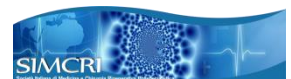


# Indications on appropriate clinical use of blood components for topical use

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# INDICATIONS ON APPROPRIATE CLINICAL USE OF BLOOD COMPONENTS FOR TOPICAL USE

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## INTRODUCTION

### THE WORKING GROUP AND ITS AIMS

Pursuant to Ministry of Health Decree (MHD) of 2nd November, 2015 (Ordinary Supplement N. 300 of Official Journal of 28th December, 2015) "Provisions relative to quality and safety standards of blood and blood components", the Italian National Blood Centre (CNS) set up and coordinated a multidisciplinary working group (MWG) the aims of which was to provide and periodically update the list of clinical conditions and grade of recommendations regarding appropriate clinical use of blood components for topical use based on the published scientific evidence regarding different clinical, medical and surgical settings.

The MWG, formed with Decree of the Director General of the CNS Prot. n. 0848.CNS.2016 of 13/04/2016, has recently changed its composition, and in addition to the scientific societies already signatories of this technical document, now includes the Italian Ophthalmological Society - SOI.

As part of its mandate, the MWG performs:

- the systematic review of scientific literature with the aim of verifying the grade of appropriateness of already known clinical conditions as well as new ones;
- the identification, through surveys, of those areas of application which, not falling under the conditions regulated by the transfusion regulations currently in force, need to be consolidated by clinical studies;
- the establishment of a multidisciplinary network of professionals with specific expertise in the production and clinical use of blood components for topical use, in order to timely update the list of clinical conditions based on the respective grades of recommendation/evidence.

The examination of the scientific literature produced up to 31/12/2020, with particular reference to the most recent meta-analyses and systematic reviews, showed that studies conducted in certain settings on the topical use of blood components had a high level of risk bias. In particular, many clinical studies appear to be neither well designed nor comparable, with insufficient statistical power also due to differences in the choice of criteria for the inclusion of patients and in the timing of treatment. On the other hand, many indications are already part of currently used clinical practices, for which scientific evidence suggests that the topical use of these products as alternative or supportive therapies in certain settings is not only efficacious but also cost-effective.

## BLOOD COMPONENTS FOR TOPICAL USE

### CLINICAL USE

Blood components for topical use are being increasingly utilised in different specialized medical and surgical fields with the following methods:

- application on skin or mucous surfaces - **topical use**
- intra-tissue or intra-articular infiltration - **infiltrative use**
- local application in surgical fields - **surgical use**.

### TYPES OF PRODUCTS

The blood components for topical use utilised for the clinical conditions mentioned in this document, are those specified in the MoH Decree of 1<sup>st</sup> August 2019 - Amendment of the MoH Decree of 2nd November 2015 “Provisions relative to quality and safety standards of blood and blood components” – in which a distinction is made between platelet-derived products, plasma-derived products and serum-based products.

For the production and utilisation of blood components for topical use, authorised medical devices of Class IIa or higher must be used pursuant to current legislation on medical devices.

### LAWS IN FORCE

Thanks to their regenerative propriety and the capacity to regenerate tissues and to facilitate the healing of skin and mucous lesions, blood components for topical use are widely utilised in various clinical settings in both private and public health facilities.

Patients can be treated while hospitalised (ordinary hospitalisation, day-hospital) or as outpatients or in day-surgery. They can be treated in public health facilities, both accredited and non-accredited private facilities, and in medical and dental surgeries.

Allogeneic and autologous blood components for topical use are prepared within Blood Establishments (BEs) and their peripheral organisational sites in compliance with the current legislation regarding their collection, preparation, biological qualification (when foreseen), storage, and distribution.

Autologous blood components for topical use can be prepared in accredited and non-accredited private health care facilities within the framework of a specific agreement between the aforementioned health care facilities and the local public health care facility where the BE is located, in compliance with Annex X, Point E of MoH Decree of 1<sup>st</sup> August 2019.

The BEs ensure the traceability of the processes and products and are responsible for all haemovigilance activities regarding blood components for topical use whether prepared and used directly by the BEs or prepared and used by public health facilities or both accredited and non-accredited private facilities under the provisions of an agreement with the BE in question.

Pursuant to paragraph 3, Art. 3 of MoH Decree of 1<sup>st</sup> August 2019, for those recommendations still not consolidated by the available scientific evidence either due to the type of production or the utilisation of blood components for topical use not specified in the laws in force, specific clinical trials must be conducted in accordance with best clinical practices and the involvement of BEs and all health facilities that will use the products. The RBCCs shall inform the CNS when the trials start and shall update on the results obtained.

As regards providing therapeutic treatments that foresee the utilisation of blood components for topical use, in Annex 4D of the Decree of the Prime Minister “*Definition and updating of the essential levels of care, referred to in Article 1, paragraph 7, of Legislative Decree of 30th December 1992, N. 502*” of 12th January, 2017 regarding specialised outpatient services, the following codes were introduced:

- 99.07.2 - APPLICATION ON SKIN OR MUCOUS SURFACES;
- 99.07.3 - INTRA-TISSUE, INTRA-ARTICULAR INFILTRATION OR LOCAL APPLICATION IN SURGICAL FIELDS.

For the application of the above-mentioned codes, the Decree of the Prime Minister of 12th January, 2017 refers to note n. 89 (Annex 4D of the Decree of the Prime Minister of 12th January, 2017) that reads: Deliverability conditions as specified in the Decree through the implementation of Articles 3 and 21 of Law 219/2005.

## CLASSIFICATION OF CLINICAL CONDITION

The classification of clinical conditions for the utilisation of blood components for topical use stems from the systematic evaluation of available scientific literature, conducted according to the methods described in Appendix 1.

For the purposes of this document, the term appropriateness is intended as the proper or correct utilisation of blood components for topical use in specific clinical and health settings, as well as criteria of efficacy, safety and effectiveness based on supporting scientific evidence.

After closely examining the available scientific literature three groups of clinical conditions were identified:

1. Clinical conditions for the use of blood components for topical use based on **strong recommendations**.
  - ✓ Clinical conditions with **grade of recommendation 1B** (Table I, Appendix 1): strong recommendations, likely to apply to most patients.
  
2. Clinical conditions for the use of blood components for topical use based on **weak recommendations**.
  - ✓ Clinical conditions with **grade of recommendation 2B** (Table I, Appendix 1): Weak recommendation; alternative approaches likely to be better for some patients under certain circumstances.
  
3. Clinical conditions for the use of blood components for topical use based on **very weak recommendations**.
  - ✓ Clinical conditions with **grade of recommendation 2C** (Table I, Appendix 1): Very weak recommendations; other alternatives may be equally reasonable.

**TABLE OF CLINICAL CONDITIONS AND GRADE OF RECOMMENDATION**

<b>CLINICAL CONDITIONS</b>	<b>GRADE OF RECOMMENDATION</b>
DIABETIC FOOT ULCERS (for cycles of 12 applications)	<b>1B</b>
CHRONIC ULCERS AND WOUNDS (for cycles of 12 applications)	<b>1B</b>
BURN INJURIES	<b>1B</b>
GRADE 1-3 KNEE AND HIP OSTEOARTHRITIS ACCORDING TO THE KELLGREN-LAURENCE SCALE (for cycles of 3 applications)	<b>1B</b>
TEMPOROMANDIBULAR JOINT OSTEOARTHRITIS (for cycles of 3 applications)	<b>2B</b>
ANKLE OSTEOARTHRITIS (for cycles of 3 applications)	<b>2B</b>
TREATMENT OF PSEUDOARTHRITIS	<b>2B</b>
RECONSTRUCTION OF ANTERIOR CRUCIATED TENDON	<b>2B</b>
TREATMENT OF ANTERIOR CRUCIATE LIGAMENT LESIONS	<b>2B</b>
TREATMENT OF ROTULAR TENDONS DISORDERS	<b>2B</b>
INFILTRATION TREATMENT OF EPICONDYLITIS	<b>2B</b>
TREATMENT OF ACHILLES TENDON LESIONS	<b>2B</b>
ROTATOR CUFF REPAIR	<b>2B</b>
OTHER BONE, MUSCLE, AND TENDON DISORDERS (e.g. PLANTAR FASCIITIS)	<b>2B</b>
MAXILLARY SINUS LIFT	<b>2B</b>
PERIDONTAL REGENERATION	<b>2B</b>
COADJUVANT TREATMENT IN POST-EXTRACTIVE ALVEOLAR REGENERATION	<b>2B</b>
COADJUVANT HEALING TREATMENT FOLLOWING POST-EXTRACTIVE AND IMPLANT SURGERY IN PATIENTS WITH SYSTEMIC DISEASES	<b>2B</b>
ORAL SURGERY (IMPACTED TEETH REMOVAL, EXERESIS OF CYSTIC LESIONS) TO ENHANCE THE EPITHELISATION OF WOUND AND TO ACCELERATE THE FORMATION OF THE MUCOSAL SEAL	<b>2B</b>
ORAL SURGERY IN PATIENTS IN IV BISPHOSPHONATES AND ANTI-ANGIOGENIC THERAPY	<b>2B</b>
SURGICAL EXERESIS OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)	<b>2B</b>
IMPLANT OPERATIONS	<b>2B</b>
BONE GRAFT AND REGENERATION OPERATIONS TO ENHANCE THE HEALING OF SOFT TISSUES AND COADJUVANT OF GRAFT MATERIALS	<b>2B</b>
DRY EYE SYNDROME	<b>2B</b>
OCULAR SURFACE BURNS	<b>2B</b>
LESIONS AND ULCERS OF THE CORNEAL SURFACE	<b>2B</b>
TREATMENT OF EARLY ANDROGENETIC ALOPECIA	<b>2B</b>
TREATMENT OF EARLY ALOPECIA AREATA	<b>2B</b>
TREATMENT OF SCARRING DISEASES	<b>2B</b>
GRADE 4 KNEE AND HIP OSTEOARTHRITIS ACCORDING TO THE KELLGREN-LAURENCE SCALE (for cycles of 3 applications)	<b>2B</b>
REGENERATION OF INTERVERTEBRAL DISCS	<b>2C</b>
ANTI-AGEING PLASTIC SURGERY	<b>2C</b>
TREATMENT OF MALE AND FEMALE GENITAL LICHEN	<b>2C</b>
TREATMENT OF ORAL LICHEN	<b>2C</b>

## CONCLUSIONS

This document is the result of a shared, organic and systematic evaluation of the available scientific literature with the aim of updating therapeutic indications on the clinical use of blood components for topical use in various clinical, medical and surgical settings.

Both the list of clinical conditions and the grade of evidence will be periodically updated and revised taking into account new available scientific evidence on the subject.

The evaluation of the scientific evidence currently available shows that several clinical trials provided inadequate data for comparison and were statistically weak due to the differences in the choice of patient inclusion criteria, in the timing of the treatment, and in the clinical outcomes taken into account.

Therefore, it is desirable that more and better production of scientific evidence be encouraged based on well-designed and adequately powered randomized clinical trials with a low risk bias, also through the close collaboration between blood establishments and the health facilities that utilise blood components for topical with the active support of the scientific societies in question.

## APPENDIX 1 - APPROACH TO GRADES OF RECOMMENDATIONS

For the definition of the grade of recommendation and the scientific evidence in the clinical conditions reported in literature, the Consensus Conference of the American College of Chest Physicians of 2004<sup>1</sup> was adopted. The grade of recommendation is expressed in Arab numbers (1, 2), depending on the strength, and in letters (A, B, C), according to the evidence examined and the type of studies conducted (Table 1).

Table 1 - Grade of recommendation

GRADE OF RECOMMENDATION	CLARITY OF RISK/BENEFIT	METHODOLOGICAL STRENGTH OF SUPPORTING EVIDENCE	IMPLICATIONS
1A	Clear	RCTs without important limitations.	Strong recommendation; can apply to most patients in most circumstances without reservation.
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies.	Strong recommendation; can apply to most patients in most circumstances.
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws).	Strong recommendations; likely to apply to most patients.
1C	Clear	Observational studies.	Intermediate-strength recommendation; may change when stronger evidence is available.
2A	Unclear	RCTs without important limitations.	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values.
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies.	Weak recommendation; best action may differ depending on circumstances or patients' or societal values.
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws).	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C	Unclear	Observational studies.	Very weak recommendations; other alternatives may be equally reasonable.

<sup>1</sup> Guyatt G, Schünemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; 126: S179-87.



Literature published up until 30th December 2020, was analysed.

The evaluation of the scientific literature was conducted starting with the articles supplied by scientific societies with representatives who participated in the MWG as well as articles from PubMed/Medline, Cochrane and Call Detail Recording (CDR) databases. The research was conducted with the use of additional restrictions in order to exclude those which did not meet the inclusion criteria.

In particular, the following types of scientific articles were examined:

- Cochrane Systematic Reviews;
- Systematic Reviews, meta-analysis and reviews;
- Controlled clinical trials, randomized clinical trials and observational studies published after the last systematic review/ meta-analysis, when available.

The examined articles were divided according to the clinical condition or the medical/surgical setting.

After the analysis of each single article, the relative level of evidence regarding the therapeutic efficacy of blood components for topical use was extracted; subsequently, where sufficient evaluation elements were available the grade of recommendation resulting from the aforementioned levels of evidence was formulated.

When discrepancies in the conclusions of the studies examined were found, the grade of recommendation was formulated taking into account methodology, and the limitations and date of publication of each article analysed.

At present, for certain clinical conditions, there are no clinical studies meeting the criteria adopted for the purpose of this document.

However, the authors acknowledge that when it comes to the clinical utilisation of blood components for topical use, strong recommendation may not always apply to all patients in all circumstances, and that certain weaker recommendations could be affective in some patients and some circumstances, for example where alternative therapies do not exist.

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