Chlorag+ard® Technology Information

Introduction and Rationale for Antimicrobial Catheters:

Infection is the leading complication associated with intravascular devices, and there is a strong need to develop products to help prevent complications and increase safety for patients and providers. The National Nosocomial Infection Surveillance System (NNIS) tracks central line-associated bloodstream infection (BSI) rates in adult and pediatric intensive care units from 300 participating hospitals. This report serves as a benchmark for other hospitals to use in comparing their rates with the national rates. Approximately 90% of catheter-related bloodstream infections (CRBSIs) occur with central lines.[7] Mortality attributable to CRBSIs has been reported to be between 4% to 20% resulting in prolonged hospitalization (a mean stay of 7 days) and increased hospital costs. Peripherally Inserted Central Catheters (PICCs) are associated with similar rates of CRBSI as Central Venous Catheters (CVCs), placed in internal jugular or subclavian veins (2 to 5 per 1,000 catheter days).[8]

Vascular catheter infections develop for many reasons. They begin when a catheter becomes colonized by microorganisms entering through one or both of two routes: 1) colonization of the outside surface of the catheter or 2) colonization of the inside surface of the catheter. This colonization may be caused by any of five sources: environmental contamination, skin organisms, post-placement subcutaneous tract infection, intraluminal contamination or hematogenous seeding.[9]

Introduction and Rationale for Antithrombogenic Catheters:

Clinically symptomatic and detectable catheter-related venous thrombosis rates associated with peripherally inserted central venous catheters range from 3.4% to as high as 20%.[11] However, when diagnostic methods (ultrasound, contrast injection, etc) are used to assess for asymptomatic venous thrombosis, the incidence dramatically increases up to 58%.[11] Occlusive and/ or thrombotic events of peripherally inserted central venous catheters, described as inability to infuse solutions or withdraw blood, have an incidence of 7 to 25%.[5]

Catheter-related thrombus can be distinguished as either intraluminal, with clots occurring inside the lumen of the catheter, or extraluminal, with clots outside of the catheter and within the blood vessel (vein thrombosis). Formation of clot in the catheter lumen can lead to loss of its patency. If left untreated, extraluminal clot can cause complete occlusion of the blood vessel and can lead to a serious clinical condition called Deep Vein Thrombosis (DVT). The introduction of a venous catheter into the bloodstream triggers host responses to the presence of a foreign body. These host/biomaterial interactions occur on the external surface of the catheter, the internal surface of the venous wall, and the luminal surface of the catheter. The interactions of blood components, primarily proteins, platelets, and white blood cells in contact with the catheter material occur in a sequence of events. Within seconds of the catheter's exposure to the blood, protein adsorption and contact activation occur, followed by platelet adhesion, complement activation, and leukocyte adhesion minutes to hours later. The adhered bacteria, platelets and White Blood Cells (WBCs) become enmeshed within layers of fibrin forming a sheath on the surface of the catheter.

Product Description:

Catheters with Chlorag+ard Technology are processed with an external surface treatment that uses antimicrobial chlorhexidine acetate on the catheter body and juncture hub nose, as well as an internal lumen impregnation utilizing an antimicrobial combination of chlorhexidine acetate and chlorhexidine base for the catheter body, juncture hub, extension line(s) and extension line hub(s). The maximum total amount of chlorhexidine applied to a JACC may be up to 14.5 mg, with smaller French sizes and shorter lengths containing less chlorhexidine.

Characterization of Chlorhexidine:

Chlorhexidine is characterized as having a broad antimicrobial activity spectrum, including bacteriostatic and bactericidal effects on gram positive bacteria, gram negative bacteria and fungi.[3,4,6,10] Whether chlorhexidine is bacteriostatic or bactericidal depends largely on the concentration of the agent and the susceptibility of specific organisms. Chlorhexidine ($C_{26}H_{38}Cl_2N_{10}O_4$) is demonstrated to be stable at pH levels consistent with body surfaces

Technology Sheet

and tissues, but also continues to show stability at lower or higher pH levels to ensure infused chemotherapy or other IV fluids are not impacted.[3,13] Chlorhexidine also has been shown to be effective against viruses with a lipid component in their coats or with an outer envelope,[1,2,12] but these properties have not been evaluated with this product.

The antithrombogenic effect of Chlorag+ard Technology on catheters appears to be a function of thrombin inhibition by chlorhexidine via intrinsic and common pathways of blood coagulation, causing delayed blood clotting response and thrombus accumulation on catheter surface.

Chlorhexidine is a cationic compound. Its positively charged molecules are strongly attracted to the negative surface charges present on microbial surfaces. The outer membrane of gram negative bacteria, cell wall of gram positive bacteria or cytoplasmic membrane of yeasts then becomes weakened from increased permeability caused by chlorhexidine being adsorbed onto the cell surface. Chlorhexidine exhibits bacteriostatic effects at low concentrations due to the release of substances characterized by low molecular weights (i.e., phosphorus and potassium ions) from the cell. This damage is enough to inhibit bacterial cell function. Bactericidal activity of chlorhexidine occurs at higher concentrations by causing precipitation of proteins and nucleic acids.[3]

Chlorhexidine is poorly absorbed from the gastrointestinal tract. In human and animal studies, the average plasma level peaked at 0.206 µg/g in humans 30 minutes after ingesting 300 mg of chlorhexidine. Excretion occurred primarily through the feces (about 90%), and less than 1% was excreted in urine. Chlorhexidine is metabolized in the same manner as most other foreign substances. The majority will be excreted without being metabolized.[3]

Preclinical biocompatibility studies support the conclusion that there is a negligible risk of adverse effects from Chlorag+ard antimicrobial/antithrombogenic catheters.

Indications for Use:

The Arrow Pressure Injectable Jugular Axillo-subclavian Central Catheter™ (JACC) with Chlorag+ard Antimicrobial and Antithrombogenic Technology is indicated for short-term or long-term access to the central venous system for intravenous therapy, blood sampling, infusion, pressure injection of contrast media, and allows for central venous pressure monitoring. The maximum pressure of pressure injector equipment used with the Arrow Pressure Injectable JACC may not exceed 300 psi. The maximum pressure injection flow rate for the specific lumen being used for pressure injection is printed on the extension line hub.

Chlorag+ard Technology treatment on the external surface of the catheter body as well as the entire fluid pathway of the catheter has been shown to be effective in reducing microbial colonization on catheter surfaces. Antimicrobial effectiveness was evaluated using in vitro and in vivo test methods and no correlation between these testing methods and clinical outcome has currently been ascertained. It is not intended to be used for the treatment of existing infections.

Contraindications:

The Chlorag+ard antimicrobial/antithrombogenic catheter is contraindicated for patients with known hypersensitivity to chlorhexidine.

⚠ **Warning: Remove catheter immediately if adverse reactions occur after catheter placement.**

NOTE: Perform sensitivity testing to confirm allergy to catheter antimicrobial agents if adverse reaction occurs.

Refer to enclosed product Instructions for Use (IFU) for additional Warnings and Precautions.

Hypersensitivity Potential:

Benefits of the use of this catheter should be weighed against any possible risk. Hypersensitivity reactions are a concern with antimicrobial catheters and can be serious and even life-threatening. Since antimicrobial catheters were introduced into the market, there have been some reports of hypersensitivity occurrences outside the United States. This hypersensitivity potential has been reported to occur more frequently in Japan.

Pre-Clinical Evaluations:

Chlorag+ard Technology has demonstrated reduction in colonization by gram-positive and gram-negative bacteria and yeast in *in vitro* and *in vivo* studies for up to 30 days for external surface and *in vitro* studies for up to 30 days for fluid pathway.[10]

In addition, Chlorag+ard Technology has also demonstrated reduction in thrombus accumulation on catheter surfaces for up to 30 days in *in vivo* testing. *In vitro* testing has exhibited reduction in platelet adhesion on catheter surface and catheter occlusion.[10]

Refer to enclosed product Instructions for Use (IFU) for specific indications, procedural technique(s) and potential complications associated with catheter insertion procedures.

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