CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Leflunomide STADA 10 mg, 20 mg, and 100 mg film-coated tablets
STADA Arzneimittel AG, Germany

leflunomide

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/1811/001-003/DC
Registration number in the Netherlands: RVG 106041,106043-4

22 December 2010

Pharmacotherapeutic group:	selective immunosuppressants
ATC code:	L04AA13
Route of administration:	oral
Therapeutic indication:	active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD); active psoriatic arthritis (both in adult patients)
Prescription status:	prescription only
Date of authorisation in NL:	23 May 2011
Concerned Member States:	Decentralised procedure with AT, BE, ES, LU (all strenghts); FI, FR (not for 100 mg)
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 Leflunomide STADA 10 mg, 20 mg, and 100 mg film-coated tablets, from STADA Arzneimittel AG. The date of authorisation was on 23 May 2011 in the Netherlands. The product is indicated for or the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.

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

Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties. Leflunomide is rapidly converted into the active metabolite, A771726, by first-pass metabolism in gut wall and liver. A771726 inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity. Peak plasma levels can occur between 1 hour and 24 hours after single oral administration.

This decentralised procedure concerns a generic application claiming essential similarity with Arava 10 mg, 20 mg and 100 mg film-coated tablets (EU License EU/1/99/118) which have been registered through a centralised procedure by Sanofi-Aventis Deutschland GmbH since 1996.
In the Netherlands Arava 10 mg, 20 mg, and 100 mg have been registered by Sanofi Aventis Deutschland GmbH since 1999.

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 two bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Arava 20 mg and 100 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 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 leflunomide, an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is soluble in chloroform, dimethylsulphoxide, ethanol, ethyl acetate and methanol, sparingly soluble in dichloromethane and (practically) insoluble in hexane and water. Leflunomide has no chiral centers but does exhibit 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 CEPs.

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph of leflunomide with additional tests as stated on the CEP on residual solvents by one manufacturer and on other residual solvents by the other manufacturer. The specifications are acceptable in view of the route of synthesis and the Ph.Eur. Additionally the particle size of the API has been controlled. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
For one manufactuere, the CEP states a retest period of 2 years for the API when adequately stored.
For the other manufacturer, the CEP states a retest period of 5 years for the API when adequately stored.

** 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
The drug products are white to off-white (10 mg and 100 mg) or yellow (20 mg), round, biconvex film-coated tablets containing 10 mg, 20 mg or 100 mg leflunomide. No break-marks are present.

The excipients are:
Tablet core - lactose monohydrate, maize starch, povidone (E1201), crospovidone (E1202), colloidal anhydrous silica, magnesium stearate (E470b),
Tablet coating - hypromellose, macrogol 8000, talc (E553b), titanium dioxide (E171) and yellow iron oxide (20mg only).

The different strengths are dose proportional. The drug product is packed in Polyamide/Alu/PVC-Al blisters. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The particle size limit of Leflunomide is in line with the API used in the bio-batches. Wet granulation is chosen for the manufacturing process. The choice of container closure system is justified. The pharmaceutical development of the product has been adequately performed. A solubilizer was used in the dissolution medium to achieve sink conditions for all strengths. The 10 mg, 20 mg and 100 mg tablets are considered to be essentially similar with more than 85% dissolved in 15 minutes. The discriminating nature of the dissolution method has been demonstrated. The equivalence of the innovator product with the innovator products of all member states involved is inferred as it is centrally registered.

Manufacturing process

The drug product was manufactured by wet granulation. The manufacturing process has been validated according to relevant European guidelines for final blend. The proposed sizes of the full-scale batches justifies the batch size of the biobatch. The product is manufactured using conventional manufacturing techniques and the process is considered as standard. The manufacturing process has been adequately validated. The MAH has committed to perform process validation on the first production scale batch of each strength.

Container closure system

The drug products are packed in Alu-Alu blisters . Specifications, CoAs and a declaration of compliance with EU Directive 2002/72/EC have been provided for the aluminium and the plastic foil. For the laminated OPA/Alu/PVC foil, compliance has been stated with Ph.Eur monograph 3.1.11. The packaging material is deemed acceptable.

Excipients

All excipients are tested in accordance with their respective Ph.Eur. monograph, except for iron oxide yellow, which is tested according to the USP/NF*. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance, average mass, identification (HPLC, UV and colouring agents), disintegration, dissolution, assay, related substances, uniformity of dosage units (content uniformity) and microbiological requirements. The shelf-life specifications are the same as the release specification. The analytical methods have been adequately described and validated. The stability indicating nature of the assay and related substances methods has been demonstrated.
Batch analytical data from the proposed production site have been provided on five pilot scaled batches of each strength, demonstrating compliance with the release specifications.

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. Microbiological tests will be performed as per Ph.Eur., which is acceptable.

Stability tests on the finished product

Stability data on the active drug product has been provided on three pilot-scale batches of each strength, stored at 25°C/60% RH (48 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al blisters.
The proposed shelf-life of 48 months can be accepted with the storage condition '*store in the original package in order to protect from light and moisture*'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A TSE declaration has been provided by the MAH for lactose monohydrate as it is of animal origin. Magnesium stearate is of vegetable origin.

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

II.2 Non clinical aspects

This product is a generic formulation of Arava film-coated tablets, which are 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 leflunomide 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

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profiles of the test products Leflunomide STADA 20 mg and 100 mg film-coated tablets (STADA Arzneimittel AG, Germany) are compared with the pharmacokinetic profile of the reference products Arava 20 mg and 100 mg film-coated tablets (Sanofi-Aventis Deutschland GmbH, Germany).

Arava tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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

In both studies the plasma concentration of both leflunomide and the active metabolite A771726 were measured. However, pharmacokinetic evaluation for bioequivalence was based on concentrations of A771726 only. This is acceptable as no evaluable concentration-time profiles for leflunomide were observed.

Bioequivalence study with 20 mg film-coated tablets
A single center, open-label, single dose, randomized, parallel group design bioequivalence study was carried out under fasted conditions in 80 healthy male subjects (40 subjects test, 40 subjects reference). A parallel group design is justified as the half-life of A771726 is very long, approximately 2 weeks. Single oral doses (20 mg) of the assigned formulation (40 subjects test, 40 subjects reference) were administered together with 240 mL of water. The subjects had fasted for at least 10 hours before administration and the consumption of xanthine-containing or alcoholic food and beverages and grapefruit juice was prohibited from 48 hours prior to dosing until discharge. Water was not allowed 1 hour before and until 1 hour after dosing and the subjects were not allowed to lie down during the first four hours postdose (except for measurements). A wash-out period was included for safety reasons and did not contribute to the bioequivalence study itself. The subjects took wash-out treatment (colestyramine three times daily) for 11 days to enhance drug elimination. Wash-out was controlled with blood samples on study days 16 and 30 and if the A771726 plasma concentration was not below 20 ng/mL in both samples, the wash-out period was extended for further 11 days.

Blood samples were collected predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, and 72 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.

Results
Ninety-four adverse events were observed during the study, 48 under the test product and 46 under the reference product. Most common adverse events were gastrointestinal disorders, mainly related to the wash-out treatment with colestyramine. Clinically nonsignificant increase in liver transaminase was observed in number of subject. No clinically relevant differences in safety were observed between the test and reference products. All subjects completed the entire course of the study and were included in the pharmacokinetic evaluation.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD (CV%), t_{max} (median, range)) of active metabolite A771726 under fasted conditions.

Treatment N=80	**AUC_{0-72h}** ng.h/ml		**C_{max}** ng/ml	**t_{max}** h	
Test	94298±15396 (16.33)		1824±343 (18.80)	3.00 (1.00-24.00)	
Reference	93451±16961 (18.15)		1834±357 (19.49)	1.52 (1.00-7.07)	
***Ratio (90% CI)**	1.0 (0.94-1.09)		1.00 (0.92-1.08)	---	

$AUC_{0-\infty}$ 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_{0-72h} 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 active matabolite A771726 under fasted conditions, it can be concluded that Leflunomide STADA 20 mg film-coated tablets and the Arava 20 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study with 100 mg film-coated tablets
A single center, open-label, single dose, randomized, parallel group design bioequivalence study was carried out under fasted conditions in 80 healthy male subjects (40 subjects test, 40 subjects reference). A parallel group design is justified as the half-life of A771726 is very long, approximately 2 weeks. Single oral doses (100 mg) of the assigned formulation (40 subjects test, 40 subjects reference) were administered together with 240 mL of water. The subjects had fasted for at least 10 hours before administration and the consumption of xanthine-containing or alcoholic food and beverages and grapefruit juice was prohibited from 48 hours prior to dosing until discharge. Water was not allowed 1 hour before and until 1 hour after dosing and the subjects were not allowed to lie down during the first four hours postdose (except for measurements). A wash-out period was included for safety reasons and did not contribute to the bioequivalence study itself. The subjects took wash-out treatment (colestyramine three times daily) for 11 days to enhance drug elimination. Wash-out was controlled with blood samples on study days 16 and 30 and if the A771726 plasma concentration was not below 20 ng/mL in both samples, the wash-out period was extended for further 11 days.

Blood samples were collected predose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 24, 36, 48, and 72 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.

Results
84 adverse events were recorded during the study, 31 under the test product and 53 under the reference product. Most common adverse events were gastrointestinal disorders, mainly related to the wash-out treatment with colestyramine. Headache was observed more frequently under the reference product. Clinically nonsignificant increase in liver transaminase was observed in a number of subjects. No clinically relevant differences in safety were observed between the test and reference products. All subjects completed the treatment phase and were included in the pharmacokinetic evaluation. Seven subjects were lost to follow-up after two wash-out phases.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD (CV%), t_{max} (median, range)) of active metabolite A771726 under fasted conditions.

Treatment N=80	**AUC_{0-72h}** ng.h/ml		**C_{max}** ng/ml	**t_{max}** h	
Test	565060±97170 (17.20)		11153±1990 (17.85)	3.00 (1.00-36.00)	
Reference	515801±85874 (16.65)		10654±2043 (19.17)	3.02 (1.00-48.00)	
***Ratio (90% CI)**	1.10 (1.03-1.17)		1.05 (0.98 -1.12)	---	

$AUC_{0-\infty}$ 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_{0-72h} 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 active matabolite A771726 under fasted conditions, it can be concluded that Leflunomide STADA 100 mg film-coated tablets and the Arava 100 mg film-coated 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
The MAH applied for approval for the 10 mg strength considering that:
- The qualitative composition of the three strengths is identical.
- The ratio between the excipients is similar for the three strengths.
- Plasma concentrations of A 771726 are dose-proportional over dose range of 5-25 mg.
- All three strengths are produced by the same manufacturer and with the same method.
- All three strengths show comparable dissolution profiles

The results of the bioequivalence studies performed with the 20 mg and the 100 mg film-coated tablets therefore also apply to the 10 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).

Risk management plan

Leflunomide was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of leflunomide 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.

However, recently a RMP for another generic leflunomide has been constituted, which will be followed by the innovator. The MAH was requested to adhere to this RMP, where appropriate.

Product information

SPC

The innovator product Arava concerns a product that has been authorised through the centralized procedure (EU/I/99/118/001-010), which is last updated during variations EMEA/H/C/235/II/43 and EMEA/H/C/235/II/46. The MAH has kept section 4 and 5 of the product information of this generic application in line with the innovator product, which is agreed. The shelf-life was changed to 4 years and the storage conditions have been amended to "*Store in the original package in order to protect from light and moisture*".

Readability test

No user test has been submitted in the dossier. The MAH justifies the absence of a user test with the argumentation that the text of the PIL has been brought in line with the text of the PIL of the innovator Arava. User testing has been performed and accepted for the PL of Arava. Furthermore, for the layout of the PIL the MAH uses the house style of STADA, which has been developed based on the comments made by test participants during several Readability User Tests accomplished during the last 3 years.

The justification for absence of a user test regarding text and layout of the PIL can be considered sufficient and is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Leflunomide STADA 10 mg, 20 mg, and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Arava 10 mg, 20 mg and 100 mg film-coated tablets. Arava 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 innovator 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 Leflunomide STADA 10 mg, 20 mg, and 100 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 October 2010. Leflunomide STADA 10 mg, 20 mg, and 100 mg film-coated tablets are authorised in the Netherlands on 23 May 2011.

Leflunomide is not found in the list published by the Heads of Medicines Agencies with an EU Harmonised Birthday and related Data Lock Point (DLP). The MAH will follow the PSUR cycle of the innovator, which is currently 1 year. The next DLP of the first PSUR is September 2011, to be submitted within 60 days after DLP.

The date for the first renewal will be: 26 July 2015

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

<u>Pharmacovigilance</u>
- The MAH has committed to address the following identified and potential risks and missing information by means of routine pharmacovigilance and special focus in PSUR: Hepatic reactions, interstitial lung disease, teratogenicity, interactions with other DMARDs (methotrexate), lymphoproliferative disorders, progressive multifocal leukoencephalopathy (PML), renal failure, and interaction with biologic and other DMARDs.
- In addition, the MAH has committed to address the following identified and potential risks and missing information by means of routine pharmacovigilance: Blood cytopenia, severe skin reactions, infections, hypertension, male-mediated foetal toxicity, and use in children.
- The MAH has committed to participate in DHPCs where needed and commits to follow the hitherto known risk minimisation activities of the innovator.
- The MAH has committed to produce and provide physicians with educational material for patients, when applicable. In addition, the MAH commits to incorporate any future amendments to educational material of the innovator into their own material.

<u>Quality - medicinal product</u>
- The MAH has committed to perform further process validation on the first production scale batch of each strength.

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
CoAs	Certificate of Analysis
CV	Coefficient of Variation
DHODH	Dihydroorotate Dehydrogenase
DHPC	Direct Healthcare Professional Communication
DMARD	Disease-Modifying Antirheumatic Drug
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