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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the need for revision of the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Peripheral Arterial Occlusive Disease (CHMP/EWP/714/98 rev 1)

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| Agreed by Cardiovascular Working Party | September 2018 |
| Adopted by CHMP for release for consultation | 18 October 2018 |
| Start of public consultation | 12 November 2018 |
| End of consultation (deadline for comments) | 30 June 2019 |

The proposed guideline will replace Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Peripheral Arterial Occlusive Disease (CHMP/EWP/714/98 rev 1).

Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

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| Keywords | *Peripheral arterial diseases (PADs), lower extremity artery disease (LEAD), concept paper, Peripheral Arterial Occlusive Disease (PAOD)* |

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# 1. Introduction

Peripheral arterial diseases (PADs) encompass all arterial diseases other than coronary arteries and the aorta.

Currently, the main focus of pharmacotherapy has been on the lower extremity artery disease (LEAD) and this is also reflected in the scope of the current CHMP Note for Guidance (peripheral arterial occlusive disease affecting the arteries of the lower extremities). The recent clinical guidelines (ESC 2017 Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases) have broadened their focus to also discuss interventions in the context of other peripheral arterial diseases, including the carotid and vertebral, upper extremities, mesenteric and renal arteries.

Drug therapy has mainly been targeted at symptoms of the chronic ischaemia in the lower extremity, but also on the general prevention of adverse cardiovascular outcomes beyond the management of the disease related to a specific site of atherosclerosis, less so on promoting the amputation free survival. Invasive vascular procedures and surgery are the current methods of choice to address advanced disease locally and combining these with further preventive medication has sparked interest.

There have been recent development programmes in the field of ATMP (cell therapy) which target vasculogenesis, angiogenesis, arteriogenesis and immunomodulation and may possibly aim at limb salvage in addition to symptomatic benefit.

# 2. Problem statement

In light of the developments in the field of PADs, the title/scope of the guideline needs to be re-discussed to decide if other locations in addition to the lower extremities need to be covered or the title adapted to reflect limiting the guidance on the lower extremity disease only. The Note for Guidance also excludes the peripheral vascular disorders of inflammatory or immunologic origin (e.g. thromboangiitis obliterans or Buerger's disease and necrotic vasculitis). The general cardiovascular (CV) prevention is covered in other guidance documents and is not to be in the scope of this guideline.

The recent clinical development programmes have used the Rutherford classification instead of the Fontaine classification that is currently advocated by the guideline to describe the severity of the disease. The differences (the addition of objective non-invasive data) and possible benefits of this change need to be discussed and if the scope is to be broadened the description of the severity in other locations may need to be addressed. The increasing diabetic population may necessitate inclusion of further considerations to reflect the clinical specifics of PADs in these patients.

The primary endpoint proposed in recent clinical development programmes (e.g. clinical response defined as a change in Rutherford classification from CLI Category 4 or 5 to Category 3 or lower at 12 months) deviates from the endpoint recommended in the currently approved guideline. The separation of the benefits regarding symptoms and disease progression may need to be discussed/re-emphasized.

It should be discussed if the emergence of advanced therapies necessitates addressing any specific points in the guideline (e.g. mechanism of action, safety) or modification of the current advice. The developments in study methodology on estimands and sensitivity analyses need to be incorporated where relevant.

## 3. Discussion (on the problem statement)

An update of the Note for Guidance is foreseen.

The following points are proposed to be addressed in the update:

1. Scope/title of the document will be refined to reflect the evolution in clinical definitions and guidelines on the diagnosis and treatment of PADs;

2. Clinical classifications to describe the symptomatic severity of the disease will be further discussed and the recommendations updated to reflect the current practice. Also the relevance of anatomic classification systems and angiosome terminology will be discussed in light of the localised advanced therapies. Further classification issues relevant for the increasing population of patients with coexisting diabetes and PADs (e.g. WIfI, wound, ischemia and foot infection classification) may need to be included;

3. Endpoints to establish efficacy in different settings may need to be revised to add clarity, to reflect the value of preventing major adverse limb events when pharmacological therapy is used in conjunction with other treatment modalities, to discuss the acceptable ways of establishing symptomatic benefit or to base the efficacy demonstration on complete ulcer healing or other local endpoints;

4. The concept of estimands will be briefly contextualised in the field of PAD trials (intercurrent events need to be considered in the description of a treatment effect on a variable of interest because both the value of the variable and the occurrence of the event may depend on treatment);

5. Issues specific to ATMP development for PAD will be covered in relevant sections of the document, most foreseeably under pharmacodynamics/mechanism of action, local efficacy endpoints and safety evaluation.

## 4. Recommendation

The Cardiovascular Working Party (CVS WP) at the EMA recommends revising the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Peripheral Arterial Occlusive Disease (CPMP/EWP/714/98 rev.1)* taking into account the issues identified above.

## 5. Proposed timetable

This Concept Paper is released for 6 months public consultation. It is anticipated that the draft Guideline may be released 18 months after adoption of the Concept Paper by the CHMP. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 12 months.

## 6. Resource requirements for preparation

The drafting process will involve the co-operation between the Cardiovascular Working Party (CVSWP), the Biostatistics Working Party and the Scientific Advise Working Party at the EMA.

## 7. Impact assessment (anticipated)

The document is intended to update methodological aspects when developing products for the treatment of PADs. It should also provide a basis for the CHMP when assessing efficacy and safety data from studies for these products.

## 8. Interested parties

The interested parties in the guideline include the Industry, Regulators and Academia including learned societies (e.g. European Society for Cardiology [ESC], the European Society for Vascular Surgery [ESVS], Cardiovascular Intervention of Radiological Society of Europe, the European Stroke Organization [ESO]) and clinical trialists in the cardiovascular field.

## 9. References to literature, guidelines, etc.


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