HAUTE AUTORITÉ DE SANTÉ

REASSESSMENT OF CATEGORIES OF MEDICAL DEVICES

Bone substitutes

Short text

May 2013

The full report supporting for this assessment can be downloaded from
www.has-sante.fr

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Composition of the working group

1. Steering Group

The steering group was made up of the following professionals:

- **Dr André Chaine**, maxillofacial surgeon, Pitié Salpêtrière Hospital, Paris (75);
- **Dr Gilles Dolivet**, ENT surgeon, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy (54);
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2. Rating Group

The rating group was made up of the following professionals:

- **Dr Mohamed Allaoui**, neurosurgeon, Lille Regional University Hospital, Lille (59);
- **Dr Jean-Luc Barat**, neurosurgeon, Clairval Private Hospital, Marseilles (13);
- **Dr Thierry Camponovo**, stomatologist, Besançon (25);
- **Dr Jean-Baptiste Charrier**, ENT surgeon, Paris (75);
- **Dr Marie-Laure Colombier**, dental surgeon, Louis-Mourier Hospital, Colombes (92);
- **Dr Philippe Esposito**, neurosurgeon, Établissement des Diaconesses, Strasbourg (67);
- **Prof. Olivier Hauger**, radiologist, Pellegrin Hospital, Bordeaux (33);
- **Dr Patrick Jammet**, maxillofacial surgeon, University Hospital, Montpellier (34);
- **Dr Patrick Le Couteur**, orthopaedic surgeon, Polyclinique de l'Atlantique, Saint-Herblain (44);
- **Prof. Ludovic de Gabory**, ENT surgeon, Pellegrin Hospital, Bordeaux (33);
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- **Dr Jean-Patrick Rakover**, orthopaedic surgeon, Du Pré Surgical Clinic, Le Mans (72);
- **Dr Bernard Schweitz**, dental surgeon, Paris (75);
- **Dr Éric Steimle**, dental surgeon, Strasbourg (67).

The members of the working group were appointed by the CNEDiMTS board from among the experts proposed by the national professional councils of the medical specialities concerned, experts who responded to an appeal for candidates and experts known to HAS.

In accordance with decree No. 2004-1139 of 26 October 2004 (Article R. 161-84 to R.161-86 of the Social Security Code), all members of the working group have completed a public declaration of interest, mentioning direct or indirect links with any company or body involved in the field covered by the missions of HAS.

The analysis of the declarations of interests was carried out in accordance with the criteria of the HAS "Guide des déclarations d'intérêts et de gestion des conflits d'intérêts" [Guide to declarations of interest and the management of conflicts of interest] (adopted by the HAS Board on July 2013[1]).

This analysis of the working group members' interests did not reveal any interests that were likely to lead to a significant conflict. The makeup of the working group and declarations of interest were published on the HAS website (http://www.has-sante.fr) before the group's first meeting. These were also restated at the start of the group meeting and when presenting the working group's position to the CNEDiMTS.

These experts' declarations of interest are published on the HAS website (http://www.has-sante.fr).

[1]Haute Autorité de Santé – Guide des déclarations d'intérêts et de gestion des conflits d'intérêts [Guide to declarations of interest and the management of conflicts of interest] – July 2013 [link].

Short text

Background

Bone substitutes are used in various disorders as bone fillers. Several specialities are involved in the use of biomaterials in this indication (orthopaedic surgery, neurosurgery, dental surgery, maxillofacial surgery, ENT and cervical surgery, tumour surgery, etc.).

Since 2005, CNEDiMTS (National Committee for the Evaluation of Medical Devices and Health Technologies) has been reviewing all products and services included under generic categories in the list of products and services qualifying for reimbursement (LPPR). The review described in this report relates to bone substitutes of synthetic origin and those obtained from or containing derivatives or non-viable tissues of animal origin. The scope of the assessment thus concerned reviewing five generic categories and 189 brand names.

Objectives – Working method

The objectives of this work were to assess the bone substitutes in order to:

- determine their indications in the diseases concerned;
- define their place in therapeutic use;
- assess their clinical value for each indication;
- characterise the technical specifications which determine their actual benefit (AB), so as to avoid classification errors and clarify which devices are covered by the current generic categories;
- define the conditions of prescribing and using products to be included on the LPPR;
- put forward an updated nomenclature;
- estimate their target population;
- define the level of evidence and the assessment criteria required for trials submitted with applications for inclusion under the brand name.

The working method is based on a systematic review of the literature and an analysis of the dossiers submitted by manufacturers, and draws on the expertise of healthcare professionals. The available clinical data, which are insufficiently robust as regards the efficacy of bone substitutes, and the multiplicity of clinical situations concerned have required the formalisation of the opinions of healthcare professionals on the subject. The method adopted was that of the Formal Expert Consensus (FEC). It relies on the rigorous and explicit modelling of opinions, which allows the level of agreement and disagreement between experts on a representative panel of prescribers to be quantified[2].

The members of the working group declared their interests at the start and throughout the project. Two independent experts unconnected with this assessment were also consulted.

[2] Haute Autorité de Santé. Developing good practice guidelines. Practice guidelines by the “Formal consensus” method. Quick Methodology Guide. Saint-Denis La Plaine: HAS; 2010.
http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-01/guide_methodologique_consensus_formalise.pdf

Assessment – Data analysis

Literature data

Analysis of the literature identified 1527 references of interest, including three guidelines, seven systematic reviews or meta-analyses, 20 randomised controlled trials and one clinical study. The assessment criteria were clinical (function, quality of life, pain), radiological or histological and/or focused on complications.

The data show that several therapeutic domains use biomaterials as a bone filler and confirm their interest in this indication. However, irrespective of the clinical situation, the selected studies do suffer from many methodological limitations, and it is not possible on the basis of these studies to draw any firm conclusions as to the value of bone substitutes, whether synthetic or of animal origin, when compared with other fillers. The diverse nature of the available clinical data and the lack of prospective comparison studies make it impossible to pick out a reference bone substitute from among those assessed.

Data from the formal expert consensus (FEC)

In view of the difficulties in interpreting the literature data, it was decided to organise a formal expert consensus.

A steering group worked out the proposals, which were then submitted to a rating group with a view to eliciting professional agreement and thus formalise the working group opinion on questions raised by this assessment. Of the 65 proposals put forward, 20 received a strong consensus in favour, 24 a weak consensus in favour and 21 didn't lead to any professional consensus. Not a single consensus against was recorded.

The results of the rating enabled proposals to be made, in particular on drawing up a draft nomenclature. The professional agreements secured related principally to:

- coming up with a generic definition of a bone substitute;
- define the nomenclature (developing the synthetic and animal nomenclatures on the basis of a similar pattern, creating generic categories clarifying the notions of volume and form, etc.);
- the minimum CNEDiMTS requirements for the inclusion of a new bone substitute.

Data from expert hearings

In light of the questions raised during the FEC, two biomaterials specialists who were not involved in this assessment were given a hearing. Their main suggestions were the following:

- they put forward a nomenclature based on the composition/origin of the bone substitutes, their form and their volume. They also recommended a list of biomaterials making up bone substitutes which, according to them, would be common to all of the bone substitutes;
- in terms of clinical data, the two experts put forward a minimum level of evidence that trials have to meet before a new bone substitute can be added to the LPPR. The methodology and follow-up must match the product claims;
- as regards the technical information on the bone substitutes, companies should, according to the experts, provide information about the precise conditions under which particular parameters were determined, such as rate of resorption and compression resistance.

Position of the working group

The proposals of the working group are based essentially on the opinions of experts (FECs, hearings, working meetings), on account of the limited literature on the specific interest of bone substitutes.

The working group's main proposals on the nomenclature concerned:

- coming up with a generic definition of a bone substitute;
- deciding on the minimum technical specifications, covering such aspects as composition and filling volume;
- proposals for listing of bone substitutes made up of biomaterials of animal origin under generic categories;
- withdrawing the term "cement" in relation to bone substitutes and developing generic categories for "injectable" and "modelable" forms;

- developing generic categories for custom-made bone substitutes intended for the reconstruction of the facial skeleton and of the skull, as well as a warning about the need to observe the legislation regarding “custom-made” manufacture;
- listing of interposition wedges and centro-medullary cement plugs under their generic categories in the section on “accessories for joint implantation” in the LPPR;
- the proposal to retain inclusion under brand name for composite bone substitutes consisting of a synthetic ceramic material combined with a bovine collagen.

Conclusion of the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS)

CNEDiMTS accepted the main points of the working group proposals. The wording of the indication was made more explicit, as were the requirements in terms of the clinical studies relating to bone substitutes under a generic category.

Depending on the characteristics of bone substitutes, the CNEDiMTS recommends either the development of generic categories defined in particular by accurate technical specifications, or inclusion under brand name.
When inclusion under a generic category is recommended, the actual benefit is regarded as sufficient.

CNEDiMTS differentiates between two major categories of bone substitutes:
- synthetic bone substitutes not containing any derivative or tissue of biological origin or not obtained from such derivatives;
- bone substitutes obtained from or containing derivatives or non-viable tissues of animal origin.

In the absence of data allowing a comparison of the efficacy and advantages of one type compared with the other, CNEDiMTS recommends that all devices complying with the generic categories put forward by the working group, of whatever type, should be included for reimbursement.
CNEDiMTS recommends a common indication for all the generic categories defined, i.e.: “use of bone substitute (for filling, reconstruction, fusion), when autologous solutions are inapplicable or insufficient”.
The recommended nomenclature differentiates between synthetic substitutes and bone substitutes composed of biomaterials of animal origin. The indications for both product categories are nonetheless identical.

CNEDiMTS recommends inclusion under brand name for all bone substitutes that do not meet the agreed technical specifications. The company concerned does need to submit a dossier for a specific assessment before the item can be included in the list of products and services qualifying for reimbursement (LPPR).

With the available data it is impossible to state categorically that one type of bone substitute is better than another, nor to identify a reference bone substitute from among the same category of biomaterials. The Committee has ruled that there is no improvement in actual benefit (IAB V) between the various generic categories relating to synthetic substitutes and bone substitutes containing derivatives of animal origin.
Moreover, CNEDiMTS has defined the criteria for assessing new devices under their brand name if they do not meet the technical specifications of the proposed generic categories:
- when the company has no special claims, one high-quality observational study is the minimum requirement, with an assessment criterion appropriate to the claimed indication and a follow-up of 6 to 24 months, depending on the clinical situation concerned;
- when the company claims an improvement in actual benefit in comparison with products already listed on the LPPR, at least one comparative clinical study is required. The choice of comparator must be justified. The assessment criterion must be in accordance with the stated claims (e.g.: if osteoinductive power is claimed, the assessment criterion may be faster bone

consolidation in cases of fracture or, in dentistry, improved implant survival). The expected minimum follow-up is from 6 to 24 months, depending on the clinical situation concerned.

Glossary

- **Osteoconduction:** passive property of a material to receive new bone growth by vascular and cellular migration from recipient tissue in contact with this material

- **Osteoinduction:** process of stimulation by proteins leading to proliferation and/or differentiation of stem cells in a mineralisable bone matrix

- **Osteogenesis:** process of formation of the bone matrix, without any indication as to the origin of the cells (whether from the graft or from the host)

List of abbreviations

AB	Actual benefit
AFIDEO	Association of European manufacturers, importers and distributors of orthopaedic and traumatological implants
AFSSAPS	French Healthcare Product Safety Agency (now ANSM)
ANSM	French National Medicines and Health Products Safety Agency (ex-AFSSAPS)
BS	Bone substitutes
CCAM	Joint classification of medical procedures
CEPP	Committee for the Assessment of Products and Services (now CNEDiMTS)
CEPS	Committee for the Pricing of Healthcare Products
CNAMTS	National Salaried Workers' Health Insurance Fund
CNEDiMTS	National Committee for the Evaluation of Medical Devices and Health Technologies (previously CEPP)
CPG	Clinical Practice Guideline
DBM	Demineralized Bone Matrix
DCP	Di-Calcium Phosphate
DCPD	Di-Calcium Phosphate Dihydrate – DCPD, so-called "brushite"
DGOS	Directorate General for the Provision of Healthcare
DGS	Directorate-General for Health
DSS	Social Security Directorate
ENT	Ear, nose and throat
FEC	Formal Expert Consensus
FGF	Fibroblast Growth Factor
GBR	Guided bone regeneration
GESTO	Group for the study of tissue and bone substitutes in orthopaedics
GTR	Guided Tissue Regeneration
HA	Hydroxyapatite
HAS	Haute Autorité de Santé (French National Authority for Health)
IAB	Improvement in Actual Benefit
ICD-10	International Classification of Diseases version 10
LPPR	List of products and services qualifying for reimbursement
NGAP	General Nomenclature of Medical Procedures
NS	Non-significant
PDGF	Platelet-Derived Growth Factor
PMMA	Polymethylmethacrylate
PMSI	Programme for clinical information systems
PRP	Platelet Rich Plasma
RCT	Randomised controlled trial
rhBMP	Bone Morphogenetic Protein
RSA	Anonymised discharge summaries
RSI	Health and retirement scheme for independent workers
SED	Medical Devices Assessment Department
SFNC	French Society of Neurosurgery
SFORL	French Society of Otorhinolaryngology
SFPIO	French Society of Paradontology and Oral Implantology

SFR	French Society of Radiology
SFSCMF	French Society of Stomatology and Maxillofacial Surgery
SNATIH	National System of Information on Hospital Admissions
SNITEM	National union of the medical technology industry
SOFCOT	French Society of Orthopaedic and Trauma Surgery
SOFROT	French Society of Orthopaedic and Trauma Research
TGFβ	Transforming Growth Factor β
TSE	Transmissible Spongiform Encephalopathy
βTCP	β-Tri-Calcium Phosphate