Public Assessment Report

UK PAR

Dexamethasone 4 mg Tablets
Dexamethasone 8 mg Tablets

PL 00289/2198-2199

Teva UK Limited
LAY SUMMARY

Dexamethasone 4 mg Tablets
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This is a summary of the Public Assessment Report (PAR) for Dexamethasone 4 mg Tablets (PL 00289/2198, formerly PL 30306/0717) and Dexamethasone 8 mg Tablets (PL 00289/2199, formerly PL 30306/0718). For ease of reading, the products may be collectively referred to as ‘Dexamethasone Tablets’ or ‘Dexamethasone 4 mg and 8 mg Tablets’ in this lay summary. The summary explains how the applications for Dexamethasone 4 mg and 8 mg Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Dexamethasone 4 mg and 8 mg Tablets.

For practical information about using Dexamethasone 4 mg and 8 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone Tablets and what are they used for?
Dexamethasone Tablets are hybrid applications. This means that Dexamethasone Tablets are similar to a reference medicine already authorised in the UK called Dexamethasone Tablets BP 2.0mg (PL 39699/0056; Aspen Pharma Trading Limited, Ireland), which was authorised in the UK following a Change of Ownership CoA procedure of Dexamethasone Tablets BP 2.0mg (PL 00065/5045R; Organon Laboratories Limited) on 22 May 2014. Dexamethasone Tablets BP 2.0mg (PL 00065/5045R; Organon Laboratories Limited, UK) was approved in the UK on 29 March 1990. This product was the subject of a Product Licence of Right (PLR); because Dexamethasone Tablets BP 2.0mg (Organon Laboratories Limited, UK) was on the market before the Medicines Act 1968 came into force in 1971.

Dexamethasone Tablets are recommended for the treatment of:
- rheumatic and autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, polyarthritis nodosa),
- diseases of the respiratory tract (e.g. bronchial asthma, croup),
- diseases of the skin (e.g. erythroderma, pemphigus vulgaris),
- tuberculous meningitis, only in conjunction with anti-infective therapy,
- diseases of the blood (e.g. idiopathic thrombocytopenic purpura in adults),
- cerebral oedema,
- treatment of symptomatic multiple myeloma, acute lymphoblastic leukemia, Hodgkin’s disease and non-Hodgkin’s lymphoma in combination with other medicinal products,
- palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and vomiting caused by chemotherapy,
- prevention and treatment of vomiting after an operation, within antiemetic treatment.

How do Dexamethasone Tablets work?
Dexamethasone Tablets contain the active substance, dexamethasone. Dexamethasone belongs to a group of medicines called steroids. Dexamethasone is a synthetic glucocorticoid. Glucocorticoids are hormones produced by the cortex of adrenal glands. This medicine has anti-inflammatory, analgesic and anti-allergic effects, and suppresses the immune system.

How are Dexamethasone Tablets used?
Dexamethasone Tablets are taken by mouth. Dexamethasone should be taken with or after food. The tablets should be swallowed whole with some water. Drinks containing alcohol or caffeine should be avoided.
Dexamethasone Tablets can only be obtained with a prescription. These medicines should be taken, by the patient, exactly as advised by his/her doctor or pharmacist. The patient should check with the doctor or pharmacist if not sure.

Please read section 3 of the package leaflet (PL), available on the MHRA website, for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

**What benefits of Dexamethasone Tablets have been shown in studies?**
As Dexamethasone Tablets are hybrid medicines, studies have been limited to tests to determine that Dexamethasone Tablets are therapeutically equivalent to the reference medicine Dexamethasone Tablets BP 2.0mg (PL 39699/0056; Aspen Pharma Trading Limited, Ireland). Two medicines are therapeutically equivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects from Dexamethasone Tablets?**
Like all medicines, Dexamethasone Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Dexamethasone, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet.

**Why are Dexamethasone Tablets approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Dexamethasone 4 mg and 8 mg Tablets outweigh the identified risks and recommended that the products be approved for use.

**What measures are being taken to ensure the safe and effective use of Dexamethasone Tablets?**
A Risk Management Plan has been developed to ensure that Dexamethasone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Dexamethasone 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/reviewed continuously as well.

**Other information about Dexamethasone Tablets.**
Marketing Authorisations (PL 30306/0717-0718) were granted in the UK to Actavis Group PTC ehf on 10 November 2017.

Subsequent to Change of Ownership procedures, the Marketing Authorisations were transferred to Teva UK Limited (PL 00289/2198-2199) on 11 December 2017.

The full PAR for Dexamethasone Tablets follows this summary.

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

This summary was last updated in January 2018.
SCIENTIFIC DISCUSSION

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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations for Dexamethasone 4 mg Tablets (PL 30306/0717) and Dexamethasone 8 mg Tablets (PL 30306/0718) to Actavis Group PTC ehf on 10 November 2017. For ease of reading, the products may be collectively referred to as ‘Dexamethasone Tablets’ or ‘Dexamethasone 4 mg and 8 mg Tablets’ in this scientific discussion.

The products are Prescription Only Medicines (POM). Dexamethasone Tablets contain the active ingredient, dexamethasone, which is a highly potent and long-acting synthetic glucocorticoid with negligible sodium retaining properties. It is used principally as an anti-inflammatory or immunosuppressant agent. Like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

Dexamethasone 4 mg and 8 mg Tablets are indicated in the following conditions:

- **Neurology**
  Cerebral oedema (only with symptoms of intracranial pressure evidenced by computerised tomography) caused by a brain tumour, neuro-surgical intervention, cerebral abscess.

- **Pulmonary and respiratory diseases**
  Acute asthma exacerbations when use of an oral corticosteroid (OCS) is appropriate, croup.

- **Dermatology**
  Initial treatment of extensive, severe, acute, skin diseases responding to glucocorticoids, e.g. erythroderma, pemphigus vulgaris.

- **Autoimmune disorders/rheumatology**
  Initial treatment of autoimmune disorders like systemic lupus erythematoses.

  Active phases of systemic vasculitides like panarteritis nodosa (treatment duration should be limited to two weeks in cases of concomitant positive hepatitis B serology).

  Severe progressive course of active rheumatoid arthritis, e.g. fast proceeding destructive forms and/or extraarticular manifestations.

  Severe systemic course of juvenile idiopathic arthritis (Still’s disease).

- **Haematological disorder**
  Idiopathic thrombocytopenic purpura in adults.

- **Infectology**
  Tuberculous meningitis only in conjunction with anti-infective therapy.

- **Oncology**
  Palliative treatment of neoplastic diseases.

  Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.


- **Various**
  Prevention and treatment of postoperative vomiting, within antiemetic treatment.

The applications were granted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications cross-referring to the medicinal product Dexamethasone Tablets BP 2.0mg.
Evidence has been provided that confirms Actavis Group PTC ehf and Auden McKenzie (Pharma Division) Limited are considered the ‘same’ (i.e. belonging to the same mother company or group of companies or which are “licencees”), per the Commission Communication (98/C 299/03). In support of these applications, the applicant sought a biowaiver based on the results of a bioequivalence study submitted to support the application for Dexamethasone 2 mg tablets (PL 17507/0053; Auden McKenzie (Pharma Division) Limited, UK). Dexamethasone 2 mg tablets (PL 17507/0053; Auden McKenzie (Pharma Division) Limited, UK) was initially granted a Marketing Authorisation in the UK on 08 December 2006, following a generic application submitted under Article 10.1 (a) (iii) of Directive 2001/83/EC, which cross-referred to the originator reference product Dexamethasone Tablets BP 2.0mg (PL 39699/0056; Aspen Pharma Trading Limited, Ireland [formerly PL 0065/5045R; Organon Laboratories Limited]).

The bioequivalence study compared Dexamethasone 2 mg Tablets (PL 17507/0053; Auden McKenzie (Pharma Division) Limited, UK) versus the reference product Dexamethasone Tablets BP 2.0mg (PL 39699/0056; Aspen Pharma Trading Limited, Ireland [formerly PL 0065/5045R; Organon Laboratories Limited]). It is stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP) requirements.

No new non-clinical or clinical studies were conducted, which is acceptable given that these were hybrid applications of a medicinal reference product that has been in clinical use for over 10 years and an acceptable biowaiver was sought for the applications.

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

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Dexamethasone 4 mg and 8 mg Tablets outweigh the risks, and Marketing Authorisations were granted.

Subsequent to CoA procedures, the Marketing Authorisations (PL 30306/0717-0718) were transferred to Teva UK Limited (PL 00289/2198-2199) on 11 December 2017.

II QUALITY ASPECTS
II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The products are round white tablets, with one side marked ‘DX 4’ (4 mg strength tablet only) or ‘DX 8’ (8 mg strength tablet only).

Each tablet contains 4 mg or 8 mg of dexamethasone, as the active substance. The tablets also contain pharmaceutical excipients namely, lactose monohydrate, microcrystalline cellulose, sodium starch...
glycolate (Type A), colloidal hydrated silica and magnesium stearate (E470b). Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in polyvinyl chloride/aluminium (PVC/aluminium) blisters, in pack sizes of 30, 50 and 100 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for the primary packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

Dexamethasone

**INN:** Dexamethasone

**Chemical Name:** 9-fluoro-11β,17-dihydroxy-17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

**Molecular formula:** C₂₂H₂₉FO₅

**Molecular mass:** 392.461g/mol

**Appearance:** A white or almost white, crystalline powder

**Solubility:** Practically insoluble in water, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride.

Dexamethasone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, dexamethasone, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, stable, tablets containing 4 mg and 8 mg of dexamethasone, which were comparable to the reference product Dexamethasone Tablets BP 2.0mg (PL 39699/0056; Aspen Pharma Trading Limited, Ireland [formerly PL 0065/5045R; Organon Laboratories Limited]). Suitable pharmaceutical development data have been provided for these applications.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products. The dissolution profiles were satisfactory.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of
lactose anhydrous is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material of any kind is used during the production of lactose monohydrate.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described that have been validated adequately. Batch data, complying with the release specifications, have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed on batches of finished product in the packaging proposed for marketing in accordance with current guidelines. Based on the results, a shelf-life of 24 months, with the special storage conditions ‘Store in the original package in order to protect from light.’ has been accepted.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for these applications for Dexamethasone 4 mg and 8 mg Tablets, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no new non-clinical data have been submitted and none are required.

The non-clinical overview 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 Pharmacodynamics
The pharmacodynamics profile of dexamethasone is well known and is adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of dexamethasone are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of dexamethasone are well known and are adequately described in the applicant’s non-clinical overview.
III.5 Ecotoxicity/Environmental risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for substitution of an already authorised product, it is not expected that environmental exposure of dexamethasone will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Dexamethasone 4 mg and 8 mg Tablets from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology, safety and efficacy of dexamethasone are well-known. The applicant has provided an adequately detailed discussion to support the proposed indications that would be appropriate for the proposed strengths.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study to support the applications. This study was previously submitted in support of the Marketing Authorisation application for Dexamethasone 2 mg tablets (PL 17507/0053; Auden McKenzie (Pharma Division) Limited, UK); biowaiver was subsequently claimed for the applications for 4 mg and 8 mg tablet strengths. The biowaiver was suitably justified according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). Actavis Group PTC ehf and Auden McKenzie (Pharma Division) Limited are considered the ‘same’ (i.e belonging to the same mother company or group of companies or which are ‘licencess”) per the Commission Communication (98/C 299/03), hence reference to this study as a basis for a biowaiver is considered acceptable. With the exception of data from the bioequivalence study detailed below, no new clinical data is provided or required for these applications.

IV.2 Pharmacokinetics
The clinical pharmacology of dexamethasone is well-known.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, two-way, crossover, bioequivalence study comparing Dexamethasone 2 mg Tablets (Auden McKenzie (Pharma Division) Limited, UK) versus the reference product Dexamethasone Tablets BP 2.0mg (Aspen Pharma Trading Limited, Ireland; formerly PL 00065/5045R; Organon Laboratories Limited, UK) in healthy, adult male, human subjects under fasted conditions.

The subjects were administered a single dose (2 mg, one tablet) of either treatment, with approximately 240 ml of water after at least a10-hour overnight fast. Blood samples were collected before, up to and including 24 hours after each administration. The washout period between the treatment phases was 15 days. A summary of the pharmacokinetic results and statistical analyses are presented below.
Pharmacokinetic Results

Table 1. Pharmacokinetic parameters (arithmetic mean ± SD, ratios and confidence intervals) for dexamethasone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t}) (ng/ml/h)</th>
<th>C(_{\text{max}}) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>160.188 ± 37.493</td>
<td>23.842 ± 4.859</td>
</tr>
<tr>
<td>Reference</td>
<td>166.303 ± 42.931</td>
<td>25.466 ± 6.300</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

| Treatment | AUC\(_{0-t}\) (91.48% - 101.72%) | C\(_{\text{max}}\) (85.36% - 102.81%) |

AUC\(_{0-t}\) Area under the plasma concentration curve from administration to last observed concentration at time t

C\(_{\text{max}}\) Maximum plasma concentration

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC\(_{0-t}\) and C\(_{\text{max}}\) values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that Dexamethasone 2 mg Tablets (Auden McKenzie (Pharma Division) Limited, UK) is bioequivalent to the reference product Dexamethasone Tablets BP 2.0mg (Aspen Pharma Trading Limited, Ireland; formerly PL 00065/5045R; Organon Laboratories Limited, UK) in healthy subjects after a single, oral dose under fasting conditions.

As Actavis Group PTC ehf and Auden McKenzie (Pharma Division) Limited are considered the ‘same’ (i.e. belonging to the same mother company or group of companies or which are ‘licencess”) per the Commission Communication (98/C 299/03) and the results with Dexamethasone 2 mg Tablets (Auden McKenzie (Pharma Division) Limited, UK) can be extrapolated to the 4 mg and 8 mg strength products, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6, the claim for biowaiver for Dexamethasone 4 mg and 8 mg Tablets (Actavis Group PTC ehf) is accepted.

IV.3 Pharmacodynamics

The clinical pharmacology of dexamethasone is well-known. No new pharmacodynamic data were submitted and none are required for applications of this type. An adequate summary of the pharmacodynamic profile of dexamethasone has been presented in the clinical overview.

IV.4 Clinical Efficacy

The clinical pharmacology of dexamethasone is well-known. No new efficacy data have been submitted and none are required for applications of this type. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical Safety

The safety profile of dexamethasone is well known. No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications.

IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan, 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 Dexamethasone 4 mg and 8 mg Tablets.
A summary of safety concerns in listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td>Important identified risks</td>
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<tr>
<td>Adrenocortical insufficiency</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Steroid withdrawal syndrome</td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Use in patients with diabetes mellitus</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>Growth retardation in infants and children</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
</tr>
<tr>
<td>Missing information</td>
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<tr>
<td>None</td>
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</tbody>
</table>

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications, from a clinical point of view.

**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 pack 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 AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compound. Therapeutic equivalence has been demonstrated between the applicant’s products and the reference product. The benefit/risk balance is therefore considered to be positive.

The grant of Marketing Authorisations is recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

Dexamethasone 4 mg Tablets:
Dexamethasone 4 mg and 8 mg Tablets

Each tablet contains 4 mg of dexamethasone.
Also contains lactose monohydrate.

Please see enclosed leaflet.

Read the package leaflet before use.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Store in the original package in order to protect from light.

MA Holder:
TEVA UK Limited,
Sandbourne,
BN22 9AF,
United Kingdom
PL 00196/0198
EA 076513

PL 00289/2198-2199
Dexamethasone 8 mg Tablets:

- Oral use
- Contains 8 mg of dexamethasone
- Contains lactose monohydrate
- Please see enclosed leaflet
- Read the package leaflet before use
- KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
- Store in the original package in order to protect from light
Dexamethasone 4 mg Tablets
Dexamethasone 8 mg Tablets

PL 00289/2198-2199

STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

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<th>Application type</th>
<th>Scope</th>
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