Arrowg+ard Blue Advance™ Protection 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.[11] Mortality attributable to CRBSIs has been reported to be between 4% to 20% with 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).[14]

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.[15]

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%.[17] However, when diagnostic methods (ultrasound, contrast injection, etc.) are used to assess for asymptomatic venous thrombosis, the incidence dramatically increases up to 58%.[17] Occlusive and/or thrombotic events of peripherally inserted central venous catheters, described as inability to infuse solutions or withdraw blood, has an incidence of 7 to 25%.[9]

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.

Technology Development:

Antimicrobial CVCs were introduced by Arrow International in 1990. The Arrow® catheter was the first commercially successful catheter capable of significantly reducing the potential for catheter colonization and subsequent catheter-related bloodstream infections.[11] The first generation antimicrobial surface treatment, referred to as ARROWg+ard Blue®, consists of two antimicrobial agents (chlorhexidine and silver sulfadiazine) which are impregnated into the indwelling external surface of the catheter. This combination has demonstrated broad spectrum *in vitro* efficacy as well as *in vivo* efficacy through prospective clinical studies. [1,5,6,11,18]

Due to the need for longer duration of protection as a result of longer dwelling time and in recognition of the role of the intraluminal pathway in catheter colonization by organisms transmitted by the hands of unit personnel,[11,15] two key areas of improvement to the ARROWg+ard Blue catheter technology were identified: 1) extend the effective duration of action of the external surface coating and 2) provide protection to the internal surfaces of the entire catheter (including extension lines and hubs). The second generation antimicrobial catheter, known as ARROWg+ard Blue PLUS® (AGB^{+e}), was developed to address these needs. This was done by increasing chlorhexidine on the outside surface of the catheter and also by protecting the entire intraluminal path with chlorhexidine. Compared to the original ARROWg+ard Blue, ARROWg+ard Blue PLUS catheters produce a significantly longer duration of antimicrobial effect against the most common catheter-related infection-causing microorganisms, including a significant reduction in intraluminal bacterial colonization when compared to untreated catheters.[12]

Technology Sheet

The third generation of antimicrobial catheter technology was introduced on PICC products as Arrow® PICC with Arrowg+ard Blue Advance™ Protection with slight modification to the clinically proven efficacy of the ARROWg+ard Blue PLUS technology. Silver sulfadiazine, the secondary antimicrobial agent, was removed, and the chlorhexidine-to-catheter material processing was optimized to provide longer duration based on the clinical requirements of PICC catheters. This technology has been shown to have antithrombogenic properties as well.

Product Description:

The Arrow PICC with Arrowg+ard Blue Advance Protection is a peripherally inserted central venous catheter manufactured with medical grade, radiopaque polyurethane. It has a non-tapered catheter body with a Blue FlexTip®, designed to be softer than a cut tip. It has a contour design to enhance maneuverability and minimize vessel trauma. The Blue FlexTip also provides visual confirmation of an intact catheter upon removal. The catheters are available in usable lengths of 40 to 55 cm and are indicated for pressure injectability.

The Arrow PICC with Arrowg+ard Blue Advance Protection is processed with an external surface treatment that uses the 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). A maximum total amount of chlorhexidine content applied to various French sizes and lengths of catheters could range up to 20.5 mg.

The Arrow PICC with Arrowg+ard Blue Advance Protection kit includes essential tools required to:

- Access patients' vasculature
- Promote compliance for reducing risk with an ergonomic, comprehensive design
- Protect patients from five sources of bloodstream infections
- Reduce instances of catheter surface thrombus accumulation and luminal occlusions
- Comply with current evidence-based guidelines for infection reduction and safety

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.[7,8,10,16] Chlorhexidine also has been shown to be effective against viruses with a lipid component in their coats or with an outer envelope,[2,3,19] but these properties have not been evaluated with this product. The antithrombogenic effect of the Arrowg+ard Blue Advance Protection on the Arrow PICC 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.

Whether chlorhexidine is bacteriostatic or bactericidal depends largely on the concentration of the agent, its pH and the susceptibility of specific organisms. Optimum stability ($C_{26}H_{38}C_{l2}N_{10}O_4$) is demonstrated between pH levels of 5.5 and 7.0, which are consistent with pH levels of body surfaces and tissues.[7,20]

Chlorhexidine is a cationic compound. Its positively charged molecules are strongly attracted to the negative 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.[7]

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.[7]

Preclinical biocompatibility studies support the conclusion that there is a negligible risk of adverse effects from the Antimicrobial/Antithrombogenic PICC products with Arrowg+ard Blue Advance Protection.

Indications for Use:

The Pressure Injectable PICC with Arrowg+ard Blue Advance Antimicrobial and Antithrombogenic Protection is indicated for short-term or long-term peripheral 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 injection equipment used with the pressure injectable PICC may not exceed 300 psi. Arrowg+ard Blue Advance Protection 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 and thrombus accumulation on catheter surfaces. Antimicrobial and antithrombogenic effectiveness were evaluated using *in vitro* and *in vivo* test methods, and no correlation between these test methods and clinical outcome has currently been ascertained. It is not

intended to be used for the treatment of existing infections or vein thrombosis.

Contraindications:

Clinical assessment of the patient must be completed to ensure no contraindications exist. The Arrow PICC with Arrowg+ard Blue Advance Protection is contraindicated in the following areas:

- Patients with known hypersensitivity to chlorhexidine
- In presence of device related infections
- In presence of previous or current thrombosis in the intended vessel or along the catheterized vessel pathway.

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:

The Arrow PICC with Arrowg+ard Blue Advance Protection 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.[16] In addition, this PICC 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.[16]

Clinical Evaluations:

Reduction in colonization or microbial growth on the antimicrobial PICC has not been shown to correlate with a reduction in infections in patients. Clinical studies to evaluate reduction in infection have not been performed on this device. Clinical effectiveness of the Antimicrobial PICC in preventing CRBSIs compared to the ARROWg+ard Blue PLUS CVC catheters has not been studied. PICC is a type of CVC. Both centrally inserted CVCs and peripherally inserted CVCs (i.e., PICCs) are used for similar clinical usage. Both are inserted vasculary and are inserted to the same depth near the heart. The PICC products, a subset of CVCs, are generally 4 to 8 inches longer in overall length since they are usually inserted in the upper arm and require extra length in order to reach the same insertion depth. The coating on both products primarily contains the antimicrobial agent chlorhexidine with similar concentration per surface area, which has been shown to be effective in reduction of colonization by microbes on catheter surfaces in *in vitro* testing. Based on similarities of the Antimicrobial PICC and ARROWg+ard Blue PLUS catheter technology and clinical usage, the studies performed on ARROWg+ard Blue PLUS antimicrobial catheters listed below may provide a useful comparison in demonstrating clinical safety and effectiveness of the chlorhexidine based technology in patients.

Clinical Study - France[4]

A prospective, multi-center, randomized, double-blind clinical study of 397 patients performed at 14 university-affiliated hospital ICUs in France from June 1998 to January 2002 using ARROWg+ard Blue PLUS antimicrobial catheters showed use of these catheters was associated with a strong trend toward reduction in infection rates of central venous catheters (colonization rate of 3.7% versus 13.1%, 3.6 versus 11 per 1000 catheter-days, p=0.01) and CVC-related infection (bloodstream infection) in 4 versus 11 (2 versus 5.2 per 1000 catheter-days, p=0.10).

Clinical Study - Germany[12]

A prospective, randomized, double-blind, controlled clinical study of 184 patients performed at the University Hospital of Heidelberg (Heidelberg, Germany) from January 2000 to September 2001 using ARROWg+ard Blue PLUS antimicrobial catheters showed these catheters were effective in reducing the rate of significant bacterial growth on either the tip or subcutaneous segment (26%) compared to control catheters (49%). Incidence of catheter colonization was also significantly reduced (12% coated versus 33% uncoated). The number of bloodstream episodes in patients with CHSS catheter was lower than in patients provided with control catheter (3 versus 7 episodes, p=0.21).

Clinical Study - United States[13]

A prospective, multi-center, randomized, double-blind, controlled clinical study of 780 patients performed at 9 university-affiliated hospitals in the United States from July 1998 to June 2001 using ARROWg+ard Blue PLUS antimicrobial catheters showed these catheters were less likely to be colonized at time of removal compared to control catheters (13.3 versus 24.1 colonized catheters per 1000 catheter-days, p<0.01). Rate of definitive catheter-related bloodstream infection was 1.24 per 1000 catheter days (CI, 0.26 to 3.26 per 1000 catheter-days) for the control group versus 0.42 per 1000 catheter days (CI, 0.01 to 2.34 per 1000 catheter-days) for the ARROWg+ard Blue PLUS catheter group (p=0.60).

No adverse events were observed from ARROWg+ard Blue PLUS catheters in any of the clinical studies.

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

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