Public Assessment Report

Decentralised Procedure

Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets

(Nortriptyline hydrochloride)

Procedure Nos: UK/H/5843/001-03/DC

UK Licence Numbers: PL 20046/0304-0306

Focus Pharmaceuticals Limited
LAY SUMMARY

Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets
(Nortriptyline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets (PL 20046/0304-0306; UK/H/5843/001-03/DC). It explains how Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets.

These products will be collectively referred to as Nortriptyline Tablets throughout the remainder of this lay summary for ease of reading.

For practical information about using Nortriptyline Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nortriptyline Tablets and what are they used for?
Nortriptyline 10 mg and 25 mg film-coated Tablets are ‘generic medicines’. This means that these Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Allegron 10 mg and 25 mg tablet (Kings Pharmaceuticals Ltd; PL 14385/0001-0002).

Nortriptyline 50 mg film-coated Tablets are a ‘hybrid medicine’. This means that they are similar to a reference medicine containing the same active substance, but are available at a higher strength (50 mg, tablets instead of 25 mg film-coated Tablets as the reference medicine).

The reference medicine for Nortriptyline 50 mg film-coated Tablets is Allegron 25 mg tablet (Kings Pharmaceuticals Ltd).

Nortriptyline Tablets relieve the symptoms of depression. Nortriptyline tablets may also be used for the treatment of bed-wetting in children 6 years and older.

How do Nortriptyline Tablets work?
The active substance in Nortriptyline Tablets, nortriptyline hydrochloride, is a tricyclic antidepressant which works by elevating the mood in patients with depression.

How are Nortriptyline Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient must check with their doctor or pharmacist if they are not sure.

The usual adult dose is 25 mg three or four times daily or the dose may be given once a day, usually at night. The dose should begin at a low level, 10 mg, 3-4 times daily, for example and be increased gradually as required. The maximum dose is 150 mg per day.

The usual dose in elderly is 30 to 50 mg a day in divided doses. Treatment may start with 10 mg three times a day. The 50 mg tablets are not appropriate for use in elderly patients.

The recommended dose in adolescent patients is 30 to 50 mg/day in divided doses. Treatment may start
with 10 mg three times a day. The 50 mg tablets are not appropriate for use in elderly patients.

Lower dosages are recommended for outpatients than for patients in hospital who will be under close supervision. Following remission maintenance treatment may be needed longer term. This should be at the lowest dose that stops the symptoms of depression coming back.

**Use in children and adolescents (for bed-wetting only)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight kg</th>
<th>Weight lb</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>20-25</td>
<td>44-55</td>
<td>10</td>
</tr>
<tr>
<td>8-11</td>
<td>25-35</td>
<td>55-77</td>
<td>10-20</td>
</tr>
<tr>
<td>Over 11</td>
<td>35-54</td>
<td>77-119</td>
<td>25-35</td>
</tr>
</tbody>
</table>

The dose should be given thirty minutes before bedtime.
The maximum length of treatment should be three months. Another course of treatment should not be started until a full physical examination has been made. The 50 mg tablets are not appropriate for use in children and adolescents.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Nortriptyline Tablets have been shown in studies?**
Because Nortriptyline Tablets are generic/hybrid medicines of Allegron 10 mg or 25 mg tablets, considerations have been limited to determine whether they can be expected to be bioequivalent and, therefore, therapeutically equivalent to the reference medicines Allegron 10 mg and 25 mg tablet. Two medicines are considered bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Nortriptyline Tablets?**
Because Nortriptyline Tablets are either generic or hybrid medicines that are considered bioequivalent/therapeutically equivalent to the reference medicines, Allegron 10 mg and 25 mg tablet, their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Nortriptyline Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Nortriptyline Tablets approved?**
It was concluded that, in accordance with EU requirements, Nortriptyline Tablets has been shown to have comparable quality and to be bioequivalent/be comparable to Allegron 10 mg and 25 mg tablet. Therefore, the MHRA decided that, as for Allegron 10 mg and 25 mg tablet; the benefits are greater than the risks and recommended that they can be approved for use.
What measures are being taken to ensure the safe and effective use of Nortriptyline Tablets?
A risk management plan (RMP) has been developed to ensure that Nortriptyline Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflet for Nortriptyline Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Nortriptyline Tablets
The UK originally agreed to grant Marketing Authorisations to Lamda Laboratories SA for Nortriptyline Tablets (PL 43945/0011-0013; UK/H/5843/001-03/DC) on 25 July 2016. Marketing Authorisations were granted in the UK on 08 August 2016.

Changes of ownership were granted on 26 August 2016 to change the Marketing Authorisation Holder to Focus Pharmaceuticals Limited (PL 20046/0304-0306).

The full PAR for Nortriptyline Tablets follows this summary.

For more information about treatment with Nortriptyline Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets (PL 20046/0304-0306; UK/H/5843/001-03/DC), are approvable. These products are prescription only medicines (POM), indicated for the relief of symptoms of depression. It may also be used for the treatment of some cases of nocturnal enuresis.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). The applications for Nortriptyline 10 mg and 25 mg film-coated Tablets were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The application for Nortriptyline 50 mg film-coated Tablets was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. For the generic Nortriptyline 10mg and 25 mg Film-coated Tablets the reference medicinal products are Allegron 10 mg and 25 mg Tablet. For the hybrid medicinal product Nortriptyline 50 mg Film-coated Tablets, the reference medicinal product was Allegron 25 mg Tablet. Allegron 10 mg and 25 mg tablets were originally authorised to Eli Lilly & Company Limited (PL 00006/5002R-5003R) on 14th February 1983. These reference licences underwent change of ownership procedures to the currently Marketing Authorisation Holder, King Pharmaceuticals Limited (PL 14385/0001-0002), on 30th March 1998.

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those of amitriptyline. It is the principal active metabolite of amitriptyline.

No bioequivalence study was submitted and these applications are based on Biopharmaceutics Classification System (BCS) class I biowaiver.

No new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic/hybrid medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS agreed to grant Marketing Authorisations for the above products at the end of the procedure (25 July 2016). After a subsequent national phase, the UK granted Marketing Authorisations (PL 43945/0011-0013) for these products on 08 August 2016.

Changes of ownership were granted on 26 August 2016 to change the Marketing Authorisation Holder to Focus Pharmaceuticals Limited (PL 20046/0304-0306).
II QUALITY ASPECTS
II.1 Introduction
Each film-coated tablet contains nortriptyline hydrochloride equivalent to 10, 25 or 50 mg nortriptyline, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Tablet core:
Lactose monohydrate, maize starch, calcium hydrogen phosphate anhydrous and magnesium stearate.

Coating:
Opadry II Clear (polyvinyl alcohol E 1203, polyethyleneglycol / macrogol and talc)

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II Clear which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets are packaged in the following presentations:
- High density polyethylene (HDPE) bottles with a low density polyethylene (LDPE), HDPE-lined screw cap containing 100 tablets.
- Aluminium (Al) - polyvinyl chloride (PVC)/ polyvinylidine chloride (PVdC) blisters in packs of 30 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Nortriptyline hydrochloride

Structural formula:

\[
\begin{array}{c}
\text{N} \\
\text{CH}_3, \text{HCl}
\end{array}
\]

Molecular formula: \( \text{C}_{19}\text{H}_{21}\text{N.HCl} \)
Molecular mass: 299.84 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Soluble in ethanol (96 %) and in methylene chloride; sparingly soluble in water.

Nortriptyline hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory
specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificate of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. **Medicinal Product**

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious tablets containing 10 mg, 25 mg or 50 mg nortriptyline per tablet, that are generic/hybrid versions of the reference products Allegron 10 mg & 25 mg tablets (Kings Pharmaceuticals Ltd). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacture of the products**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The process validation protocol to be followed for full-scale production batches has been provided and is satisfactory.

**Finished Product Specification**
The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing (HDPE containers and blisters). The data from these studies support a shelf-life of 30 months for the 10 and 25 mg tablets and 24 months for the 50 mg tablets with no special storage conditions. Once the HDPE container is opened the medicinal products must be used within 5 months.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 **Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of nortriptyline are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic/ hybrid medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
For these generic/hybrid applications, the Applicant applied for Biopharmaceutics Classification System (BCS) based biowaiver. No bioequivalence study was performed.

No new clinical data have been submitted and none are required for applications of this type. A clinical overview has been submitted to justify the biowaiver. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 BCS Biowaiver
The Applicant applied for Biopharmaceutics Classification System (BCS) based biowaiver for all tablet strengths. In line with the ‘Guideline on the investigation of bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/ Corr*), this was considered acceptable as nortriptyline hydrochloride is highly soluble with complete absorption, high permeability (BCS class I) and is not considered to be a narrow-therapeutic drug and the products are immediate release solid dose preparations for oral use with the same pharmaceutical form as the reference products. Satisfactory data has been submitted to justify the BCS biowaiver including sufficient data to support their BCS I claim for Nortriptyline 50mg tablets.
IV.3  **Pharmacokinetics**  
No new data have been submitted and none are required for applications of this type.

IV.4  **Pharmacodynamics**  
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.5  **Clinical efficacy**  
No new efficacy data were submitted and none were required for applications of this type.

IV.6  **Clinical safety**  
No new safety data were submitted and none are required.

IV.7  **Risk Management Plan (RMP) and Pharmacovigilance System**  
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine measures</th>
<th>Risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity to nortriptyline</td>
<td>SPC sections 4.3, 4.4 &amp; 4.8</td>
<td>PIL sections 2 &amp; 4</td>
<td>Prescription only medicine</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine measures</td>
<td>Additional risk minimisation measures</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Use in patients with cardiovascular disease, any degree of heart block or other cardiac arrhythmias – risk of MI, arrhythmias and stroke</td>
<td>SPC sections 4.3, 4.4 &amp; 4.8 PIL sections 2 &amp; 4 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with severe liver disease</td>
<td>SPC sections 4.3 &amp; 4.8 PIL sections 2 &amp; 4 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with bipolar disorder – risk of manic phase induction or exacerbation</td>
<td>SPC sections 4.3, 4.4 &amp; 4.8 PIL sections 2 &amp; 4 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in nursing mothers</td>
<td>SPC section 4.3 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Suicide/suicidal thoughts or clinical worsening</td>
<td>SPC sections 4.4, 4.5 &amp; 4.8 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>SPC sections 4.4 &amp; 4.8 PIL section 3 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in schizophrenic patients – risk of exacerbation of psychotic symptoms</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with a history of epilepsy due to lowering of convulsive threshold</td>
<td>SPC section 4.4 PIL section 2 and 4. Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Agitation, confusion and postural hypotension in the elderly</td>
<td>SPC section 4.4 and 4.8 PIL section 4. Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Behavioural changes in children</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
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<tr>
<td>Use in patients with narrow angle glaucoma</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with symptoms suggestive of prostatic hypertrophy</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Increased hazards with electroconvulsive therapy</td>
<td>SPC section 4.4 PIL section 2 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Elevation or lowering of blood sugar</td>
<td>SPC section 4.4 PIL sections 2 &amp; 4 Prescription only medicine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
<td></td>
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<td>------------------------------------</td>
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<td></td>
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<tr>
<td>Drug interactions</td>
<td>SPC section 4.5</td>
<td>None</td>
<td></td>
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<tr>
<td></td>
<td>PIL section 2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Prescription only medicine</td>
<td></td>
<td></td>
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<tr>
<td>Effects on driving and the use of machines</td>
<td>SPC section 4.7</td>
<td>None</td>
<td></td>
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<tr>
<td></td>
<td>PIL section 2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Prescription only medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in children</td>
<td>SPC sections 4.3 &amp; 4.9</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIL section 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects on fertility and Pregnancy</td>
<td>SPC section 4.6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIL section 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.8 Discussion on the clinical aspects**
The grant of Marketing Authorisations is recommended for these applications.

**V User consultation**
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 language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

**VI Overall conclusion, benefit/risk assessment and recommendation**
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Nortriptyline 10 mg, 25 mg and 50 mg Film-coated Tablets is presented below:
Each 50 mg tablet contains nortriptyline hydrochloride equivalent to 50 mg nortriptyline base.
The product contains lactose. See the leaflet for further information.
For oral use.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.
50 mg tablets are for adults only.
Keep out of the sight and reach of children.

MA Holder: Focus Pharmaceuticals Ltd.,
Capital House, 85 King William Street,
London EC4N 7BL, UK.
PL 2004/0386
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>