Agluna®

Silver Ions in the Clinical Setting

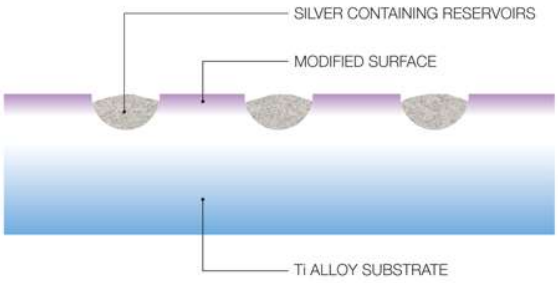
Metal ions and metal ions in complexes or compounds have been used as disinfectant for centuries. Molecular mechanisms of silver ions on bacteria and viruses have been studied extensively[1], with multiple antimicrobial mechanisms proposed[1,2], and antimicrobial efficacy found to increase with silver ion concentration[3]. Part of the ionic silver released precipitates with chloride or phosphate ions or becomes strongly bound in the form of inert complexes with albumins or macroglobulins. Metabolic pathways are similar irrespective of route and uptake[4] once taken up into the blood. Silver is processed by the liver and excreted in the bile and later the faeces[5].

Silver has been used in the clinical setting in a variety of applications - topical burn cream, wound dressings to treat burns and ulcers[6], PMMA bone cement[7,8], central venous catheters[7], urinary catheters[9], and dressings.

Agluna Surface Technology

Agluna incorporates ancillary silver ions into the implant surface. Surface density is controlled by an ion exchange reaction. When the Agluna-treated implant comes into contact with body fluids, silver ions are released, helping to reduce the incidence of periprosthetic joint infection (PJI).

Agluna involves an electrochemical process using high voltage anodisation of the implant in phosphoric acid, forming an oxide layer integral with the metal surface. Microscopic reservoirs are formed in the surface of the implant, containing hydrous titania into which silver ions are incorporated via a controlled ion exchange from a silver nitrate solution.



Safety and Efficacy Evidence

- Minimum Inhibitory Concentration (MIC): MIC of silver ions determined against clinical strains of *Staph. aureus, Coagulase -ve Staph., Pseud. aerug. (gram -ve), E. coli (gram -ve), Enter. faecalus, Strep. pyogenes, Asper. fumigatus, Candida albicans and Klebsiella pneumonia*[10]. MIC values consistent with those reported in literature. None of the tested clinical isolates exhibited results indicating resistance to silver.

- Antibacterial activity:
  - ISO22196 study showed efficacy of Agluna articles against all nine organisms tested[11].
  - ASTM E2315 study provided quantitative evaluation of antimicrobial activity using time-kill procedure. Antimicrobial effectiveness demonstrated against all microorganisms[12].

- Elution: *In vitro* studies of Agluna-treated surface (up to five-year shelf-life period) showed silver ion elution kinetics consistent with benchmark CE-Marked Agluna METS device[13].

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[10] Accentus Medical Reports ZRR_ZB_0005_09, 2009; ZRR_ZB_0007_10, 2010; ZRR_ZB_0020_09, 2009; ZRR_WA_2658_12, 2012.
[11] Accentus Medical Report ZRR_WA_2965_15, 2015.
[12] Accentus Medical Report ZRR_WA_2790_14, 2014.
[13] Accentus Medical Report AGT07-DVer.059, 2015.

- Zone of Inhibition (ZoI): *In vitro* studies demonstrated ZoI around Agluna-treated coupons tested against *MRSA*[14].

- Pharmacokinetics: *In vivo* study determined tissue distribution of eluted silver in organs/tissues over six-week time period. Cumulative silver concentration in all organs excluding liver and tibia was <2% of total silver delivered at all time points. Silver at the tested doses was not toxic to the study subjects[15].

- Osseointegration: Literature research, *in vitro* and *in vivo* studies have evidenced early osseointegration of Agluna-treated implants[16,17]. Agluna gritblast surface showed no significant difference at 12 weeks relative to untreated gritblast surface. Histological investigations demonstrated normal osteoid tissue with no evidence of necrosis or osteolysis. No indication that Agluna surface adversely affects long-term osseointegration process of an uncemented titanium alloy implant.

- Biocompatibility: ISO10993-1 studies addressing a range of biocompatibility topics: cytotoxicity[18]; sensitization[19]; irritation[20]; acute systemic toxicity[21]; 1-, 4-, 12-, 26-week implant studies[22]; genotoxicity[23]; pyrogenicity[24].

Agluna Manufacturing Process Validation

Agluna process is operated by Accentus Medical at ISO13485:2016 accredited manufacturing facility. Processing plant has been validated in accordance with regulatory requirements. Performance Qualification study carried out demonstrating process validation with customer products.

Clinical Experience

Agluna-treated limb salvage and complex revision devices successfully implanted since 2006: predominantly custom (patient specific) devices distributed in global markets by several specialist device manufacturers operating in this sector. In 2011, Agluna-treated METS (Modular Endoprosthetic Tumour System) device (Stanmore Implants Worldwide Ltd, acquired by Stryker, Inc.) received a European CE mark.

In 2015, peer-reviewed clinical paper was published in Bone & Joint Journal[25]. This study reported a case-control study at Royal Orthopaedic Hospital (ROH), Birmingham, UK. 85 patients receiving Agluna-treated tumour implants (2006 to 2011) matched with 85 control patients receiving identical un-treated implants (2001 to 2011). Key reported clinical outcomes were as follows:

- Reduction in post-operative infection rate from 22.4% (control) to 11.8% (Agluna);
- Success with DAIR (debridement, antibiotics and implant retention) increased from 31.6% (control) to 70% (Agluna);
- Persistent PJI necessitating device removal, amputation or chronic antibiotics suppression reduced from 15.3% (control) to 3.5% (Agluna);
- Success with two-stage revisions increased from 57.1% (control) to 85% (Agluna).

Post-operative clinical follow-up to 12 months, consistent with Agluna design objective.

A separate detailed evaluation of the ROH clinical data evidenced safety and performance of limb salvage and complex revision devices[26].

Published studies conclude that silver-coated megaprostheses are safe and reduce the risk of PJIs in oncologic and septic revision surgery. Additionally they appear to offer a protective effect on implant survival in the event of infection, improving DAIR success rates and decreasing the need for salvage procedures such as amputations. These latter findings require validation in larger studies[27].

In conclusion, potential risks related to Agluna-treated implants should be considered acceptable when weighed against the intended benefits for the patient.

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[15] Accentus Medical Report ZRR_WA_2782_14, 2015.
[16] Accentus Medical Reports ZTR_WA_0237_14, 2014 (Co-authorship includes J. Parvizi); ZRR_WA_2744_13, 2015.
[17] ORS Poster, UCL / Accentus Medical, 2012.
[18] Accentus Medical Report #189292 (WuxiApptec), 2013.
[19] Accentus Medical Report #189287 (WuxiApptec), 2013.
[20] Accentus Medical Report #189284 (WuxiApptec), 2013.
[21] Accentus Medical Report #189286 (WuxiApptec), 2013.
[22] Accentus Medical Reports #180054, #180055, #188188, #188187 (WuxiApptec), 2014.
[23] Accentus Medical Reports #189283, #189285, #189288 (WuxiApptec), 2013.
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[27] Sanz-Ruiz et al., Paper G53 to ICM2025.