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2 EMA/CHMP/559636/2014
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper on the need for revision of the points to**
5 **consider on the clinical investigation of new medicinal**
6 **products for the treatment of acute coronary syndrome**
7 **(CPMP/EWP/570/98 and CPMP/EWP/967/01)**
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Agreed by Cardiovascular Working Party	4 June 2014
Adopted by CHMP for release for consultation	25 September 2014
Start of public consultation	15 October 2014
End of consultation (deadline for comments)	15 January 2015

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10 The proposed guideline will replace the Guideline on clinical investigation of new medicinal products for
11 the treatment of acute coronary syndrome without existing ST-segment elevation (CPMP/EWP/570/98)
12 and the Guideline on clinical development of fibrinolytic medicinal products in the treatment of patients
13 with ST segment elevation acute myocardial infarction (STEMI) (CPMP/EWP/967).

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15 Comments should be provided using this [template](#). The completed comments form should be sent
16 to cvsWPsecretariat@ema.europa.eu

Keywords	<i>Non-ST segment elevation, acute coronary syndrome, myocardial infarction, angina, revascularisation, anticoagulants, antithrombotics, stent thrombosis</i>
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20 1. Introduction

21 Cardiovascular diseases are currently the leading cause of death in industrialized countries and are
22 expected to become so in emerging countries by 2020 (1,2). Among these, coronary artery disease
23 (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. Acute
24 coronary syndrome (ACS) has evolved as a useful operational term to refer to any constellation of
25 clinical symptoms that are compatible with acute myocardial ischemia. It encompasses ST-segment
26 elevation myocardial infarction (STEMI), Non-ST-segment elevation myocardial infarction (NSTEMI)
27 and unstable angina (UA).

28 Two CHMP documents have been developed to address ACS: the *CHMP points to consider PtC on the*
29 *clinical investigation of new medicinal products for the treatment of acute coronary syndrome (ACS)*
30 *without persistent ST-segment elevation (CPMP/EWP/570/98)*, published in 2000 and the *CHMP points*
31 *to consider on the clinical development of fibrinolytic products in the treatment of patients with ST*
32 *segment elevation myocardial infarction (CPMP/EWP/967/01)*, published in 2003 (3,4). Since that time,
33 major developments have taken place in the definitions, diagnosis, interventions and management of
34 ACS. These developments are reflected in the relevant ESC clinical practice guidelines (1,2). Currently,
35 an update is considered necessary to take these new developments into consideration, based on
36 literature review and expert advices concerning treatment initiated during the acute phase and beyond.

37 2. Problem statement

38 The leading symptom of ACS is typically chest pain. The classification of ACS is primarily based on the
39 ECG(1):

40 1. *Patients with acute chest pain and persistent (>20 min) ST-segment elevation.* This is termed ST-
41 elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these
42 patients will ultimately develop an ST-elevation MI (STEMI). The therapeutic objective is to achieve
43 rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy.

44 2. *Patients with acute chest pain but without persistent ST-segment elevation.* These patients have
45 rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-
46 normalization of T waves, or no ECG changes at presentation. The initial strategy in these patients is to
47 alleviate ischaemia and symptoms, to monitor the patient with serial ECGs, and to repeat
48 measurements of markers of myocardial necrosis. At presentation, the working diagnosis of non-ST-
49 elevation ACS (NSTEMI-ACS), based on the measurement of troponins, will be further qualified as non-
50 ST-elevation MI (NSTEMI) or unstable angina (UA). In a certain number of patients, coronary heart
51 disease will subsequently be excluded as the cause of symptoms.

52 A diagnostic test with high ability to rule out (negative predictive value) and correctly classify ACS
53 especially without persistent ST-elevation (positive predictive value) becomes of paramount interest in
54 the acute setting. Whereas there is much more experience with creatine kinase (CK) and its isoenzyme
55 MB (CK-MB), it is now recognised to be less sensitive and less specific for myocardial infarction (MI)
56 than the cardiac troponins. Cardiac troponins as biomarkers (mainly troponin T [TnT] and troponin I
57 [TnI]) provide robust results that are highly sensitive and specific in detecting cell necrosis and
58 distinguish between NSTEMI and UA. The choice of an imaging modality (non-invasive or invasive) can
59 also further assist in establishing the diagnosis.

60 The optimal management of ACS has the twin goals of the immediate relief of ischemia and the
61 prevention of serious adverse outcomes. The currently recommended endpoints to be investigated in
62 confirmatory clinical trials include: death, myocardial infarction; with a lesser preference to include
63 refractory angina in the main endpoint composite. Considering the global setting of the confirmatory
64 cardiovascular (CV) trials, acceptable and consistent definitions of different endpoints should be
65 implemented; for example the use of MACE (major adverse cardiac events) can lead to different
66 interpretations (8); this should be avoided. The inclusion of stroke in the primary composite endpoint
67 deserves further attention as it was not always investigated, and if investigated the results were not
68 consistent (6 and 7). Another controversial issue is the inclusion of stent thrombosis in the primary
69 endpoint. Although it is an important and serious complication following PCI, its clinical significance
70 and consequently its inclusion as a hard endpoint comparable to MI and death need further
71 assessment. Also, the reporting of stent thrombosis should follow specified definitions (10).

72 Whereas the incidence and risk of STEMI have decreased over the past 25 years, the relative
73 frequency of UA/NSTEMI has increased, and its risk has remained relatively high (now comparable to
74 that of STEMI)(5). Hence, improving ACS outcomes remains a challenge for the future. Clinical
75 guidelines indicate that treatment should not only focus on the acute phase but also on the long term
76 management plan. Fibrinolytic products have been greatly replaced by interventional procedures.
77 Secondary prevention is of paramount importance since ischaemic events continue to occur at a high
78 rate after the acute phase. Clinical trials demonstrating efficacy of recently approved anti-thrombotic
79 medicinal products were event-driven trials, with an average duration of more than one year (6,7).
80 Consequently, they are approved for administration starting from the acute phase, but with the
81 recommendation to be used for extended periods.

82 Management of ACS is based on administering anti-ischemic therapy, antithrombotic therapy, on-going
83 risk stratification, and the use of invasive procedures. More recently, given the role of inflammation in
84 the pathophysiological aspects of plaque rupture, several studies are assessing the use of anti-
85 inflammatory therapies other than statins to reduce the risk of a recurrent acute coronary syndrome
86 (11). The pharmacological profile of these agents is quite different from the commonly investigated
87 anticoagulants, which also reflects their safety profile.

88 Besides markers of myocardial necrosis, markers of pathophysiological mechanisms implicated in ACS
89 are under investigation and could become useful to determine pathophysiology, individualize
90 treatment, and evaluate therapeutic effects. These include C-reactive protein (CRP), in particular high-
91 sensitivity C-reactive protein (hsCRP) and brain natriuretic peptide (BNP) or its N-terminal prohormone
92 fragment (NT-proBNP) among others.

93 **3. Discussion (on the problem statement)**

94 An update for the CHMP PtC of new medicinal products for the treatment of acute coronary syndrome
95 (ACS) (CPMP/EWP/570/98 and CPMP/EWP/967/01) is foreseen. The following points are proposed to
96 be addressed in the update:

- 97 1. Guidance addressing ACS patients.
- 98 2. The definition and diagnosis of ACS (including STEMI, NSTEMI and UA) should follow the most
99 recent universal definition and updated diagnostic criteria (1,2,12).
- 100 3. Risk stratification using different scoring systems. Diagnosis and risk stratification are closely
101 linked. Quantitative assessment of risk is useful for clinical decision making, for example for the

102 selection of the site of care, the use of platelet glycoprotein (GP) IIb/IIIa inhibitors and interventional
103 strategies. Among several risk scores predicting short- or mid-term risk of ischaemic events, the Global
104 Registry of Acute Coronary Events (GRACE) and the TIMI risk scores are the most widely used. In
105 addition, the use of bleeding risk scores (e.g. CRUSADE) can also have a prognostic value.

106 4. Endpoints investigated in the clinical trials should be updated taking into consideration recent trial
107 experiences and regulatory assessments. The definition of the CV endpoints should follow standardised
108 definitions that are globally acceptable. The investigation of stroke and stent thrombosis as
109 components of the primary endpoint deserves some discussion.

110 5. Investigation of medical treatment options should cover not only the period of their administration
111 but may also include a period of clinical relevance after discontinuation e.g. one month in case of acute
112 administration after i.v. antithrombotics. Duration of studies and also the need or not for long-term
113 data will be discussed.

114 6. The scope of the medicinal pharmacological groups that the current guideline addresses should be
115 widened. The current guideline focuses on antiplatelet and anticoagulant agents. Attention should be
116 paid to newer classes and mechanisms, e.g anti inflammatory agents, and their implications for clinical
117 studies. This reflects also on the associated risks.

118 7. The role of biomarkers, other than those indicative of tissue damage should be addressed as this is
119 an important issue in scientific advices.

120 **4. Recommendation**

121 It is well established that ACS in their different clinical presentations share a widely common
122 pathophysiological substrate. For this reason it is currently proposed to merge both recommendations
123 on clinical investigation of new medical products in STEMI and NSTEMI in a single guideline, as the
124 endpoints are similar even if there are subtle differences in the initial treatment in both groups of
125 patients presenting with ACS.

126 The EMA Cardiovascular Working Party (CVS WP) recommends revising the PtC on the clinical
127 investigation of new medicinal products for the treatment of acute coronary syndrome (ACS)
128 (CPMP/EWP/570/98 and CPMP/EWP/967/01) and to merge them in a single document for ACS that
129 includes STEMI and NSTEMI. Given the impact that such changes will have on the development
130 programs of the relevant medicinal products, it is recommended to exchange views with the different
131 stakeholders like healthcare professionals organisations (i.e. Task Force for the management of
132 patients presenting with ACS of the ESC), industry and patients organisations. Proposed timetable

133 This CP is released for 3 months public consultation. It is planned to release the draft Guideline within
134 6 months after completion of external consultation on the CP. The draft Guideline will be released for 6
135 months public consultation and following the receipt of comments it will be finalised within
136 approximately another 6 months.

137 **5. Resource requirements for preparation**

138 The preparation will involve the CVS WP at the EMA. Two rapporteurs from the CVS WP will be involved
139 in drafting the update to the Guidelines that is to be discussed during 2 CVS WP meetings.

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141 **6. Impact assessment (anticipated)**

142 The document is intended to provide guidance to industry and investigators when performing clinical
143 trials to develop medicinal products for patients with ACS. It should also provide a clear basis for the
144 CHMP and the SAWP when assessing data or giving advice pertaining to clinical development programs
145 for medicinal products intended for the management of ACS.

146 **7. Interested parties**

147 Healthcare professional organisations (Task Force for the management of ACS in patients presenting
148 with STEMI and ACS without persistent ST-segment elevation of the European Society of Cardiology),
149 pharmaceutical industry and patients organisations

150 **8. References to literature, guidelines, etc.**

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