NOVAGENIT®

DAC®

DEFENSIVE ANTIBACTERIAL COATING

THE HYDROGEL BARRIER TO INFECTION

THE MECHANISM OF INFECTION: THE RACE TO THE SURFACE

In case of contamination of the implant surface, colonisation by pathogens results in formation of a barrier known as **Biofilm.**
Biofilm is an impervious polymeric matrix, able to make the bacterial colony resistant to antibiotic treatment and the patients immune system[13;14;15;16].

THE INFECTION MECHANISM FOLLOWS THREE STAGES IN QUICK SUCCESSION

Immediately after surgery

Pathogens begin to adhere to the prosthetic surface.

Few minutes after surgery

Pathogens start to multiply and irreversibly fix themselves to the implant.

Few hours after surgery

In the absence of a reaction of the organism, the bacterial colony starts biofilm production.

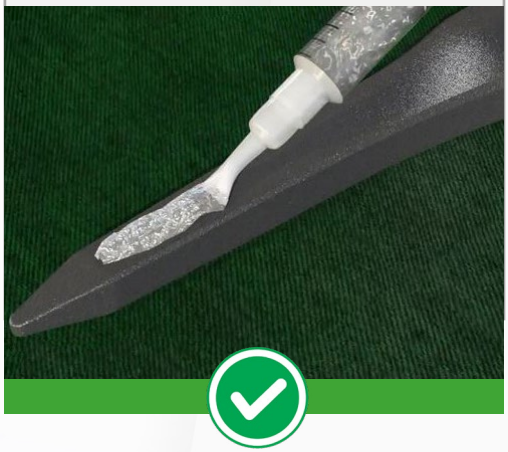
DAC® HYDROGEL: THE BARRIER EFFECT

The application of **DAC®** disrupts the ability of pathogens to bind to the implant surface, inhibiting the initial stages of bacterial colonisation that would then result in biofilm formation.

DAC® forms a hydrogel that acts as a temporary barrier, providing an effective mechanism for prevention of bacterial infection.

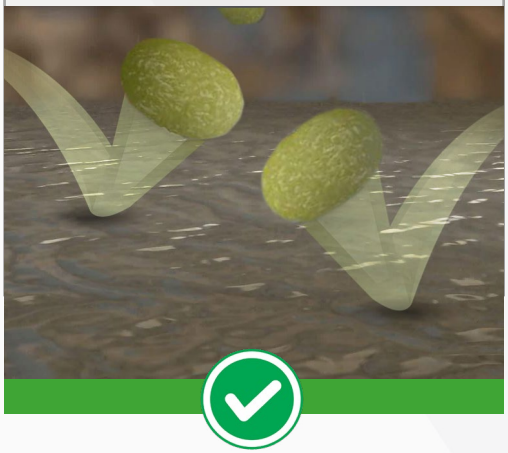
THE DAC® HYDROGEL DEFENSIVE MECHANISM CAN BE ILLUSTRATED IN THREE STAGES:

Immediately before surgery



The implant surface is evenly coated with the **DAC®** hydrogel.

Immediately after surgery



Bacterial adhesion and colonisation of the implant surface is interrupted by the **DAC®** hydrogel layer and by its hydrophilic properties.

Few days after surgery

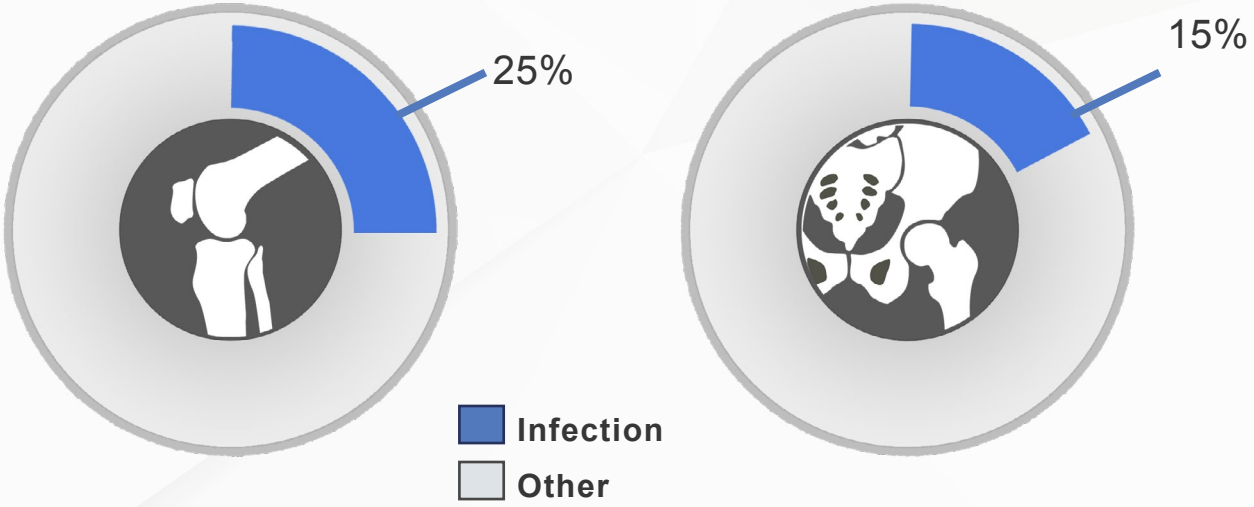
Bacteria left on the implant surface or on the hydrogel are identified and attacked by the immune system.

THE BURDEN OF INFECTION

Infection is the principal cause for failure of primary total knee implants and a significant cause of failure of primary total hip replacement[1;2;3;4], with a rate varying between 0.5% and 4%[5;6;7].

Infection accounts for respectively 25% and 15% of all TKA and THA revisions.

REASONS FOR REVISIONS



Intraoperative bacterial contamination

In spite of modern aseptic procedures, the risk of peri-operative bacterial contamination cannot be completely eliminated. One study demonstrated how 63% of surgical fields show evidence of bacterial contamination[12].

Factors contributing to raised infection risk:[19]

- Autoimmune diseases e.g. Rheumatoid Arthritis[8]
- Diabetes[9]
- Obesity[10]
- Immunosuppression[11]

ANTI-BACTERIAL BIO-ABSORBABLE COATING

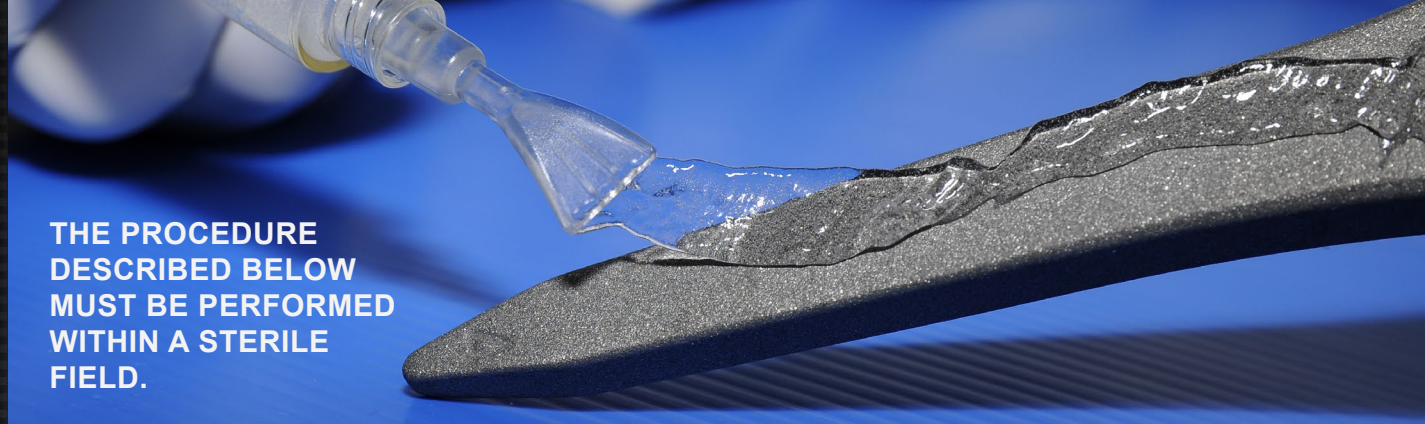
DAC® is a kit for the preparation of a bio-absorbable hydrogel containing hyaluronic acid and polylactid acid, with the following indications:

- Uncemented orthopaedic prostheses
- Osteo-synthesis devices for Traumatology
- Mega-prostheses for Oncology

Experimental studies demonstrated that, as a complement to its barrier effect, the hydrogel powder could be hydrated with a solution of water for injectable preparations containing a final concentration between 2% and 5% of Vancomycin or Gentamycin. *In vitro*, *in vivo*, as well as clinical studies demonstrated how these antibiotics are compatible with **DAC®**, with no negative effect on the hydrogel. Optional antibiotic usage (they are not included in the **DAC®** procedure kit) did not result in any adverse effect in the clinical studies to date. The decision to add antibiotics is the decision and responsibility of the operating surgeon.

The hydrogel it is completely absorbed within 72 hours from its application, and therefore it has no adverse effect on osseointegration or the bone healing process[17].

DAC® KIT PREPARATION AND APPLICATION

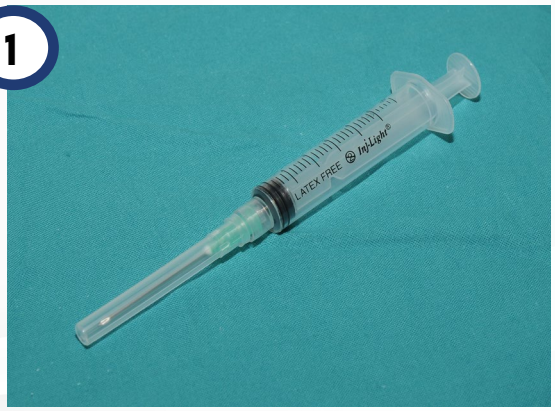


THE PROCEDURE DESCRIBED BELOW MUST BE PERFORMED WITHIN A STERILE FIELD.

Before starting product preparation, ensure the availability of sterile water and syringe needles for injectable preparation.

NOTE: Saline solutions not to be used.

1

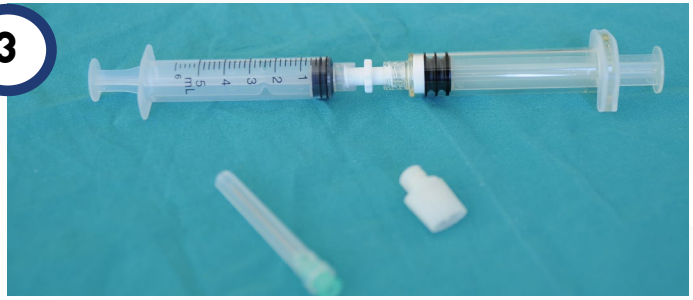


Open the blister containing the empty graduated syringe and draw a suitable quantity of water for injectable preparation. Remove the needle and replace it with the luer-lock connector.

Open the syringe containing the **DAC®** powder. Slightly retract the syringe piston and gently tap the syringe to loosen the powder, making reconstitution easier. The backstop (extension flange) may be attached to the syringe tor easier handling if required.

2

3

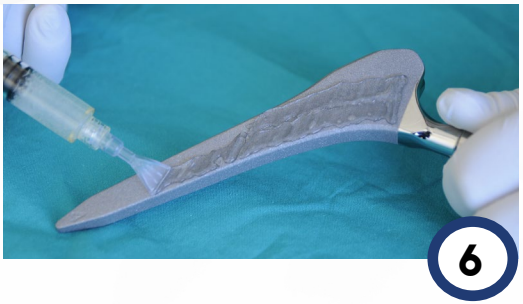


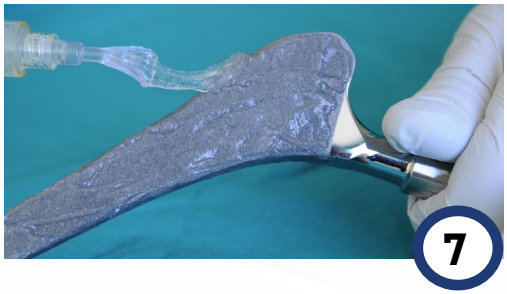
Remove the cap from the syringe containing the **DAC®** powder and connect it to the syringe containing the water.

Hold the two syringes near vertically; with the syringe containing the **DAC®** powder inferiorly. Retract the piston of the latter while at the same time pressing on the syringe with water. Transfer the gel several times from one syringe to the other until a homogenous gel is formed. Leave the gel loaded syringe to rest for 5-10 minutes before use. Finally, disconnect the empty syringe and connector.

DAC® HYDROGEL APPLICATION

The gel can be spread on the implant surface directly from the syringe, or by using a spreader attachment on the syringe to coat wider surfaces.





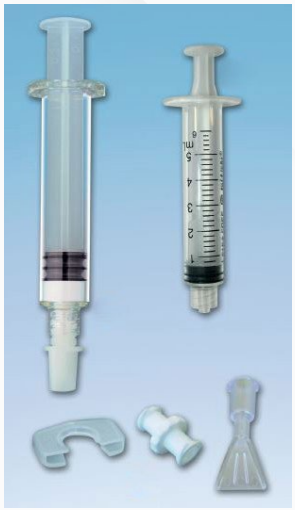
DAC® IN VIVO AND IN VITRO STUDIES [17,18,19,20, 21,22]

DAC® safety has been demonstrated by executing:

- All the *in vivo* and *in vitro* bio-compatibility tests required by the ISO 10993-1 standard;
- *In vitro* degradation studies according to ISO 10993-9, ISO 10993-13, ISO 13781;
- Osseointegration *in vivo* studies;
- Clinical studies performed according to ISO 14155 employing the hydrogel in combination with some commonly available antibiotics.

The barrier effect against bacterial adhesion provided by the **DAC®** hydrogel has been tested with a series of *in vitro* studies demonstrating that:

- **DAC®** forms an homogeneous adhesive layer on the implant surfaces;
- **DAC®** interferes with the bacterial adhesion on the implant surfaces;
- **DAC®** can dislocate those bacteria possibly present on implant surfaces;
- **DAC®** inhibits biofilm formation.



A range of DAC® kit sizes are available offering different quantities of hydrogel according to requirements

DAC® KIT code	Composition	Note
DAC001800	Single Kit composed by 1 sterile **DAC®** syringe containing 180mg of dry powder; 1 complete **DAC®** sterile components set (connector; back-stop; spreader), 1 empty 5ml graduated syringe.	To prepare 3 ml **DAC®** Hydrogel.
DAC003000	Single Kit composed by 1 sterile **DAC®** syringe containing 300 mg of dry powder; 1 complete **DAC®** sterile components set (connector; back-stop; spreader), 1 empty 10ml graduated syringe.	To prepare 5 ml **DAC®** Hydrogel.
DAC003002	Double Kit composed by 2 sterile **DAC®** syringe containing 300mg of dry powder; 2 complete **DAC®** sterile components sets (connector; back-stop; spreader), 2 empty 10 ml graduated syringe.	To prepare 10 ml **DAC®** Hydrogel.
DAC003003	Triple Kit composed by 3 sterile **DAC®** syringe containing 300mg of dry powder; 3 complete **DAC®** sterile components sets (connector; back-stop; spreader), 3 empty 10 ml graduated syringe.	To prepare 15 ml **DAC®** Hydrogel.

The DAC® Kit is a Class III sterile disposable medical device, according to the attached IX of the European Directive 93/42 CEE. Syringe and accessories are double blister packed for use in an Operating Room sterile field.

References:

1. Australian National Joint Register 2012 Report. • **2.** Swedish National Joint Register 2012 Report. • **3.** Bozic K et al. The Epidemiology of Revision Total Hip Arthroplasty in the United States. J Bone Joint Surg Am. 2009 Jan;91(1):128-33. • **4.** Bosic K et al. The Epidemiology of Revision Total Knee Arthroplasty in the United States. Clin Orthop Relat Res. 2010 Jan;468(1):45-51. • **5.** Bohm P et al. Is there a future for hinged prostheses in primary total knee arthroplasty? A 20-years survivorship analysis of the Blauth Prosthesis. J Bone Joint Surg Br. 1998 Mar;80(2):302-9. • **6.** Madey SM et al. Charnley total hip arthroplasty with use of improved techniques of cementing. The results after a minimum of fifteen years of follow-up. J Bone Joint Surg Am. 1997 Jan;79(1):53-64. • **7.** Salvati E et al. Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered air-flow system. J Bone Joint Surg Am. 1982 Apr;64(4):525-35. • **8.** Bongartz T et al. Incidence and Risk Factors of Prosthetic Joint Infection After Total Hip or Knee Replacement in Patients With Rheumatoid Arthritis. Arthritis Rheum. 2008 Dec 15;59(12):1713-20. • **9.** Iorio R et al. Diabetes Mellitus, Hemoglobin A1C, and the Incidence of Total Joint Arthroplasty Infection. J Arthroplasty. 2012 May;27(5):726-9. • **10.** Kerkhoff GM et al. The Influence of Obesity on the Complication Rate and Outcome of Total Knee Arthroplasty: A Meta-Analysis and Systematic Literature Review. J Bone Joint Surg Am. 2012 Oct 17;94(20):1839-44. • **11.** M.V. Ragni et al. Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts < or = 200/mm3. J Arthoplasty 1995 Dec; 10 (6): 716-21. • **12.** N. Davis et al. Intraoperative bacterial contamination in operations for joint replacement. J Bone Joint Surg Br. 1999 Sep;81(5):886-9. • **13.** Costeron JW. How Bacteria Stick. Sci Am. 1978 Jan;238(1):86-95. • **14.** Gristina AG et al. Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. J Bone Joint Surg Am. 1985 Feb;67(2):264-73. • **15.** Gristina AG. Biomaterial-Centered Infection: Microbial Adhesion vs. Tissue Integration. Science. 1987 Sep 25;237(4822):1588-95. • **16.** Gristina AG and Others. Infections from biomaterials and implants: a race for the surface. Med Prog Technol. 1988-1989;14(3-4):205-24. • **17.** Biocompatibility Test Report Data on File Novagenit s.r.l. • **18.** Report: Evaluation of the Aantiadhesive Properties of DAC® Hydrogel. Data on file Novagenit s.r.l. • **19.** Romanò, CL et al. Antibacterial resorbable coating of orthopaedic implants: an in vitro and in vivo study. CORS meeting, 2013, October 13-16, Venice, Italy. • **20.** Romanò CL et al. Hyaluronic Acids and Its Composites as a Local Antimicrobial/Antiadhesive Barrier. J Bone Joint Infect. 2017 Vol. 2. • **21.** Romanò CL. Et al. Does an Antibiotic-Loaded Hydrogel Coating Reduce Early Post-Surgical Infection After Joint Arthroplasty? J. Bone Joint Infect 2016; 1: 34-41. doi: 10.7150/jbji.15986 • **22.** Malizos K et al. Fast-resorbable antibiotic-loaded hydrogel coating to reduce post-surgical infection after internal osteosynthesis: a multicenter randomized controlled trial - J Orthopaed Traumatol July 2016 DOI 10.1007/s10195-017-0442-2.

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