

FDA Review Summary

Device: **510(k) Number: K040429**
CoolGard 3000/Icy Heat Exchanger Catheter
Thermal Regulating System
Alsuis Corporation

Introduction

This report presents the FDA summary of the clinical, statistical, and pre-clinical testing review memorandums regarding K040429 for the CoolGard 3000/Icy Heat Exchange Catheter Thermal Regulating System submitted by Alsuis Corporation.

510(k) Chronology

Information supporting the device was submitted as a 510(k) (K040429) on March 8, 2004. Requests for additional information (AI Letters) were issued by FDA to the sponsor on June 4, 2004 and October 5, 2005. The sponsor submitted responses to these letters on July 2, 2004 and November 8, 2004, respectively.

Device Description

The Alsuis CoolGard™ 3000 thermal regulating system consists of the Alsuis CoolGard™ 3000 control unit and the Icy Catheter. The CoolGard™ 3000 controller consist of a temperature monitor, a temperature controller unit, a heat exchange unit, and a roller pump. The CoolGard™ 3000 controller controls the temperature of the circulating saline that flows through the Icy Catheter and is also responsible for monitoring patient temperature. The Icy Catheter is a 3 lumen catheter with a nominal diameter of 8.5 F. Two of the lumens are used to circulate the saline and the third lumen is a standard guide wire lumen and could also be used as an infusion lumen. The Icy catheter is a closed-loop catheter system through which the cooled or warmed saline passes, allowing the catheter to function as an internal heat exchanger. The catheter is placed in the inferior vena cava through either the femoral, jugular or subclavian vein. A more complete device description is included in **Tab 3** of your panel pack.

Device History

The CoolGard™ 3000 Thermal Regulating System has been previously cleared by 510(k) for the following indications:

1. The Alsuis CoolGard™ 3000 and Cool Line™ Catheter Thermal Regulation System is indicated for use in fever reduction, as an adjunct to other antipyretic therapy, in patients with cerebral infarction and intracerebral hemorrhage who

require access to the central venous circulation and who are intubated and sedated. (K014241)

2. The Alsius CoolGard™ 3000 Catheter Thermal Regulation System, using either the Icy™ or Fortius™ model catheter, is indicated for use in cardiac surgery patients to achieve and/or maintain normothermia during surgery and recovery/intensive care, and, to induce, maintain and reverse mild hypothermia in neurosurgery patients in surgery and recovery/intensive care (K030421)

This current 510(k) application has been submitted to revise the indications for use to include the following indication:

“For use in the induction, maintenance, and reversal of mild hypothermia in the treatment of unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation (VF)”.

The previous 510(k) clearances for the CoolGard™ 3000 were based on clinical data that showed the device to perform equivalently to other cooling devices for the same indications for use. The CoolGard™ 3000 System in this 510(k) is identical to the previously cleared device.

A Circulatory Systems Devices Advisory Panel meeting was held on September 21, 2004, in part, to discuss the general clinical trial issues related to devices indicated for delivering hypothermia to victims of cardiac arrest who have return of spontaneous circulation. A summary of the panel’s deliberations at this meeting are given in **Tab 11** of this package. This previous panel meeting discussed general clinical trial issues and did not consider specific data for any manufacturer’s device.

Clinical Data

In this 510(k) submission, the sponsor provided data and analyses that were intended to address the following two objectives:

1. To assess the effectiveness of mild therapeutic hypothermia, delivered via any method, in improving survival and neurological recovery in primary survivors of cardiac arrest.
2. To assess the effectiveness and safety of mild endovascular therapeutic hypothermia, applied via Alsius CoolGard™ device, in improving survival and neurological recovery in primary survivors of cardiac arrest.

The sponsor used the following four sources of data in their analyses:

1. Allgemeines Krankenhaus (AKH) Cardiac Arrest Registry (August 1991 - September 2003): This is an observational study of patients treated after

successful resuscitation from cardiac arrest at the Emergency Department of the Vienna General Hospital. Various methods of providing therapeutic hypothermia have been used at the AKH, and some patients in this cohort were treated with therapeutic hypothermia via the Alsius CoolGard System. Patient-level data were made available to Alsius Corporation for analysis. A summary report of the analyses done using the AKH Cardiac Arrest Registry Data are located in Section 2.9 of the sponsor's clinical data summary (**Tab 4** of your package).

2. The Hypothermia after Cardiac Arrest (HACA) Study (March 1996 - January 2001): This is a randomized controlled international multicenter study that did not use the Alsius CoolGard™ System. Patients enrolled in this study received either standard care with normothermia or mild therapeutic hypothermia by means of cool air. The results of this study were published and a copy of the article is available in **Tab 7** of your panel pack. The full data set for this study were made available to Alsius Corporation for analysis.
3. Bernard Study (September 1996 - June 1999): This is an Australian multicenter randomized controlled hypothermia study that did not use the Alsius CoolGard™ System. Patients enrolled in this study received either standard care (normothermia) or therapeutic hypothermia by ice packs around the neck. The results of this study were published and a copy of the article is available in **Tab 7** of your panel pack. Alsius Corporation extracted data from this published report for their analysis.
4. Hachimi-Idrissi Study (over six month period within 2000 and 2001): This is a single-center randomized controlled feasibility study that did not use the Alsius CoolGard™ System. Patients enrolled in this study received either standard care (normothermia) or therapeutic hypothermia by means of a cooling helmet. The results of this study were published and a copy of the article is available in **Tab 7** of your panel pack. Alsius Corporation extracted data from this published report for their analysis.

To evaluate the effectiveness (in general) of mild therapeutic hypothermia in improving survival and neurological recovery in primary survivors of cardiac arrest (the first objective), Alsius Corporation performed a meta-analysis using the three randomized controlled trials discussed above (HACA, Bernard, and Idrissi). A summary of the results of this meta-analysis is discussed in Section 2.7 of the Sponsor's clinical data summary provided in **Tab 4** of your panel package. A copy of the complete meta-analysis report (including statistical tables) is found in **Tab 5** of your panel package. In the meta-analysis, two endpoints were evaluated: (1) Survival (for HACA trial, survival was defined as 6-month mortality status, while for the other two trials, survival was defined as hospital discharge); (2) Survival (alive after 6 months for HACA study and alive until hospital discharge for the other two trials) and good neurological recovery (cerebral performance

categories (CPC) 1 or 2). The sponsor used fixed effects models to combine the point estimates from these three randomized trials, and assessed statistical heterogeneity using Cochran's Q test.

As discussed above, the survival endpoints reported in the references differed. In the HACA trial, mortality was assessed at 6 months, in the Bernard study it was assessed at hospital discharge and in the Idrissi trial, it was assessed at the end of the study (which was 4 hours after applying therapeutic hypothermia). More over, the definitions of good neurological recovery are also different in these three trials. The HACA study used CPC score of 1 or 2 as good neurological recovery. (A description of the CPC scale is found in **Tab 8** of your panel pack). The Bernard study defined good neurological outcome as discharge home or to a rehabilitation facility. The Hachimi-Idrissi trial did not explicitly describe good neurological recovery. This difference in the definitions of the two effectiveness endpoints (i.e., survival, survival and good neurological recovery) among the three studies may affect the validity of the meta-analysis.

Alsuis Corporation also provided data from the Allgemeines Krankenhaus (AKH) Cardiac Arrest Registry to evaluate the safety and effectiveness of mild therapeutic hypothermia provided via the Alsuis CoolGard™ 3000 System in improving survival and neurological recovery in primary survivors of cardiac arrest (the second objective discussed above). In this analysis, the sponsor used all patients from the AKH Cardiac Arrest Registry who did not receive hypothermia as controls, and used all patients from the same registry data who received hypothermia via Alsuis CoolGard™ device as treatment group. The endpoints for the analysis were: (1) 30-day survival status; (2) 30-day survival status and good neurological recovery (defined as CPC 1 or 2). Patients who died within 24 hours of treatment were excluded. Since the AKH Registry analysis was an observational study, the sponsor used propensity scores (probit model) to match the treated patients with control patients in the effectiveness analysis. A summary of the AKH Registry analysis is found in Section 2.9 of the Sponsor's clinical data summary (**Tab 4** of your panel package). A copy of the complete report (including statistical tables) for the AKH registry analysis is found in **Tab 5** of your panel package. We are also including a summary report from an audit done by Alsuis Corporation personnel of the AKH site (**Tab 6** of your panel package). We have requested that the sponsor provide (1) a description of how the registry data are collected (2) the protocol used for data extraction for this analysis and (3) the clinical protocol used to treat patients with hypothermia at this site. This information will be provided to you in a second mailing when it is available.

The sponsor also provided two safety analyses. In the first safety analysis, the sponsor used patients from the AKH Registry who received Alsuis CoolGard™ (treatment group) and those who did not receive hypothermia and also met the inclusion criteria for the CoolGard™ patients (control group). In the second safety analysis, the sponsor compared patients treated with Alsuis CoolGard™ device in the AKH Registry (treatment group) with patients treated in the HACA trial with hypothermia via cool air (control group). Both safety analyses were carried out using contingency tables and Fisher's exact tests, but were not corrected for

multiple testing. A summary of these safety analyses are found in Section 2.9.4 of the Sponsor's clinical data summary (**Tab 4** of your panel package).

FDA Analysis of Clinical Data Provided

After reviewing the data provided in the 510(k) submission, FDA had the following issues with the data submitted.

AKH Registry Data:

- The AKH Registry data are observational and were not collected as part of a randomized trial. There is a possibility of introduction of bias in the selection of the non-hypothermic control group identified in the AKH data. Some control patients were those treated in the era before this institution used hypothermia, other patients were those who required cardiac or neurological imaging studies, but it is unclear why the remainder of the patients were chosen to not have hypothermia in a center where the standard of care is hypothermia. The possible role of selection bias and unknown covariates makes comparison of these two groups difficult.
- FDA has requested additional information regarding the propensity score analysis, including:
 - the list of covariates collected in the data set and used in the propensity score analysis
 - the missing covariates in the propensity score analysis and how missing data was handled
 - the distribution of the propensity scores in the treated and the control group (graphical presentation)

Once this information is submitted by the sponsor, it will be provided to you in a second mailing, along with FDA's review of this information.

- Of the 66 subjects in the AKH database who received treatment with the CoolGard™ device, only 41 patients had 6 month outcome data available. Of these 41 patients, only 28 patients presented with documented VT/VF (the specific indication for which they are seeking FDA clearance).

Meta-analysis:

- Uncertainty regarding the meta-analysis exists because:
 - a. The subject device was not used;
 - b. Different definitions were used for survival and neurological outcome in the studies;
 - c. Different methods of cooling were used;
 - d. Cooling was started at different times;
 - e. Inclusion and exclusion criteria were different;
 - f. Rewarming was different.

- Differences exist between endovascular and surface cooling with regard to the rates of cooling, heterogeneity of tissue temperatures, time to initiating cooling, and the expected adverse event profiles, making it difficult to apply the results of the meta-analysis to support the safety and effectiveness of endovascular cooling.

- In the Bernard study, patients were cooled to 33 Deg for 12 hours, while in the HACA study, patients were cooled to 32-34 degrees for 24 hours. The minimum time needed for possible benefit from hypothermia is unknown.

Supplementary Clinical Information

The sponsor conducted a small feasibility study in the U.S. of the CoolGard 3000/ICY catheter system in patients suffering out of hospital cardiac arrest (IDE number G000207). This study enrolled 13 patients at four institutions. A brief summary of the results is provided in Section 2.8 of the sponsor's clinical data summary in **Tab 4** of your panel pack.

During the course of our review, FDA asked the sponsor to address a number of deficiencies regarding the clinical data provided in this 510(k). The responses to these deficiencies are found in **Tab 9** of your panel pack.

The sponsor has recently submitted additional information prior to the Panel Meeting including follow-up on additional subjects from the AKH registry. That data will be sent to you in a second mailing, along with FDA's review of the information.

Proposed Labeling and Instructions for Use

A copy of the proposed labeling and instructions for use are found in **Tab 10** of your panel pack.

