Active substance(s) (INN or common name):	Acetylsalicylic Acid
Pharmaco-therapeutic group (ATC Code):	B01AC06
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Oltrola

Data lock point for current RMP	01 November 2012	Version number	1.3
Date of final sign off	26 March 2014		

6.2. ELEMENTS FOR A PUBLIC SUMMARY

6.2.1. Overview of Disease Epidemiology

6.2.1.1. Myocardial Infarction (MI)

Each year the number of new heart attacks (or MI) that occur in the US is 600,000.[1] In Europe, a study from Denmark reported that about 20,414 new patients were diagnosed with MI in 1 year.[2] Overall, surveys show that 7% of the people in the US and 4.8% in Europe have had MI.[3] The percentage of MI that result in death ranges from 7% to 13%.[4,5,6] The risk of MI increases with age, smoking, diabetes, high cholesterol levels and high blood pressure.

6.2.1.2. Stroke

Stroke is a leading cause of death and disability in the US and Europe. Each year in the US, about 780,000 people experience new or recurrent stroke.[1] In a large study in Europe, new cases of stroke increased with age, and were reported more frequently in men in most of the age groups.[7] Stroke causes 9% of all deaths around the world[8] and in 2004, it was the third leading cause of death in the US. The risk of stroke increases with factors such as age, diabetes, and past history of cardiovascular disease.

6.2.1.3. Angina (stable or unstable)

Angina pectoris is a form of severe chest pain that is cardiac in nature and relates to a reduction of oxygen to the heart and could be due to obstruction of the coronary arteries. Overall in the US, angina is found in 3.3% of white men, 2.8% of white women, 2.4% of black men and 5.4% of black women.[9] In Europe, the percentage of angina ranges from 3.57% in France to 4.12% in Italy.[10] Similar to MI, the risk of angina increases with age, smoking, diabetes, high cholesterol and high blood pressure.

6.2.1.4. Coronary Artery Bypass Grafting (CABG) or Infra-inguinal bypass surgery

Coronary artery bypass grafting (CABG) is a type of surgery to treat people with severe heart disease.[11] Risk of heart disease increases with factors such as high blood pressure, diabetes, smoking and age.[12,13] A study in Europe conducted within six countries found that 63% of cardiac patients had received CABG from September to November 1995.[14] In 2010 in the US, about 0.4 million CABG were performed, of which 40% were in those aged 45-64 years and 60% were in those over 65 years of age.[15] One study reported that the percentage of death in those who received CABG was 3% between 1999 to 2001 in California and 2% in New York.[16] In a study from Scotland, death rate from CABG was 6.7% from 1997 to 1999.[17]

Infra-inguinal bypass surgery (IIBS) is used as treatment for patients with peripheral arterial disease, especially in those with obstruction to blood flow in the arteries leading to the legs.[18] The risk of peripheral arterial disease increases with age, diabetes, smoking and high blood pressure.[19] In Europe the number of IIBS performed per year between 2005 and 2009 ranged from 369 in Finland to 3.426 in Italy.[20] In the US a study done in private hospitals found that IIBS was performed more among whites (68% of procedures) than blacks (19%).[21] The overall death rate among IIBS patients was 2.7% and major complications have been reported in 18.7% of those who had this surgery.[22]

6.2.1.5. Coronary Angioplasty, with the exception of the acute phase

Coronary angioplasty (also called balloon angioplasty) is a type of surgery to treat people with severe heart disease. The risk of heart disease increases with high blood pressure, diabetes, smoking and age.[12,13] In the US, about 500,000 balloon angioplasties were performed in 2010 of which 220,000 were in those aged 45-64 years and 257,000 were in those over 65 years of age.[15] The percentage of those surviving three years after a coronary angioplasty is 94.6% in a US study.[23]

6.2.2. Summary of Treatment Benefits

Oltrola contains acetylsalicylic acid (ASA), which belongs to a group of medicines called anti-platelet agents. Platelets are cell fragments in the blood that cause the blood to clot and are involved in thrombosis. When a blood clot occurs in an artery, it stops the blood flow and cuts off oxygen supply to the areas of the body beyond the clot. When this happens in the heart, it can cause a heart attack or angina; in the brain it can cause a stroke.

Oltrola is taken to reduce the risk of blood clot formation and thereby prevent heart attack, stroke, and cardiovascular problems in patients who suffer from stable or unstable angina.

Oltrola is also used to prevent the formation of blood clots after certain types of heart surgery that are performed to widen or to unblock the blood vessels.

6.2.2.1. Effectiveness of Oltrola

ASA is well-established as an effective and well tolerated treatment for secondary prevention of cardiovascular events in the proposed indications.

6.2.3. Unknowns Relating to Treatment Benefits

ASA has been marketed for over 100 years and has been in well-established medicinal use for secondary prevention of cardiovascular (heart-related) events for over 20 years. During this time, the clinical efficacy and safety have been thoroughly investigated and well understood as documented in published literature. There is no evidence to suggest that efficacy is reduced or enhanced in any target subpopulation.

6.2.4. Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Bleeding in the gut (Gastrointestinal Haemorrhage)	Drugs like Oltrola, as a class, can cause bleeding in the gut.	Patients who have had bleeding in their gut should not use Oltrola.
Heavy menstrual bleeding during menstrual cycle (Increased Menstrual Bleeding during Menorrhagia)	Drugs like Oltrola, as a class, can cause increased menstrual bleeding during the menstrual cycle in certain women who have abnormally heavy or prolonged menstrual periods.	Oltrola is not recommended for patients with abnormally heavy or prolonged menstrual periods because it may increase menstrual bleeding.
Bleeding (Haemorrhage)	Drugs like Oltrola, as a class, can cause bleeding.	There is an increased risk of bleeding particularly during or after surgeries (even in cases of minor procedures, e.g. pulling teeth) or in patients who have certain conditions that affect blood clotting. Use with caution before surgery, including pulling teeth. It may be necessary to stop treatment for a period of time before surgery. Certain medications should not be taken together with Oltrola.
Allergic-type response (Hypersensitivity Reactions)	Drugs like Oltrola may cause breathing difficulties, rash or itchy skin reactions.	Patients who have had allergic responses to ASA or other non-steroidal anti-inflammatory medicines (NSAIDS) should not use Oltrola.
High levels of uric acid (a laboratory value) in the blood (Hyperuricaemia)	Drugs like Oltrola, as a class, may decrease uric acid clearance and painful gout attacks in certain patients may occur.	Patients who have had gout should discuss the benefits and risks of using Oltrola.
Stomach or gut sores (Gastric or Duodenal Ulcer)	Drugs like Oltrola, as a class, can cause a sore (ulcer) to form in the gut.	If ulcers in the gut occur, the treatment should be stopped.
Serious allergic-type skin reactions (Severe Cutaneous Adverse Reactions)	Drugs like Oltrola, as a class, may cause serious allergic skin reactions.	Seek medical advice at the first sign of allergic-type skin reactions.
A decrease in kidney function (Deterioration of Renal Function)	Drugs like Oltrola, as a class, can cause the kidneys to be less effective in clearing substances from the body and producing urine.	Oltrola should be used with caution in patients with decreased kidney function (or not used if this condition is severe), or in patients who are dehydrated.

Important Potential Risks

Risk	What is Known
(Reye's Syndrome)	Oltrola is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. ASA may be a contributory factor in the causation of Reye's syndrome, a potentially fatal disease that can damage the brain and the liver, in some children. Assessment of potential risk is ongoing. If indicated, changes to the SmPC will be undertaken.
High blood pressure (Hypertension)	Oltrola is to be used with caution in cases of high blood pressure. Assessment of potential risk is ongoing. If indicated, changes to the SmPC will be undertaken.

Missing Information

Risk	What is Known
Ability to drive or operate machinery	No studies on the effects on the ability to drive and use machines have been performed with Oltrola. Oltrola may produce a spinning sensation (vertigo). You should not drive or operate machines until you know whether this medicine affects your ability to perform these activities.

6.2.5. Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Oltrola can be found in the Oltrola's EPAR page.

This medicine has no additional risk minimisation measures.

6.2.6. Planned Post Authorisation Development Plan

No post-authorisation studies are planned.

Studies Which are a Condition of the Marketing Authorisation

There are no requirements for additional studies as a result of conditions of the marketing application.

6.2.7. Summary of Changes to the Risk Management Plan Over Time

Table 1. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	27 Nov 2012		Initial RMP
1.1	14 June 2013	None	Reformatted initial RMP to current EU template. Non-clinical information was added. Epidemiological information (related to the indications of stable and unstable angina, graft occlusion post CABG, and coronary angioplasty) was expanded upon.
1.2	03 February 2014	None	Updated in response to RMS Day 120 Draft Assessment report (DK/H/2277/001-002/DC)
1.3	26 March 2014	None	Updated in response to RMS Day 180 Assessment report (DK/H/2277/001-002/DC)

6.3. REFERENCES

[1] Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008; 117(4): e25-146.

[2] Koek HL, Kardaun JW, Gevers E, et al. Acute myocardial infarction incidence and hospital mortality: routinely collected national data versus linkage of national registers. Eur J Epidemiol 2007; 22(11): 755-62.

[3] Gikas A, Sotiropoulos A, Panagiotakos D, et al. Prevalence trends for myocardial infarction and conventional risk factors among Greek adults (2002-06). QJM 2008; 101(9): 705-12.

[4] Roger VL. Epidemiology of myocardial infarction. Med Clin North Am 2007; 91(4): 537-52; ix.

[5] Gentil A, Bejot Y, Lorgis L, et al. Comparative epidemiology of stroke and acute myocardial infarction: the Dijon Vascular project (Diva). J Neurol Neurosurg Psychiatry 2009; 80(9): 1006-11.

[6] Kostis WJ, Deng Y, Pantazopoulos, et al. Trends in mortality of acute myocardial infarction after discharge from the hospital. Circ Cardiovasc Qual Outcomes 2010; 3(6): 581-9.

[7] Di Carlo A, Launer LJ, Breteler MMB, et al. Frequency of stroke in Europe: A collaborative study of population-based cohorts. ILSA Working Group and the Neurologic Diseases in the Elderly Research Group. Italian Longitudinal Study on Aging. Neurology 2000; 54(11 Suppl 5): S28-33.

[8] Murray CJ and Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349(9061): 1269-76.

[9] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. Jan 1 2013;127(1):e6-e245.

[10] Peterson E. The burden of angina pecoris and its complications complications. Clin Cardiol. 2007;1-10:1-15.

[11] NIH. National Heart, Lung, Blood Institute. "What Is Coronary Artery Bypass Grafting?" http://www.nhlbi.nih.gov/health/health-topics/topics/cabg/ Accessed on May 24, 2013.

[12] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. May 12 1998;97(18):1837-1847.

[13] Torpy JM, Burke AE, Glass RM. JAMA patient page. Coronary heart disease risk factors. JAMA. Dec 2009;302(21):2388.

[14] Nashef SA, Roques F, Michel P, et al. Coronary surgery in Europe: comparison of the national subsets of the European system for cardiac operative risk evaluation database. Eur J Cardiothorac Surg. Apr 2000;17(4):396-399.

[15] Centers for Disease Control and Prevention. Inpatient Surgery. http://www.cdc.gov/nchs/fastats/insurg.htm. Accessed on May 19, 2013.

[16] Carey JS, Danielsen B, Gold JP, Rossiter SJ. Procedure rates and outcomes of coronary revascularization procedures in California and New York. The Journal of thoracic and cardiovascular surgery. Jun 2005;129(6):1276-1282.

[17] Pell JP, Walsh D, Norrie J, et al. Outcomes following coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in the stent era: a prospective study of all 9890 consecutive patients operated on in Scotland over a two year period. Heart. Jun 2001;85(6):662-666.

[18] Lee ES, Santilli SM, Olson MM, Kuskowski MA, Lee JT. Wound infection after infrainguinal bypass operations: multivariate analysis of putative risk factors. Surg Infect (Larchmt). Winter 2000;1(4):257-263.

[19] Ouriel K. Peripheral arterial disease. Lancet. Oct 13 2001;358:1257-1264.

[20] Lees T, Troeng T, Thomson IA, et al. International variations in infrainguinal bypass surgery - a VASCUNET report. Eur J Vasc Endovasc Surg. Aug 2012;44(2):185-192.

[21] Barshes NR, Menard MT, Nguyen LL, Bafford R, Ozaki CK, Belkin M. Infrainguinal bypass is associated with lower perioperative mortality than major amputation in high-risk surgical candidates. J Vasc Surg. May 2011;53(5):1251-1259 e1251.

[22] LaMuraglia GM, Conrad MF, Chung T, Hutter M, Watkins MT, Cambria RP. Significant perioperative morbidity accompanies contemporary infrainguinal bypass surgery: an NSQIP report. J Vasc Surg. Aug 2009;50(2):299-304, 304.e1-304.e4.

[23] Hannan EL, Racz MJ, McCallister BD, et al. A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. Jan 1999;33(1):63-72.