEP procedure is used. 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.

Manufacture
The manufacturing process of cisplatin, described in the ASMF consists of three steps. In the last step deionized water and hydrochloric acid are used. The active substance has been adequately characterized in the ASMF and acceptable specifications have been adopted for the starting material, solvents and reagents.

Specification
The drug substance specification of the applicant is in line with the CEPs, DMF and the Ph.Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches per drug substance provider. The MAH committed to tighten the limit for the insolubles test for one of the active substance manufacturers.

Stability
For one supplier, stability data on the active substance have been provided for three batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No out of specifications have been observed. A retest period of three years without storage conditions was granted.
For the second supplier, it has been established that the active substance is stable for four years when stored in a high-density polyethylene container inside a polyethylene bag. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
For the third supplier, information on unknown impurities during storage is missing. Therefore, neither a retest period nor storage conditions could be granted. The MAH committed to provide information on photostability for one of the active substance manufacturers. Since this information is not yet available, the drug product should be stored in the original package.

For the retest period, the MAH refers to the CEPs and the DMF. Moreover, the MAH states that cisplatin drug substance will be retested at Pharmachemie after a storage period of 2 years at NMT 25ºC. This is acceptable for the drug substance from the second supplier. The granted retest period of the drug substance from the first supplier is 36 months without a storage conditions. However, questions are raised regard to the stability information included by the third supplier. Therefore, neither a retest period nor storage conditions can be granted for the drug substance from the third supplier.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Cisplatine 0,5 mg/ml PCH contains as active substance 0.5 mg/ml of cisplatin, and is a clear, light yellow solution free from visible particles.
The concentrate for solution for infusion is packed in brown, type I glass vials of 20, 50 and 100 ml with butyl rubber stop, aluminium closing and plastic snap-cap.

Cisplatine 1 mg/ml PCH contains as active substance 1 mg/ml of cisplatin, and is a clear, light yellow solution free from visible particles
The concentrate for solution for infusion is packed in brown, type I glass vials of 10, 50 and 100 ml with butyl rubber stop, with aluminium closing and plastic snap-cap.

The excipients for both strengths are: water for injections, sodium chloride, hydrochloric acid for pH adjustment, sodium hydroxide for pH adjustment.

The excipients and packaging are usual for this type of dosage form. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Sterilisation of the drug product is performed by aseptic filtration through a sterilising membrane filter and the solution is aseptically filled in sterilized vials. The choice for this sterilisation process is sufficiently justified. The pharmaceutical development of the products has been adequately performed.

Manufacturing process
Sodium chloride is dissolved in part of the water for injections. The pH of the solution is adjusted and cisplatin is dissolved in the solution while protecting the solution from light. Water for injections is added to final weight and homogenised. The solution is filtered and aseptically filled in the vials. The filtration of the bulk solution is performed prior to filling into a stainless steel container instead of in-line while filling the vials.
The manufacturing process has been described into sufficient detail. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for 3 batches of each strength in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation. The vials are sterilised by dry-heat in a sterilisation tunnel at a temperature of NLT 290°C for not less than 3 minutes.

Quality control of drug product
The finished product specification is adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, extractable volume, particulate contamination, closure integrity, assay of sodium chloride, assay of trichloroammineplatinate, related substances, assay of cisplatin, sterility and bacterial endotoxins. The release and shelf-life requirements are identical except for pH, assay of trichloroammineplatinate, total related substances and assay of cisplatin. The parameters and requirements were deemed acceptable.

The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three batches per strength, demonstrating compliance with the release specification. The results all comply with the specification. The MAH committed to provide certificates of analysis of batches of the drug product with drug substance from one of the active substance suppliers.

Stability tests on the finished product
Stability data on the product has been provided for three 0.5 mg/ml batches of 20 ml as well as 100 ml volume and for three 1.0 mg/ml batches of each volume. The batches are of pilot scale and are stored at 25°C/60% RH (at least 38 months) and 40°C/75% RH (6 months). The 0.5 mg/ml products are also stored at intermediate conditions for 12 months. For the 1.0 mg/ml product, only the lower volume (10 ml) is stored at intermediate conditions (12 months). The conditions used in the stability studies are according to the ICH stability guideline.
For the 0.5 mg/ml product out of specifications were seen for one impurity if stored at accelerated conditions. For the 1.0 mg/ml product out of specifications for the same impurity only occurred for the 10 ml volume but after storage at as well accelerated as long term conditions. From the results it appears that some batches which are stored inverted, show more degradation than when stored upright. The MAH committed to place two production scale batches per volume of each supplier in the stability program. The MAH also committed to include the test on sub-visible particles in the new stability program. The specification will be acceptable in view of the Ph.Eur.
On basis of the data above, the following shelf life was granted: 18 months for the 10 ml 1.0 mg/ml product, 24 months for the 20 ml and 50 ml 0.5 mg/ml products, and 36 months for the 100 ml 0.5 mg/ml product, 50 ml and 100 ml 1.0 mg/ml products, if not stored above 25°C for the 0.5 mg/ml strength and if stored at 15-25°C for the 1.0 mg/ml strength and kept in the outer carton. For labelling conditions see section 6.4 of the SPC.
Stability data has been provided demonstrating that the product remains stable for 14 days following dilution, when stored at room temperature under protection from light.

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

II.2 Non clinical aspects

This product is a generic formulation of Platinol, 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 cisplatin 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

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

Cisplatine 0,5 mg/ml PCH, concentrate for solution for infusion and Cisplatine 1 mg/ml PCH, concentrate for solution for infusion are parenteral formulations in aqueous solution and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Cisplatine 0,5 mg/ml PCH, concentrate for solution for infusion and Cisplatine 1 mg/ml PCH, concentrate for solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety

profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Clinical efficacy

The MAH has presented a comprehensive review of the recent literature up to the end of 2006, reflecting the well established efficacy of cisplatin in treating a wide range of tumours and also discussing the adverse effects which may be expected to occur in many body systems. Although new types of anti-cancer therapy for some of these tumours are being developed, cisplatin, despite its sometimes severe side effects, still forms the mainstay of many chemotherapy regimens.

The indications claimed in the SPC are "the treatment of advanced and metastasised testicular carcinoma, advanced and metastasised ovarian carcinoma, advanced and metastasised bladder carcinoma, advanced and metastasised squamous cell carcinoma of the head and neck, advanced and metastasised lung tumours and cervical carcinoma.
Cisplatin can be used as monotherapy and in combination therapy."

These indications include tumours of the lung, bladder and cervix, which are not included in the Cisplatin Eurocept SPC in procedure NL/H/0118/001-003/R002. Cisplatin is however considered to be of established benefit in both small cell and non-small cell lung carcinoma and in bladder carcinoma. Moreover, several cisplatin products have been authorised for treatment of non-small cell lung carcinoma and for treatment of bladder carcinoma in both national and European applications.

Cisplatin has already been approved in Europe via an MRP (NL/H/0118/001-003/R002, SPC updated in 2007) for the treatment of tumours of the testis and ovary and in the treatment of squamous cell carcinoma of the head and neck. The efficacy in the other indications requested has been discussed below.

Lung Tumours

Small Cell Lung Carcinoma (SCLC): Since the 1980's, platinum-based combination chemotherapy regimens have been the mainstay of poly-chemotherapy treatment in both limited-stage and extensive-stage SCLC with cisplatin and etoposide being the most used combination. The use of newer cytotoxic agents or combinations of three or four agents has not yet been shown to improve survival (Lally et al., The Oncologist, 12(2007)1096).

Non-small Cell Lung Carcinoma (NSLC): In the mid-1990's following an extensive meta-analysis of 52 trials (Non-small Cell Lung Cancer Collaborative Group. BMJ 311(1995)899) it was recognised that cisplatin based chemotherapy offered a modest survival benefit following surgical resection. Since then the improved survival using cisplatin based modern chemotherapy regimens in resectable NSLC has been confirmed (Pignon et al., J. Clin. Oncol. 24(2006)366s). As regards palliative treatment of NSLC, cisplatin is used as a single agent or as part of a two-drug combination. Differences between combinations of chemotherapeutic regimens have been small, although the available data suggest that doublets containing cisplatin may offer slight advantages compared to those based upon carboplatin or those not containing a platinum compound. (Ardizzoni et al., J Natl Cancer Inst. 99(2007)847).

Bladder carcinoma

Metastatic bladder carcinoma is moderately sensitive to chemotherapy. The regimens currently most in use are cisplatin based: Methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC); Cisplatin, methotrexate, vinblastine; and Cisplatin – gemcitabine (GC). These treatments have a similar response rate (up to about 70%) and a similar median overall survival which still is only in the region of 12 – 16 months. (Perabo et al., Annals of Oncology, 18(2007)835; Laffaioli et al., Annals of Oncology, 18(supplement 6)(2007)vi153). The GC regimen has been found to be less toxic.

Cervix carcinoma

It has been reported in the literature that the addition of cisplatin to radiotherapy for the treatment of locally advanced cervix carcinoma significantly improves the progression free survival and the overall survival (Monk et al., J. Clin Oncology 25(2007)2952).

The evidence in the literature concerning the optimal choice of treatment in advanced and metatstatic cervix carcinoma is not unequivocal. In patients with metastatic cervix carcinoma or recurrences that cannot be treated with local therapy, several single chemotherapy agents and combination regimens are active. Single-agent cisplatin treatment has given response rates of 18% to 38% and median survival of less than 7 months (Long H.J 3rd, J Clinical Oncology 25(2007)2966). Paclitaxel has also shown similar response rates and overall survival and other agents (topotecan, vinorelbine, ifosfamide) have been shown to have modest effect (Long H.J 3rd, J Clinical Oncology 25(2007)2966). Although several combination regimens cisplatin/ifosfamide, cisplatin/paclitaxel cisplatin/topotecan, or carboplatin/paclitaxel) have been used as first-line therapy, the modest improvement in survival (three months in the cisplatin/topotecan trial) may be gained at the cost of significant treatment-related toxicity (Long H.J 3rd, J. Clin. Oncology 23(2005)4626).

Clinical safety

Cisplatin is an antineoplastic agent and has severe, dose-dependent side effects and (cumulative) toxicity. The most frequently reported adverse effects are nephrotoxicity, neurotoxicity (principally peripheral neuropathy), ototoxicity (sensory hearing loss), electrolyte disturbances (hyponatraemia, hypokalaemia, hypomagnesaemia and hypocalcaemia), myelosupression, nausea and vomiting. These and other less common adverse effects have been extensively reported in the literature and have been reviewed in the Clinical Overview submitted. Special attention to hydration and diuresis before, during and after administration of cisplatin is essential in minimising nephrotoxicity. Overdose can be fatal.
Cisplatin should only be prescribed and administered under the supervision of a physician experienced in cancer chemotherapy.

Pharmacovigilance

The MAH has submitted an updated description of the pharmacovigilance system. The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan

Cisplatin was first approved in December 1978 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of cisplatin 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. 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 indications proposed in the SPC are confined to those which are well established (treatment of tumors of the testis, ovary, bladder, head and neck and lung (advanced or metastatic)), as well as for cervix carcinoma, although it's use in advanced and metastatic carcinoma is still a matter for discussion.
The dosage range of 50-120 mg/m^2 as a single intravenous injection or 15-20 mg/m^2 intravenously for 5 consecutive days recommended in the SPC, is in line with that recommended in the Clinical Overview submitted and with that reported in the literature for adults and children (Holdsworth et al., Cancer 2006(106)931-40; Choong et al., CA Cancer J Clin 2008 (58)32-53; Long III J Clin Oncol 2007(25)2966-2974).

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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Recruitment aimed to ensure that participants of mixed age (>18 years), gender and

educational ability were included. Interviews were structured and conducted on a one to one basis. Interviewees were given time to read the leaflet and were permitted to keep the leaflet during questioning. Participants were asked not just to repeat information in the PIL but also to respond to questions using their own words. Questions concerning section 2a/b (contraindications) and section 2c (warnings) lead to the identification of problems with respect to traceability and comprehensibility. Suggestions for improvement were given and followed, which lead to improvement of the PIL.
The results complied with conventional acceptance criteria. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cisplatine 0,5 mg/ml PCH, concentrate for solution for infusion and Cisplatine 1 mg/ml PCH, concentrate for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Platinol. Platinol is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current products are intended for parenteral use, no bioequivalence study is deemed necessary.

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 other cisplatin containing products.

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 Cisplatine 0,5 mg/ml PCH and Cisplatine 1 mg/ml PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 November 2008. Cisplatine 0,5 mg/ml PCH and Cisplatine 1 mg/ml PCH were authorised in the Netherlands on 16 January 2009.

A European harmonised birth date has been allocated (19 December 1978) and subsequently the first data lock point for cisplatin is December 2009. The first PSUR will cover the period from November 2008 to December 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 August 2010.

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

Quality - active substance

- The MAH committed to provide information on photostability for one of the active substance manufacturers.

Quality - medicinal product

- The MAH committed to provide certificates of analysis of batches of the drug product with drug substance from one of the active substance suppliers.
- The MAH committed to include the test on sub-visible particles, in compliance with Ph.Eur., in the new stability program.
- The MAH committed to place two production scale batches per volume of each supplier in the stability program.

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