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/2175/001-002/MR
Registration number in the Netherlands: RVG 34332-34333

26 October 2011

Pharmacotherapeutic group: other antiepileptics
ATC code: N03AX12
Route of administration: oral
Therapeutic indication: epilepsy; treatment of peripheral neuropathic pain
Prescription status: prescription only
Date of first authorisation in NL: 24 January 2008
Concerned Member States: Mutual recognition procedure with BE, CZ, ES
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 Gabapentine Apotex 600 mg and 800 mg, film-coated tablets from Apotex Europe B.V. The date of authorisation was on 24 January 2008 in the Netherlands.

The product is indicated for:

- **Epilepsy**
  - as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above
  - as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

- **Treatment of peripheral neuropathic pain**
  - Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults

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

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha2-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including GABAA, GABAB, benzodiazepine, glutamate, glycine or N-methyl-daspartate receptors.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Neurontin, for which the first marketing authorisation was granted to Pfizer France on 12 October 1994 for the 100 mg strength. Neurontin 600 mg and 800 mg film-coated tablets (NL License RVG 25247-25248) have been authorised in the Netherlands by Pfizer bv since 27 November 2000 through MRP DE/H/0899/004-005. In addition, reference is made to Neurontin 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 two bioequivalence studies in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products Neurontin 600 mg and 800 mg tablets registered in France. 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 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 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 gabapentin, an established active substance described in the US Pharmacopoeia (USP*). It is a white to off-white crystalline powder, which is soluble in water and in alkaline and acidic solutions. Different polymorphic forms exist, but only form II is used.

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 is described in two main steps. No metal catalysts are used in the manufacturing process. The active substance is adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the USP monograph, with appropriate additional requirements. 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 six production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 26 full-scale batches stored at 25°C/60% RH (maximum 60 months) and/or 40°C/75% RH (maximum 6 months). All values remained well within specification. The proposed retest period of 4 years without any special storage condition is acceptable.

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

Medicinal Product

Composition
Gabapentine Apotex 600 mg is a white, oval, biconvex film-coated tablet with “GAB” engraved above the fracture line and “600” below fracture line on one side, “APO” engraved on the other side.
Gabapentine Apotex 800 mg is a white, oval, biconvex film-coated tablet with “GAB” engraved above the fracture line and “800” engraved below fracture line on one side, “APO” engraved on the other side.
The tablets can be divided into equal halves.

The film-coated tablets are packed in OPA/Al/PVC-aluminium blister packs and HDPE (high-density polyethylene) bottles with blue propylene cap.
The excipients are:
*Tablet core* – copovidone, magnesium stearate (E572)
*Coating* - hypromellose 2910 (E464), hydroxypropylcellulose type LF (E463), macrogol 8000, titanium dioxide (E171).

The two strengths are fully dose proportional.

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. Several trial batches were manufactured with different concentrations of excipients in order to find the formulation with the best physical characteristics. The composition of the biobatches is the same as that proposed for marketing. Both tablet strengths are included in BE studies. Studies have been performed to compare the dissolution of Apotex Gabapentin 600 mg and 800 mg to Neurontin 600 mg and 800 mg tablets. The dissolution profiles were similar. The tablets contain a score line and were tested for divisibility. They were broken manually and content uniformity of the halves was determined. Compliance with the requirements on breakability has been demonstrated. The pharmaceutical development of the product has been adequately performed.

**Manufacturing process**
The manufacturing process is a dry granulation process and is divided into seven steps. It includes milling, blending, compaction, compression and film-coating steps. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

**Control of excipients**
The excipients comply with the Ph.Eur. monographs. These specifications are acceptable.

**Quality control of drug product**
The product specification includes tests for appearance, identification, average weight, dissolution rate, uniformity of dosage units, degradation products, assay, microbiological purity and subdivision of tablets. The release and shelf-life requirements are identical except for one identified impurity. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches for the 600 mg and 800 mg tablets, demonstrating compliance with the release specification.

**Stability of drug product**
Stability data on the product has been provided for 3 full-scale batches of each strength stored at 25°C/60% RH (maximum 24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HDPE bottles (different sizes) with PP caps or OPA/Al/PVC-Al blister packagings. Only at accelerated storage conditions an out-of-specification result was noted. No other trends are observed. A photosensitivity study was conducted on the 600 mg and 800 mg tablets for directly exposed tablets and tablets in the immediate packaging. Testing in the immediate packaged did not result in out-of-specifications, but the directly exposed product showed sensitivity to light. Therefore the statement is included to store the tablets in the original blister packaging or bottle for protection against light. Based on the data provided, a shelf life of 24 months was granted when stored below 25°C.

**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 Neurontin, 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 gabapentin 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

Gabapentin 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 profile of the test products Gabapentine Apotex 600 mg and 800 mg, film-coated tablets (Apopex Europe B.V., NL) is compared with the pharmacokinetic profile of the reference products Neurontin 600 mg and 800 mg tablets (Pfizer, FR). Besides, both products were compared to the innovator product registered in Australia. Only the French reference product is considered relevant for this application, as the Australian reference product is not registered in the EEA. Therefore, only the data of the French reference product were used for assessment.

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 I – 600 mg tablet

Design
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 18-35 years. Each subject received a single dose (600 mg) of one of the 3 gabapentin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, and 48 hours after administration of the products.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study on medical grounds on the day of check in of period II, and one subject was withdrew for personal reasons. The remaining 22 subjects completed the study entirely and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of gabapentin under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=22</th>
<th>AUC₀-₁ µg.h/ml</th>
<th>AUC₀-∞ µg.h/ml</th>
<th>Cmax µg/ml</th>
<th>tmax h</th>
<th>t₁/₂ h</th>
</tr>
</thead>
</table>

5 of 10
### Study II – 800 mg tablet

**Design**
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-43 years. Each subject received a single dose (800 mg) of one of the 3 gabapentin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, and 48 hours after administration of the products.

**Analytical/statistical methods**
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

**Results**
One subject was withdrawn from the study because he got malaria, and another subject was withdrawn because of protocol violation (drug abuse). The remaining 22 subjects completed the study entirely and were eligible for pharmacokinetic analysis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;0-t&lt;/sub&gt; (µg.h/ml)</strong></td>
<td>38.69 ± 9.94</td>
<td>36.97 ± 11.14</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (µg.h/ml)</strong></td>
<td>39.12 ± 9.93</td>
<td>37.52 ± 11.16</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</strong></td>
<td>3.68 ± 0.79</td>
<td>3.59 ± 0.79</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;max&lt;/sub&gt; (h)</strong></td>
<td>2.71 ± 1.09</td>
<td>2.66 ± 0.89</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</strong></td>
<td>7.0 ± 1.2</td>
<td>7.4 ± 1.8</td>
</tr>
</tbody>
</table>

* *Ratio (90% CI)*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> 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 gabapentin under fasted conditions, it can be concluded that Gabapentine Apotex 600 mg and Neurontin 600 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.
The 90% confidence intervals calculated for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$, and $C_{\text{max}}$ 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 gabapentin under fasted conditions, it can be concluded that Gabapentin Apotex 800 mg and Neurontin 800 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Gabapentin may be taken with or without food. From the literature it is known that food does not interact with the absorption of gabapentin. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence studies have 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**

Gabapentin was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of gabapentin 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 approved during the mutual recognition procedure in line with the latest SPC of the innovator product Neurontin (DE/H/0899/004-005)

**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 2 participants, followed by two rounds with 10 participants each. The questionnaire contained 17 questions specific to Gabapentin Apotex 600 & 800 mg, film-coated tablets and the format of the PIL. It had 3 questions that solicit positive and negative feedback from the participants about the user friendliness of the leaflet. A satisfactory test outcome was when, for each question, 90% of the subjects of the interviews were able to find the information within the PIL, and 90% could show that they understood and could act upon it. The results have shown that the key messages for safe use can be found and understood by the subjects. The conclusions of the readability test suggest a good readability and traceability of the PIL. The readability test is regarded acceptable.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gabapentine Apotex 600 mg and 800 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Neurontin 600 mg and 800 mg. Neurontin 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. Gabapentine Apotex 600 mg and 800 mg, film-coated tablets were authorised in the Netherlands on 24 January 2008.

There was no discussion in the CMD(h). The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gabapentine Apotex 600 mg and 800 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 18 August 2011.

The date for the first renewal will be: 28 October 2013.

There were no post-approval commitments made during the procedure.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
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<th>Type of modification</th>
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<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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