

**FORM 51-102F3**

**MATERIAL CHANGE REPORT**

**1. Name and Address of Company**

Cardiome Pharma Corp.  
6190 Agronomy Rd, Suite 405  
Vancouver, BC V6T 1Z3

**2. Date of Material Change**

November 21, 2013

**3. News Release**

November 21, 2013 - Vancouver, Canada

**4. Summary of Material Change**

Cardiome Pharma Corp. announced that a publication titled, *Pharmacological Cardioversion of Atrial Fibrillation with Vernakalant: Evidence in Support of the ESC Guidelines*, was published in *Europace*, the official Journal of the European Heart Rhythm Association, and was made available in the advanced online article access section. The authors conclude that BRINAVESS is an efficacious and rapid acting pharmacological cardioversion agent, for recent-onset atrial fibrillation (AF,) that can be used first line in patients with little or no underlying cardiovascular disease and in patients with moderate disease, such as stable coronary and hypertensive heart disease.

**5. Full Description of Material Change**

See attached press release

**6. Reliance on Subsection 7.1(2) or (3) of National Instrument 51-102**

Not Applicable.

**7. Omitted Information**

Not Applicable.

**8. Executive Officer**

Name: Jennifer Archibald  
Title: Chief Financial Officer  
Phone No.: 604-677-6905

**9. Date of Report**

November 21, 2013

Per:           “Jennifer Archibald”            
Jennifer Archibald,  
Chief Financial Officer

**SCHEDULE “A” – PRESS RELEASE**

**EUROPACE PUBLISHES DATA SUPPORTING USE OF BRINAVESS™  
(VERNAKALANT) AS A FIRST LINE AGENT FOR  
PHARMACOLOGICAL CARディオVERSION OF ATRIAL FIBRILLATION**

**Vancouver, Canada, November 21, 2013** -- Cardiome Pharma Corp. (NASDAQ: CRME / TSX: COM) today announced that a publication titled, *Pharmacological Cardioversion of Atrial Fibrillation with Vernakalant: Evidence in Support of the ESC Guidelines*, was published in *Europace*, the official Journal of the European Heart Rhythm Association, and was made available in the advanced online article access section. The authors conclude that BRINAVESS is an efficacious and rapid acting pharmacological cardioversion agent, for recent-onset atrial fibrillation (AF,) that can be used first line in patients with little or no underlying cardiovascular disease and in patients with moderate disease, such as stable coronary and hypertensive heart disease.

“The recent update of the ESC Guidelines on atrial fibrillation includes a discussion of the evidence base for the use of BRINAVESS and recommends its use as a first line agent for the conversion of AF to sinus rhythm,” stated Dr. John Camm, Professor of Clinical Cardiology at St. George’s University in London, UK. “Based on completed clinical trials, BRINAVESS is effective, fast acting and well tolerated, and provides acute care physicians with an opportunity to pharmacologically cardiovert recent-onset AF patients including those with no or moderate structural heart disease.”

In this publication, Savelieva et al., point out that pharmacological cardioversion would be the preferred method of converting patients from AF to sinus rhythm provided there was a safe, effective and fast acting pharmacological agent available on the market. Older agents have treatment limitations, including contraindications which prevent use in structural heart disease for some, proarrhythmia or slow onset of action which may explain the need for longer hospital stays in others.

The authors of this publication explain that the benefits of pharmacological cardioversion include no need for general anaesthesia, conscious sedation, or fasting as well as a lower risk of immediate recurrence of AF and possibly lower psychological impact on some patients. They point out that the choice of an antiarrhythmic drug for AF cardioversion is determined by the underlying heart disease. In a subgroup analysis in 274 patients with ischaemic heart disease (41% with previous myocardial infarction) enrolled in ACT I-IV trials, no increased risk of serious adverse events was associated with BRINAVESS when compared to patients without ischaemic heart disease. In addition, there were no drug related cases of torsade de pointes, ventricular fibrillation, or death in the subgroup with ischaemic heart disease, and the placebo-extracted efficacy of vernakalant was comparable (45.7% vs. 47.3% ischemic vs. non-ischaemic).

According to the 2012 focused update of the ESC Guidelines on the management of AF, BRINAVESS was granted a Class I recommendation with a level of evidence A for

cardioversion of AF patients with structurally normal hearts or minimal heart disease and a Class IIb recommendation with a level of evidence B for cardioversion of AF patients with moderate structural heart disease.<sup>1,2</sup> The development program for BRINAVESS has provided evidence to support recent recommendations, in the updated ESC Guidelines, to use the drug as a first line agent for the management of AF patients including those with moderate structural heart disease which is described as heart failure NYHA class I-II, stable coronary artery disease, and moderate left ventricular hypertrophy.

In this publication, the authors refer to a Buccelletti publication in which a meta-analysis of five controlled studies, (CRAFT, ACT I, ACT II, ACT III, AVRO) in 810 recent-onset AF patients, showed that BRINAVESS was 8.4 times more likely to convert AF to sinus rhythm when compared to placebo or amiodarone (95% CI, 4.4-16.3,) without excess risk of serious adverse events (risk ratio, 0.91; 95% CI, 0.6-1.36). Over 95% of patients that cardioverted to sinus rhythm after receiving BRINAVESS remained in sinus rhythm at 24 hours. Furthermore while discussing the efficacy of BRINAVESS, Savelieva et al., referred to a real world experience, observational study from a single centre in Malmö, Sweden, where the drug has been used in AF patients since 2011. In this study 70% of 251 patients treated with BRINAVESS in the emergency room converted to sinus rhythm within 2 hours after start of the infusion with a median time to conversion of 11 minutes.

In the publication by Savelieva et al., BRINAVESS is presented as an efficacious, fast acting, and well tolerated pharmacological agent for the cardioversion of recent-onset AF with strong evidence supporting its recommendations for use in the ESC Guidelines for the Management of AF.

#### **References:**

1. Savelieva, I. et al. Pharmacological Cardioversion of Atrial Fibrillation with Vernakalant: Evidence in Support of the ESC Guidelines. *Europace*. Advance access published Oct 9, 2013, doi: 10.1093/europace/eut274.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. Focused Update of the ESC Guidelines for the Management of Atrial Fibrillation: an Update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation. *Europace*. 2012; 14: 1385-413.

#### **About Cardiome Pharma Corp.**

Cardiome Pharma Corp. is a specialty biopharmaceutical company dedicated to the development and commercialization of new therapies that will improve the health of patients suffering from heart disease around the world. Cardiome has two marketed products, BRINAVESS<sup>TM</sup> (vernakalant IV), approved in Europe and other territories for the rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults, and AGGRASTAT<sup>®</sup> (tirofiban HCl) a reversible GP IIb/IIIa inhibitor indicated for use in Acute Coronary Syndrome patients.

Cardiome is traded on the NASDAQ Capital Market (CRME) and the Toronto Stock Exchange (COM). For more information, please visit [www.cardiome.com](http://www.cardiome.com).

#### **Forward-Looking Statement Disclaimer**

Certain statements in this news release contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 or forward-looking information under applicable Canadian securities legislation that may not be based on historical fact, including without limitation statements containing the words “believe”, “may”, “plan”, “will”, “estimate”, “continue”, “anticipate”, “intend”, “expect” and similar expressions.

Forward-looking statements may involve, but are not limited to, comments with respect to our objectives and priorities for the remainder of 2013 and beyond, our strategies or future actions, our targets, expectations for our financial condition and the results of, or outlook for, our operations, research and development and product and drug development. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause the actual results, events or developments to be materially different from any future results, events or developments expressed or implied by such forward-looking statements. Many such known risks, uncertainties and other factors are taken into account as part of our assumptions underlying these forward-looking statements and include, among others, the following: general economic and business conditions in the United States, Canada, Europe, and the other regions in which we operate; market demand; technological changes that could impact our existing products or our ability to develop and commercialize future products; competition; existing governmental legislation and regulations and changes in, or the failure to comply with, governmental legislation and regulations; availability of financial reimbursement coverage from governmental and third-party payers for products and related treatments; adverse results or unexpected delays in pre-clinical and clinical product development processes; adverse findings related to the safety and/or efficacy of our products or products; decisions, and the timing of decisions, made by health regulatory agencies regarding approval of our technology and products; the requirement for substantial funding to expand commercialization activities; and any other factors that may affect our performance. In addition, our business is subject to certain operating risks that may cause any results expressed or implied by the forward-looking statements in this presentation to differ materially from our actual results. These operating risks include: our ability to attract and retain qualified personnel; our ability to successfully complete pre-clinical and clinical development of our products; changes in our business strategy or development plans; intellectual property matters, including the unenforceability or loss of patent protection resulting from third-party challenges to our patents; market acceptance of our technology and products; our ability to successfully manufacture, market and sell our products; the availability of capital to finance our activities; and any other factors described in detail in our filings with the Securities and Exchange Commission available at [www.sec.gov](http://www.sec.gov) and the Canadian securities regulatory authorities at [www.sedar.com](http://www.sedar.com). Given these risks, uncertainties and factors, you are cautioned not to place undue reliance on such forward-looking statements and information, which are qualified in their entirety by this cautionary statement. All forward-looking statements and information made herein are based on our current expectations and we undertake no obligation to revise or update such forward-looking statements and information to reflect subsequent events or circumstances, except as required by law.

**For Further Information:**

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