

Safety Addendum to Clinical Review
Banu Karimi-Shah, MD
NDA 22-383
Arcapta Neohaler (indacaterol maleate)

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

March 8, 2011

ADDENDUM TO FDA BRIEFING PACKAGE- CLINICAL BRIEFING DOCUMENT

NDA 22-383

Indacaterol maleate (Arcapta Neohaler) for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema

I. Introduction

Arcapta Neohaler (indacaterol maleate inhalation powder) is a long-acting beta-agonist (LABA) proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Applicant seeks approval of two doses of indacaterol, 75 and 150 mcg. The efficacy and overall safety of indacaterol have been discussed in detail in the FDA Clinical Briefing Document. The primary objective of this addendum is to discuss the respiratory safety of indacaterol, specifically the serious adverse events of respiratory-related death, hospitalization, and intubation in patients with COPD, and the possible impact these respiratory-related adverse events might have on which dose(s) should be approved, if any.

II. Background

The major safety concern with LABAs is the increase in asthma-related deaths, hospitalizations, and intubations. Although the mechanism by which inhaled beta-agonists cause these asthma-related serious adverse events has not been elucidated, historical and epidemiological data suggest that the use of less selective beta-agonists and use of higher doses may be risk factors.

Similar concerns have been raised within the indacaterol development program with two deaths in the 300 mcg treatment arm (n= 268 in arm, total study n = 805) of a single 26-week asthma study (Study B2338) while receiving concurrent ICS. Serious adverse events (SAEs) related to asthma exacerbation or respiratory events also seemed to be more common in patients treated with indacaterol in various asthma studies. The two deaths and incidence of SAEs are described in detail in the Division Director's Memorandum. The deaths raise concern for three reasons: 1) both the deaths occurred in patients treated with the 300 mcg dose, a dose not far removed from the 150 mcg dose currently proposed for marketing; 2) asthma-related deaths in LABA asthma development programs, even when LABAs were used alone without concomitant ICS, are rare to nonexistent; and 3) a post-marketing death occurred in a 44-year old COPD patient that was reported as being asthma-related.

Although the submitted application for indacaterol is for a COPD indication, and thus far a similar signal of worsening disease with LABA use does not appear to pertain to COPD, given the nature of the signal and the Applicant's large safety database, the Agency decided that further safety analysis was warranted.

To that effect, on December 16, 2010, the Agency asked Novartis to conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. The Agency believed that such an analysis was necessary to provide balancing safety data to justify the proposed higher dose (150 mcg) of indacaterol. The absence of this balancing safety data showing that there was no unacceptable safety disadvantage with the higher dose was a deficiency noted during the first review cycle and communicated to the Applicant in the action letter. Also, based on historical knowledge that serious asthma-related adverse events (deaths, hospitalizations, and intubations) may be related to higher doses of beta-agonists, the Agency decided that it was important to evaluate whether such a signal might exist in COPD. An overview of the results of this meta-analysis, based on the Agency's review, will be presented here.

III. Methodology

The Agency requested that the Applicant conduct an analysis to evaluate the incidence of respiratory-related death, intubation, and hospitalization related to asthma, COPD, or pneumonia in indacaterol-treated patients compared to control. The Agency requested that the Applicant implement an adjudication committee to provide an independent assessment of all serious adverse events (SAEs) occurring during the development of indacaterol, in both COPD and asthma. The committee was charged with categorizing which deaths, hospitalizations, and intubations were respiratory-related. They were further asked to classify events according to whether they were asthma-, COPD-, or pneumonia-related. Only events that occurred on-treatment were to be included in the meta-analysis. The procedure for adjudication of narratives is described in detail in the Applicant's addendum to the briefing document. The Agency Information Request dated December 16, 2010 is attached at the end of this document.

Per FDA request, the Applicant included all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration in patients with both asthma and COPD, in which indacaterol maleate was delivered using the single dose dry powder inhaler Concept 1 (or similar) device, whether or not the trials were submitted as part of the NDA. Specifically, the meta-analysis included studies in which indacaterol was administered as a randomized treatment, either with or without a concomitant inhaled corticosteroid or other adjunctive therapy, and studies with indacaterol combination products that had a blinded indacaterol treatment arm. Details regarding the conduct of the meta-analysis are presented in detail in the Applicant's addendum to the briefing document.

The Applicant analyzed the data in six defined populations based on whether the studies included were in asthma or COPD patients, and whether they were active- or placebo-controlled. These six populations are described in detail in the Applicant's briefing document. For the purposes of the Agency's review, we focus our discussion here on the All-treated COPD Safety Population I, which consisted of all patients who took at least one dose of study treatment in any COPD study, whether it was active- or placebo- controlled. This data is most relevant to the committee for two reasons: 1) indacaterol is being proposed for a COPD indication and 2) the preponderance of data presented in the meta-analysis comes from a COPD patient population. Following the discussion in COPD patients will be a brief summary of the findings in the smaller asthma population.

IV. Summary of Results

All-Treated COPD Safety Population I

The All-treated COPD Safety Population included a total of 11,755 patients in 23 studies. The majority of the studies were greater than 12 weeks in duration and were conducted with the to-be-marketed Concept1 (Neohaler®) device. Of the 11,755 COPD patients, 6863 were treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n = 842, and salmeterol n = 1010). These studies ordered by treatment duration are presented in Table 1.

Table 1 COPD Studies Included in the Meta-Analysis

ID	Study type	N	Study duration	Indacaterol Dose (mcg)*	Control	Device
B2205	DR, DB, PG/XO	660	7 days	400	PBO	RS01
QVA A2204	DB, XO	140	7 days	300, 600	PBO	Concept1
B2305	DB, XO	78	14 days	300	PBO, SAL	Concept1
B2318	DB, XO	24	14 days	300	PBO	Concept1
B2331	DB, XO	148	14 days	150, 300	PBO, TIO	Concept1
B2340	DB, XO	54	14 days	300	PBO	Concept1
B2356	DR, DB, PG	576	14 days	18.75, 37.5, 75, 150	PBO, SAL	Concept1
QVA A2203	DB, PG	250	14 days	300	PBO	Concept1
B2311	DB, XO	83	21 days	300	PBO	Concept1
B2201	DB, PG	148	28 days	400, 800	PBO	RS01
B1302	DB, PG (Japan)	336	12 weeks	150, 300	PBO	Concept1
B2341	DB, PG	1126	12 weeks	150 + TIO	None**	Concept1
B2346	Pivotal, DB, PG	290	12 weeks	150	PBO	Concept1
B2349	DB, PG	1084	12 weeks	None**	SAL	Concept1
B2350	DB, PG	1568	12 weeks	150	TIO	Concept1
B2351	DB, PG	1126	12 weeks	150 + TIO	None**	Concept1
B2354	Pivotal, DB, PG	326	12 weeks	75	PBO	Concept1
B2355	Pivotal, DB, PG	326	12 weeks	75	PBO	Concept1
B2333	DB, PG (China)	558	26 weeks	150, 300	PBO	Concept1
B2335						
- S	DB, PG	1945	2-26 weeks	75, 150, 300, 600	PBO, FOR	Concept1
- SE	DB, PG	409	26 weeks	150, 300	PBO	
B2336	DB, PG	972	26 weeks	150	PBO, SAL	Concept1
B2334	DB, PG	1716	52 weeks	300, 600	PBO, FOR	Concept1

* Indacaterol dosing frequency is once-daily unless otherwise noted
 ** Only blinded-treatment arms are listed; "None" indicates that treatment or control administration was not blinded, so that treatment arm was not included in the analysis
 DR: dose ranging, DB: double-blind; XO: crossover; PG: parallel group; Dreg: dosing regimen; PBO: placebo; SAL: salmeterol; TIO: tiotropium; FOR: formoterol;

In the All-treated COPD-safety population I, a total of 239 of 11,755 patients were identified as having had a respiratory-related event. Of these 239 patients, there were 219 patients who had an acute respiratory-related hospitalization or intubation. There were no acute respiratory-related deaths in this population. The incidence of total and acute respiratory-related events is depicted in Table 2. "Total" refers to any respiratory related event (e.g. pulmonary embolus, lung cancer), while "acute" includes only those respiratory-related deaths which were adjudicated to be asthma-, COPD-, or pneumonia-related. Table 3 shows whether acute respiratory-related events were adjudicated as having been related to either COPD or pneumonia.

Table 2: Total and Acute Respiratory-Related Events: All-treated COPD Safety Population I										
	Indacaterol Treatment Groups (mcg)^a						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL^b n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Hospitalizations, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Intubations, n(%)										
Total	0	1 (<0.1)	1 (<0.1)	2 (0.1)	0	4 (0.1)	4 (0.7)	0	0	1 (<0.1)
Acute	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)

a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted

b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device

Total: Includes those patients who had any respiratory related event

Acute: Includes those events that were deemed COPD/pneumonia related;

For: formoterol; Tio: tiotropium; Sal: salmeterol

Hospitalizations: admission or emergency room visit > 24 hours in duration (± corticosteroid treatment)

Intubations: endotracheal intubation for mechanical ventilation for the treatment of acute hypoxemic or hypercapnic respiratory failure

Source table: re2.1c1 pages 478-483

Table 3: Total and Acute Respiratory-Related Events: All-treated COPD Safety Population I										
	Indacaterol Treatment Groups (mcg)^a						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL^b n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite, n(%)										
<u>Acute</u>	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
COPD-related	5 (0.9)	36 (1.3)	14 (1.2)	41 (2.9)	13 (2.2)	109 (1.6)	30 (5.4)	5 (0.6)	10 (1.0)	47 (1.9)
PNA-related	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Hospitalizations, n(%)										
<u>Acute</u>	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
COPD-related	5 (0.9)	36 (1.3)	14 (1.2)	40 (2.8)	13 (2.2)	108 (1.6)	29 (5.2)	5 (0.6)	10 (1.0)	47 (1.9)
PNA-related	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Intubations, n(%)										
<u>Acute</u>	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)
COPD-related	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)
PNA-related	0	1 (<0.1)	0	0	0	1 (<0.1)	1 (0.2)	0	0	0
<p>a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted</p> <p>b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device For: formoterol; Tio: tiotropium; Sal: salmeterol; PNA: pneumonia</p> <p>Source table: Response to FDA Information Request, Table re2.1c1, Pages: 478-483.</p>										

The incidence of acute respiratory related events as a composite endpoint, and then broken down by hospitalizations and intubations, is shown in Table 2. Of note, these incidences are not adjusted for exposure. At the time of this review, we have asked the Applicant to provide exposure-adjusted incidences. Deaths as described elsewhere in the Agency’s clinical briefing document do not appear in this table because there were no on-treatment deaths adjudicated to be

acutely respiratory-related in the COPD Safety Population I. Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related (Table 3) as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations. When patients were analyzed by reversibility to bronchodilator (12% and 200 mL; yes or no) and duration on treatment (> 12 weeks or <12 weeks), the trend appeared consistent across these subgroups. In the All-Treated COPD Safety Population II, which excluded any studies that were not placebo-controlled, a similar numerical trend towards a dose-related safety signal was observed.

Although this table does not portray exposure-adjusted incidences, one can argue that the presence of a numerical trend towards an increase in a respiratory safety signal in a population expected to derive respiratory benefit from the drug, is an issue that warrants consideration and further discussion. The possibility that such a signal may exist in COPD rather than asthma further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.

All-treated Asthma Safety Population I

The All-treated Asthma Safety Population I included a total of 1914 patients in 7 studies. Of the 1914 asthma patients, 1307 were treated with indacaterol, 254 with placebo, and 353 with a salmeterol active control. These studies ordered by treatment duration are presented in Table 4.

Table 4 Asthma Studies Included in the Meta-Analysis

ID	Study type	N	Study duration	Indacaterol Dose (mcg)*	Control	Device
A2208	DR, DB, XO	120	7 days	100, 200, 300, 400, 600	PBO	RS01
A2216	DB, PG	372	7 days	400	PBO	RS01
D2301	XO	32	7 days	400	PBO	Concept1
B2357	DR, DB, PG	558	14 days	18.75, 37.5, 75, 150	PBO, SAL	Concept1
B2223	DReg, DB, PG	192	16 days	37.5 BID, 75, 150 QOD	PBO	Concept1
A2210	DB, XO	148	28 days	400, 800	PBO	RS01
B2338	DB, PG, Safety	750	26 weeks	300, 600	SAL	Concept1

* Indacaterol dosing frequency is once-daily unless otherwise noted
 * Only blinded-treatment arms are listed
 DR: dose ranging, DB: double-blind; XO: crossover; PG: parallel group; Dreg: dosing regimen; PBO: placebo; SAL: salmeterol; TIO: tiotropium; FOR: formoterol.

The meta-analysis included far fewer patients with asthma when compared with the COPD patient population. It is notable, however, that even in this relatively small cohort of asthma patients, asthma-related serious adverse events occurred at a relatively high frequency. There was 1 death and 1 intubation in the 300 mcg indacaterol group (study B2338, n~268/arm, total n=805) versus none in the placebo group. Additionally, there were 3 hospitalizations each in the indacaterol 300 mcg and 600 mcg groups versus none in the placebo group, in patients who were taking concomitant ICS per protocol. The second death (described in detail elsewhere in this document) was not included in this meta-analysis because the patient was taken off study drug when she entered the hospital for an acute-respiratory related event, and was therefore counted as off-treatment. It is notable, however, that this patient, though enrolled in an asthma-clinical trial, was adjudicated as having had a COPD-related death and intubation. Although the Applicant is

not proposing to market indacaterol for an asthma indication, the adjudication of this death in an asthma patient as being COPD-related illustrates the clinical overlap that exists between these two disease entities and the possible safety implications that arise when considering the doses that are proposed for registration.

V. Conclusions

Arcapta Neohaler (indacaterol maleate inhalation powder) is a long-acting beta-agonist (LABA) proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Applicant seeks approval of two doses of indacaterol, 75 and 150 mcg. Due to concerns regarding asthma- and COPD-related deaths, hospitalizations, and intubations that were raised during the review of this application, the Agency asked that the Applicant conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation.

The Agency's review focused on the All-treated COPD Safety Population I as this is the indication sought by the Applicant, and the majority of data included comes from a COPD patient population. Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related, as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations. Although we realize the limitations of this type of an analysis, one can argue that the presence of a numerical trend towards an increase in a respiratory safety signal in a population expected to have respiratory benefit from the drug, is an issue that warrants consideration and further discussion. The possibility that such a signal may exist in COPD rather than asthma further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.

Safety Addendum to Clinical Review
Banu Karimi-Shah, MD
NDA 22-383
Arcapta Neohaler (indacaterol maleate)

VI. Attachment: Agency Information Request, December 16, 2010

NDA 22383

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

In our action letter for your original submission, we stated the following:

To support approval of two doses of indacaterol in COPD patients, provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.

In addition to the risk benefit assessment of indacaterol in COPD patients, another important potential safety issue noted in the action letter is possible asthma-related death. Additional information is required to address these issues. To facilitate our safety review of your product, we have the following request for information.

Conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. Use the following criteria to provide guidance in formulating your analysis.

1. Study inclusion criteria

- a. Include all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration that were conducted with indacaterol maleate delivered using the single dose dry powder inhaler Concept 1 device (to-be-marketed indacaterol product) for the treatment of COPD or asthma, whether or not the trials were submitted as part of the NDA.
- b. Include trials in which the to-be-marketed indacaterol product was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS)

or other adjunctive therapy. Include trials conducted with indacaterol combination products that have a treatment arm(s) using the to-be-marketed indacaterol product.

- c. Include trials with any dose of the to-be-marketed indacaterol product.
 - d. Include both placebo- and active-controlled trials.
 - e. Include trials in which there was a randomized blinded phase followed by an open label extension phase. However, include only the blinded phase of the trial in your analysis.
 - f. Include randomized, double-blind crossover design trials. However, include only the first cross-over period of the trial.
 - g. Do not include trials in healthy volunteers, indications other than asthma or COPD, uncontrolled trials, or trials designed primarily to obtain clinical pharmacology data (e.g., Phase I trials).
 - h. Do not include trials in children less than 12 years of age.
 - i. Do not include trials conducted solely with devices other than the Concept 1 device or with other formulations of indacaterol, such as alternative salts.
2. Identification and adjudication of events
- a. Adverse events of interest to include:
 1. all-cause death,
 2. asthma-related death,
 3. asthma-related intubation,
 4. asthma-related hospitalization,
 5. COPD-related death,
 6. COPD-related intubation,
 7. COPD-related hospitalization,
 8. pneumonia-related death,
 9. pneumonia-related intubation, and
 10. pneumonia-related hospitalization.

- b. Review all serious adverse events reported in the trials, in a manner blind to treatment, to determine whether the event involved death, hospitalization, or intubation. For events involving one or more of these outcomes, determine whether the event occurred in the setting of an acute respiratory event or was otherwise respiratory-related. Base the determination of respiratory-relatedness on the clinical judgment of an independent adjudication committee. Do not rely upon the coded adverse event term to determine respiratory-relatedness, as the reliability and validity of the specific terms may be variable.
 - c. For the analysis of individual events, a patient may have more than one respiratory event related to a single experience. For example, a patient who had an asthma-related hospitalization, followed by an asthma-related intubation and died of an asthma-related cause should be considered as having each of four events. All four events are to be counted in the analysis, not just the most critical.
 - d. Count on-treatment events, not events that occurred after treatment. Include events regardless of determination of drug-relationship.
 - e. For each patient who died during the trial, provide cause of death as determined by an independent adjudication committee. Compare the adjudicated cause to the adverse event resulting in death as determined by the investigator.
 - f. Provide narrative summaries for each patient with an adverse event of interest.
3. Statistical methods
- a. Analyze event rates based on exposure. Include time to event analyses and hazard ratios compared to placebo. Consider methods with statistical properties suited for the known incidence rates.
 - b. Consider composite endpoints of all COPD-related events, all asthma-related events, and all respiratory-related events. For composite endpoints, count only the first event if more than one event occurred for a single patient.
 - c. Include all available blinded, controlled data for a trial. Do not truncate based on an arbitrary cut off date.
 - d. Include at least the following analysis sets:
 - 1. all included studies conducted using the to-be-marketed product,
 - 2. placebo-controlled studies,
 - 3. COPD only studies,
 - 4. asthma only studies, and

5. COPD only studies greater than 7 days duration.
 - b. Complete the analyses for each individual indacaterol dose. Also do an analysis with all indacaterol dosage groups combined.
 - c. For COPD only studies, conduct a subgroup analysis of patients with baseline bronchodilator responsiveness compared to non-bronchodilator responsive patients. Define bronchodilator responsiveness according to the American Thoracic Society criteria of FEV1 change of >200 ml and >12%. [Pellegrino R, Viegi G, Brusasco RO, et al. Interpretive strategies for lung function testing. *Eur Respir J* 2005; 26:948-68.]
 - d. Summarize non-completers by treatment group. Include reasons for non-completion, follow-up time after dropout, AEs of interest before dropout, and any known AEs of interest after dropout.

Please provide your proposed analysis plan and timeline for analysis completion by COB on January 2. Also provide in your timeline the planned date of submission of your Adjudication Committee charter. Include a detailed description of the procedures for adjudicating serious adverse events and cause of death in your Adjudication Committee charter.