EU Risk Management Plan for Telmisartan (Micardis, Pritor, Kinzalmono)

Doc. No.: s00004762-08	
RMP version to be assessed as part of this application:	
RMP version number:	6.1
Data lock point for this RMP:	31 Mar 2023
Date of final sign off:	10 Oct 2023
Rationale for submitting an updated RMP:	Revision of safety concerns in line with GPV Module V, Revision 2
Summary of significant changes in this RMP:	Removal of all safety concerns: Important identified risks: • Renal dysfunction as a consequence of dual renin-angiotensin-aldosterone system blockade • Sepsis • Foetoxicity • Hypoglycaemia (in diabetic patients) Important potential risks: • Rhabomyolysis • Increase of hepatic-related adverse reactions in the Japanese population • Malignancies
Other RMP versions under evaluation:	None
RMP version number:	
Submitted on:	
Procedure number:	
Details of the currently approved RMP:	
Version number:	6.0
Approved with procedure:	EMEA/H/C/XXXX/WS/0570
Date of approval (opinion date):	26 Jun 2014
QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Telmisartan
Pharmacotherapeutic group (ATC code)	Angiotensin II receptor blocker (ARB) (ATC code: C09CA07)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH Bayer AG
Medicinal products to which this RMP refers	Micardis, Pritor, Kinzalmono
Invented names in the EEA	Micardis, Pritor, Kinzalmono
Marketing authorisation procedure	Centralised procedure
Brief description of the product	*Chemical class* Angiotensin II receptor blocker (ARB)
	Summary of mode of action Telmisartan is a specific angiotensin II receptor (type AT1) antagonist, with no partial agonist activity. By selectively blocking the binding of angiotensin II to the AT1 receptor, telmisartan blocks the effect of angiotensin II in the renin-angiotensin system cascade and induces the increase of renin and angiotensin II concentrations in plasma. The binding is long-lasting. In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.
	Important information about its composition Not applicable
Hyperlink to the Product Information	<Product information (eCTD module 1.3.1)>
Indications in the EEA	*Current* Hypertension Treatment of essential hypertension in adults Cardiovascular prevention Reduction of cardiovascular morbidity in adults with:

	• Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or • Type 2 diabetes mellitus with documented target organ damage
	Proposed Not applicable
Dosages in the EEA	*Current* 20 mg, 40 mg, and 80 mg
	Proposed Not applicable
Pharmaceutical form and strengths	*Current* Tablets; 20 mg, 40 mg, and 80 mg
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ARB	Angiotensin II receptor blocker
ATC	Anatomical Therapeutic Chemical
CV	Cardiovascular
EEA	European Economic Area
EU	European Union
GVP	Good Pharmacovigilance Practices
INN	International Non-proprietary Name
QPPV	Qualified Person Pharmacovigilance
RMP	Risk Management Plan

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

SI.1 EPIDEMIOLOGY OF HYPERTENSION

SI.1.1 Incidence

Hypertension, or high blood pressure, is a condition where in there is elevation of the arterial blood pressure above the normal range expected in a particular group. Hypertension may be of an unknown aetiology (essential hypertension). It may also result from kidney disease (renal hypertension), endocrine diseases (e.g. phaeochromocytoma or Cushing's disease), or disease of the arteries (e.g. coarctation of the aorta), where it is termed secondary or symptomatic hypertension.

The occurrence of hypertension can be quantified as an incidence rate per person-year or as a cumulative incidence (risk) within a given time-period, e.g. a 2-year, 10-year, or lifetime cumulative incidence per person studied.

SI.1.2 Prevalence

Hypertension prevalence figures vary from country to country (see SI.Table 1). This variation may reflect differences between the age of the population studied, race, rural/urban area, calendar year, awareness of hypertension, measurement techniques/devices, treatment modes, and differences in lifestyle behaviour.

The US CDC analysed data from the NHANES from 2003 to 2010, in which a total of 22 992 participants aged over 18 years were interviewed and examined. The overall prevalence of hypertension among US adults aged over 18 years in the years between 2003 and 2010 was estimated to be 30.4%, or an estimated 66.9 million patients.

SI.Table 1 Prevalence of hypertension in various countries (review article 1986-1997)

Country	Men	Women
	[%]	
Europe	49.7	38.6
Italy	44.8	30.6
Sweden	44.8	32.0
United Kingdom	46.9	36.5
Spain	49.0	44.6
Finland	55.7	41.6
Germany	60.2	50.3
Germany [R12-2500]	50.3	42.1
North America	30.4	24.8
United States	29.8	25.8
Canada	31.0	23.8

Data source: [R08-4697]

SI.1.3 Demographics of the population in the hypertension indication and risk factors for the disease

Hypertension incidence increases with age. There are inconsistent findings regarding age-specific prevalence by gender: a higher prevalence in men in France, a higher prevalence in women in the UK, and a higher prevalence in men in the US up until the age of 49, with overall prevalence being higher overall in women of ≥50 years, see SI.Table 2 to SI.Table 6

SI.Table 2 Age and gender distribution of incident hypertension by age and gender, France 1997-1998

France	Men	Women
Age [years]	[per 100 person-years]	
<30	0.7	0.0
30 - 39	1.7	0.6
40 - 49	4.9	2.1
>50	5.9	3.4
All ages	3.0	1.3

Data source: [R08-4724]

SI.Table 3 Age and gender distribution of incident hypertension by age and gender in the UK 1991-1992

UK	**Men**	**Women**
Age [years]	**[per 100 person-years]**	
45 - 64	1.9	2.0
65 - 74	2.9	3.7
75 - 84	2.3	3.3
≥85	0.7	1.0

Data source: [R08-4723]

SI.Table 4 Gender distribution of incident hypertension in Poland, 1987-1993

Poland	**Men**	**Women**
Age [years]	**[per 100 person-years]**	
45 - 64	2.7	1.3

Data source: [R08-4722]

SI.Table 5 Age and gender distribution of incident hypertension by age and gender in the US, 1971-1984

US	**Men**	**Women**
Age [years]	**[per 100 person-years]**	
US-NHANES		
45 - 64	2.2	2.5

NHANES: National Health and Nutrition Examination Survey
Data source: [R08-4721]

SI.Table 6 Incidence rates of hypertension by age and gender in the US, Framingham 1948-1981

US	Men	Women
Age [years]	**[per 100 person-years]**	
30 - 39	1.7	0.8
40 - 49	2.2	1.8
50 - 59	2.4	2.5
60 - 69	2.8	3.5
70 - 79	3.1	4.3

Data source: [R08-4720]

Cumulative incidence of hypertension

The 10-year cumulative incidence of developing hypertension in persons aged 16 to 68 years free of hypertension in France between 1988 and 2001 was 19.9% (25.4% in men and 15.8% in women) [R11-2126].

The cumulative lifetime incidence for developing hypertension (>140/90 mmHg, regardless of treatment) in persons free of hypertension in the US during the 1976-1998 time-period was 90% in both 55-and 65-year-old participants [R03-1247].
The incidence of hypertension has consistently been observed to be greater in black men and women when compared to white men and women, respectively, see SI.Table 7.

SI.Table 7 Age and gender distribution of incident hypertension by race in the US 1987-1993

	Men	Women
Populations	**[per 100 person-years]**	
45 - 64 years (White population)	2.3	1.5
45 - 64 years (Black population)	3.4	3.9

Data source: [R08-4722].

Prevalence of hypertension

The distribution of age and gender in the prevalence of hypertension varies by country and race (see SI.Table 8 to SI.Table 10).

SI.Table 8 Prevalence of hypertension in Germany and Japan

	Germany, 2008 - 2009		Japan, 1990	
Age groups [years]	**Men**	**Women**	**Men**	**Women**
			[%]	
18 - 29	8.9	5.0		
30 - 44	16.3	12.1	26.7**	15.1**
45 - 65	38.8	33.3	55.8	49.7
65+	58.1	57.8	72.4	75.7
Total	31.1	30.1		

*Prevalence of known hypertension.
**Refers to age group 35 - 44 years.
Data source: [R10-4752; R11-2545]

The following demographic profile of the target population is based upon the estimated prevalence of hypertension by age and gender within racial/ethnic groups enrolled in the US NHANES between1999 and 2004 [R09-2420].

SI.Table 9 Prevalence of persons with hypertension by age group, gender, and race in the US 1999-2004

	Non-Hispanic white		Non-Hispanic black		Mexican American	
Age groups [years]	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
				[%]		
18 - 29	5.5	0.8	9.8	3.7	3.5	1.5
30 - 39	12.5	5.4	18.5	14.5	10.6	5.7
40 - 49	23.9	19.9	33.6	45.0	23.7	20.5
50 - 59	36.5	39.8	57.3	61.2	30.4	38.9
60 - 69	56.0	58.4	74.2	84.1	53.2	62.7
70+	63.3	78.8	83.4	83.1	69.1	78.8
Total	27.5	26.9	39.1	40.8	26.2	27.5

Data source: [R09-2420]

The prevalence of controlled, uncontrolled, and borderline hypertension has been observed to increase according to age and gender [R08-4743].

SI.Table 10 Prevalence of persons with controlled, uncontrolled, and borderline hypertension in the German Health Survey 1998 by age and gender

	Controlled	Uncontrolled	Borderline	Total
		[%]		[%]
Men (n = 3495)				
All ages [years]	6.3	24.5	19.5	50.3
50 - 59	8.8	36.1	22.7	67.6
60 - 69	15.9	40.1	21.1	77.1
70 - 79	23.0	43.7	16.1	82.8
Women (n = 3651)				
All ages [years]	8.2	21.5	12.4	42.1
50 - 59	8.9	29.7	19.1	57.7
60 - 69	16.3	41.3	20.1	77.7
70 - 79	23.9	45.3	13.1	82.3

Data source: [R08-4743]

Temporal trends in age-adjusted prevalence of hypertension

Age-adjusted prevalence estimates of hypertension have been observed to increase over time in different studies and countries. There has been a progressive increase of the age-specific prevalence of hypertension in the US and in the prevalence of age-specific and age-adjusted hypertension in China, see SI.Table 11 and SI.Table 12.

SI.Table 11 Temporal trends in age-adjusted prevalence of hypertension in the US

Prevalence of hypertension [%]			
US	**1998 - 1994**	**2001 - 2002**	**2007 - 2008**
Hypertension, age-adjusted	25.5	29.7	31.2

Data source: [R11-2138]

SI.Table 12 Temporal trends in age-specific and age-adjusted prevalence of hypertension in China

China	**Prevalence of hypertension [%]**		
Age [years]	**1958 - 1959**	**1979 - 1980**	**1991**
Hypertension, age-adjusted	8.5	11.2	14.4
18 - 29	3.9	2.9	3.3
30 - 39	5.0	4.2	5.7
40 - 49	8.7	9.6	12.5
50 - 59	11.6	17.3	25.7
60 - 74	17.5	30.1	38.0

Data source: [R11-2179]

In a 1999-2000 US study, an estimated 63% of hypertensive patients were reported to be aware of their hypertension, 45% were treated, and hypertension was controlled in 53% [R08-4698]. In 1991, in China, an estimated 35.6% of adults in urban areas, and 13.9% in rural areas, were aware of their hypertension, 17.1% and 5.4% were treated, and only 4.1% and 1.2% were controlled in urban and rural areas, respectively [R11-2179].

Individuals with hypertension are at an elevated risk of developing adverse, acute events, and chronic health conditions. In contrast to acute health risks, chronic health risks become comorbidities. Comorbidities can be diagnosed before, at the time of, or after the first diagnosis of hypertension. Cardiovascular risk is affected by the presence or absence of other risk factors [R05-2299], e.g. DM, smoking status, and race. The likelihood of developing vascular complications varies with blood pressure. Hypertension is, quantitatively, the biggest risk factor for premature CVD, being more common than the other major risk factors: cigarette smoking, dyslipidaemia, and DM [R11-2154]. The onset of an increase in risk of CVD begins as the blood pressure rises above 110/75 mmHg across all age groups [R04-4255, R11-2128 R11-2127].

SI.1.4 The main existing treatment options

Life-style interventions should be used when indicated and appropriate in the treatment of hypertensive patients. Life-style interventions include: weight loss in overweight patients, exercising, low salt intake, increase in fruit and vegetable dietary intake along with reduction in saturated and total fat intake, smoking cessation and alcohol abstinence [P10-08649, R13-2649]

According to the ESH and the ESC guidelines (2013), it is recommended that antihypertensive therapy is initiated with a thiazide diuretic, an angiotensin converting enzyme inhibitor (ACEI), a calcium channel blocker, an AII ARB or a beta-blocker. A combination therapy should be embarked upon, according to well-defined criteria, if a full dose of the initial monotherapy has been ineffective in hypertensive patients [P13-06683].

In older patients (>55 years of age), or patients of Black ethnic origin of any age, blood-pressure lowering is most effective with thiazide-type diuretics or calcium-channel blockers. In young patients with active RAAS, inhibitors of the RAAS (e.g. ACEIs and ARBs) have proved to be highly effective for lowering of blood-pressure. High-risk hypertensive patients should ideally take a combination of 2 antihypertensive drugs to control their blood pressure, in addition to an HMG CoA reductase inhibitor (a 'statin') and low-dose aspirin [R13-2649].

SI.1.5 Natural history of the indicated condition in the hypertension population, including mortality and morbidity

Many cardiovascular death may be related to hypertension, as there is a strong association between hypertension and the emergence of CVD. In the US in 2007, the overall death rate from hypertension, based on death certificates mentioning hypertension as the underlying cause of death, was 17.8 per 100 000. The age-standardised rate of specifically hypertension-related deaths among individuals ≥25 years differed by race. In the US in 2007, the mortality rates per 100 000 for non-Hispanic Whites were: 15.7 for White males, 49.2 for Black males, 14.3 for White females, and 37.0 for Black females [P11-05366].

Any-mention mortality from hypertension or the extent of mortality due to hypertension, regardless of whether it was the underlying cause or a contributing cause, was observed to be 108.5 per 100 000. Death rates were: 108.6 for White males, 228.8 for Black males, 90.7 for White females, and 174.8 for Black females [P11-05366].

SI.1.6 Important co-morbidities

Important comorbidities among patients with hypertension are CHF, CHD, CKD and ESRD, DM, and PAD.

SI.1.6.1 Myocardial infarction

Hypertension is associated with a 6 times higher risk for MI compared with normotensive patients, HR: 6.34 (95% CI 4.61 - 8.72) in men and 6.01 (95% CI 4.37 - 8.28) in women [R11-2129].

In the US, between 1973 and 1990, the mortality from MI among hypertensive patients after 16 years of follow-up was 2.17 per 1000 per year [R11-2135].

SI.1.6.2 Ischaemic stroke

Hypertension is the most common and most important risk factor for stroke, the incidence of which can be markedly reduced by effective antihypertensive therapy [P97-7764]. There is a dose-response relationship between blood pressure lowering and stroke. At mean age at baseline of approximately 63 years, a 10 mmHg reduction in SBP was associated with a risk reduction in stroke of 31% [R08-0838].

There is significant evidence that both fatal and non-fatal strokes are prevented within just a few years of effective blood pressure lowering. It has been estimated that a long-term 5 to 6 mmHg reduction in DBP is associated with about 35% to 40% less stroke in prospective observational studies and of 42% (95% CI 33 - 50%) in randomised clinical trials [P02-05531].

SI.1.6.3 Congestive heart failure

Hypertension is associated with a 2 to 3 times higher risk of developing CHF than in normotensive patients, HR: 2.07 (95% CI 1.34 - 3.20) in men and 3.35 (1.67 - 6.73, 95% CI) in women. Hypertension has a high population-attributable risk of CHF, accounting for 39% of cases in men and 59% in women. Among hypertensive subjects, MI, DM, LVH, and valvular heart disease were predictive of increased risk for CHF in both sexes. Hypertension increases the risk of heart failure at all ages, with the hazard increasing with the degree of blood pressure elevation [R11-2129].

SI.1.6.4 Left ventricular hypertrophy

LVH is a common problem in patients with hypertension [R11-2157], and is associated with an enhanced incidence of heart failure, ventricular arrhythmias, death following MI, and sudden cardiac death [R11-2131].

SI.1.6.5 Coronary heart disease

Coronary heart disease comprises acute MI and other ischaemic heart disease. The risk of CHD in hypertensive patients is 2 to 7 times greater compared to that in normotensive patients in MRFIT. It has been estimated that a 5 to 6 mmHg reduction in DBP lowers the risk of CHD by 14% (95% CI 4 - 22%) [P02-05531].

In the US between 1973 and 1990, the mortality from CHD in 12 866 high-risk men aged between 35 and 57 years of age with prevalent hypertension after 16 years of follow-up was 4.1 per 1000 per year [R11-2135].

SI.1.6.6 Chronic kidney disease and end-stage renal disease

Hypertension is a risk factor for CKD and ESRD [R11-2158, R05-0336]. Even relatively modest elevations in blood pressure are an independent risk factor for increasing the risk of ESRD (see SI.Table 13 and SI.Table 14).

SI.Table 13 Age-adjusted rates of ESRD by category of blood pressure, US 1964-1985

Blood pressure category	No. of persons	No. of ESRD events	Age-adjusted rate per 100 000 person-years (95% CI)
Optimal	89 774	106	4.5 (3.6 - 5.8)
Normal, not optimal	72 192	182	9.3 (7.5 - 11.5)
High normal	56 078	192	12.9 (10.3 - 16.0)
Hypertension			
Stage 1	69 083	379	19.5 (15.8 - 24.1)
Stage 2	21 340	199	31.7 (24.6 - 41.0)
Stage 3	6626	70	34.5 (24.7 - 48.0)
Stage 4	1582	21	43.7 (26.9 - 71.1)
Total	316 675	1149	

Adjusted for phase of multiphasic study, age, sex, race, education level, smoking status, diabetes mellitus, history of myocardial infarction, serum cholesterol level, height, weight, and serum creatinine.
Data source: [R05-0336]

In a 1996 US journal article, during an average of 16 years of follow-up, 814 of 332 544 subjects with hypertension at baseline either died of ESRD or were treated for that condition (15.6 cases per 100 000 person-years of observation). The adjusted relative risk increased from 1.0 in those with optimal blood pressure (<120/<80 mmHg) to 1.9 with high normal blood pressure, 3.1 with mild hypertension, 6.0 with moderate hypertension, and 11.2 with severe hypertension. Patients with stage 1 hypertension or lower blood pressure were at very low risk of ESRD at the 16-year follow-up point (≤0.34%) [R11-2176].

SI.Table 14 Baseline blood pressure category and cumulative incidence of ESRD due to any aetiology in 332 544 men screened for MRFIT (US, 1973-1990)

Blood pressure category	Men (n)	No. with ESRD	Age-adjusted rate per 100 000 person-years	Adjusted relative risk (95% CI)
Optimal	61 089	51	5.3	1.0
Normal but not optimal	81 621	86	6.6	1.2
High normal	73 798	134	11.1	1.9
Hypertension				
Stage 1 (mild)	85 684	275	21.0	3.1 (2.3 - 4.3)
Stage 2 (moderate)	23 459	158	43.6	6.0 (4.3 - 8.4)
Stage 3 (severe)	5464	73	96.1	11.2 (7.7 - 16.2)
Stage 4 (very severe)	1429	37	187.1	22.1 (14.2 - 34.3)
Total	332 544	814	15.6	-

Blood pressure categories: optimal: systolic blood pressure <120 and diastolic blood pressure <80 mmHg; normal, not optimal: systolic 120 to 129 mmHg and diastolic <84 mmHg or diastolic 80 to 84 mmHg and systolic <130 mmHg; high normal: systolic 130 to 139 mmHg and diastolic <90 mmHg or diastolic 85 to 89 mmHg and systolic <140 mmHg; stage 1 hypertension: systolic 140 to 159 mmHg and diastolic <100 mmHg or diastolic 90 to 99 mmHg and systolic <160 mmHg; stage 2 hypertension: systolic 160 to 179 mmHg and diastolic <110 mmHg or diastolic 100 to 109 mmHg and systolic <180 mmHg; stage 3 hypertension: systolic 180 to 209 mmHg and diastolic <120 mmHg or diastolic 110 to 119 mmHg and systolic <210 mmHg; and stage 4 hypertension: systolic ≥210 mmHg or diastolic ≥120 mmHg
Data source: [R11-2176]

In the US in 2001, approximately 1.9% of hospitalisations included a discharge diagnosis of ARF [R07-2817]. A discharge diagnosis of ARF was more commonly assigned to individuals with a co-existing diagnosis of CHF, chronic lung disease, CKD, cancer, and HIV infection, but less commonly to individuals with a co-existing diagnosis of CHD, DM, and hypertension. ARF had a higher mortality rate compared with those without ARF (21.3% versus 2.3%).

SI.Table 15 illustrates the ESRD incidence and prevalence estimates for the age groups of 50 years and over from the US Renal data system (study period US 2003-2005) [R08-4685]. Rates increased with age, were higher for men than for women, and were highest in African Americans, intermediate in Asians, and lowest in the White population.

SI.Table 15 Incidence and prevalence of ESRD in the US for the period 2003-2005 per 100 000 by age and population subgroups

ESRD per 100 000; US Age [years]	Men			Women		
	White	African America	Asian	White	African American	Asian
Incidence						
50 - 59	44.0	210.4	58.5	30.5	145.3	36.6
60 - 64	78.5	304.5	106.0	56.8	256.0	69.2
65 - 69	112.2	361.8	143.0	77.2	320.6	100.8
70 - 79	166.7	415.6	205.4	101.2	358.6	152.4
80+	196.8	366.6	248.5	81.7	280.2	175.4
Prevalence						
50 - 59	232.9	1166.3	329.9	157.7	728.2	240.8
60 - 64	326.2	1591.1	545.6	230.5	1184.9	376.8
65 - 69	393.2	1696.1	645.6	282.0	1462.4	476.9
70 - 79	463.2	1675.4	789.3	294.7	1466.0	599.3
80+	455. 1	1159.1	82 3.1	192.1	901.0	569.2

Data source: [R08-4685]

In 2005, the overall mortality of ESRD was 16.2% in men and 17.4% in women, and increased with age from 11.4% in the 50 to 59 year age group to 16.1% in the 60 to 64 year age group, 20.9% in the 65 to 69 year age group, 30.2% in the 70 to 79 year age group and 46.3% in the 80+ year age group.

As established in other settings, there is a high prevalence of hypertension, CHF, CVD, and DM in ESRD, in part due to the central role of hypertension and DM in the pathogenesis of these conditions.

SI.1.6.7 Diabetes mellitus

A 1970 US study reported the prevalence of DM among patients with hypertension as being 7.1% in men and 8.0% in women. The prevalence of DM in patients with hypertensive CHF, prior to their developing CHF, was 24% in men and 28% in women [R11-2129].

SI.1.6.8 Peripheral artery disease

In the US, between the years of 1987 and 2001, the age-standardised incidence of PAD based on ABPI of <0.9 for men and <0.85 for women was 6.9 per 1000 person-years (6.8 in men and 6.9 in women). The age-adjusted incidence of PAD (ages 45 to 74) was similar in men

and women, and in Blacks and Whites [R09-0397]. In the US between 1989 and 2000, the age-adjusted incidence of PAD was higher in men overall and in both Black and White populations: 5.1 in White men, 7.8 in Black men, 3.0 in White women and 5.6 in Black women.

SI.2 EPIDEMIOLOGY OF CORONARY HEART DISEASE

SI.2.1 Incidence

Coronary heart disease comprises recognised and clinically unrecognised MI, angina pectoris, unstable angina, and sudden and non-sudden coronary deaths. In the US, each year approximately 785 000 Americans will have a new MI, and approximately 470 000 will have a recurrent MI. It is estimated that an additional 195 000 ‘silent’ or occult MIs occur each year. The estimated annual incidence of MI is 610 000 new MIs and 325 000 recurrent MIs. The average age at first MI is 64.5 years for men and 70.3 years for women [R09-0397].

In the general population, aged between 35 and 64 years, the WHO MONICA project estimated age-standardised incidences rates of non-fatal MIs and of coronary deaths within 28 days across 21 countries. The age-standardised incidences for men ranged from 2.1 per 1000 in Spain to 8.35 per 1000 in Finland, with a mean event rate of MI of 4.34 per 1000; the death rate was 211 per 100 000, so that the mean case fatality in men was 49% (across 21 countries between 1980 and 1995). The mean coronary event rate in women aged between 35 and 64 years was 1.03 per 1000 with a death rate of 0.54 per 1000 and a mean case fatality of 54% (across 21 countries, 1980 to 1995) [R05-1391].

In the US between 1987 and 1996, the MI rate in the same age range (35 to 64 years) approximated the mean MONICA rates with a declining trend in CHD mortality over time [R08-4742]. The incidence rates of acute MI observed in the UK 4th MSGP4 survey, between 1991 and 1992, cover an older age range and showed that rates rapidly increase with age, showing up to 15.3 per 1000 in men and to 9.4 per 1000 in women of between75 and 84 years of age [R08-4723]. SI.Table 16 shows the incidence estimates for angina pectoris and MI in that study per 100 000 of the population.

SI.Table 16 Incidence of angina pectoris and MI per 1000 men and women (UK, 1991-1992)

	Angina pectoris	MI
Age [years]	**[per 1000 person-years]**	
Men		
45 - 64	10.8	5.3
65 - 74	22.5	12.6
75 - 84	27.3	15.3
≥85	20.2	14.3
Women		
45 - 64	6.6	1.5
65 - 74	17.6	5.8
75 - 84	22.4	9.4
≥85	21.7	10.4

Data source: [R08-4723]

In the US between 1987 and 2001, the age-adjusted incidence of CHD (ages 45 to 84) has been observed to be higher in White men than in White women. The average age-adjusted incidence rates for CHD per 1000 person-years (95% CIs) were as follows: Black women 5.1 (4.2 - 6.2); White women 4.0 (3.5 - 4.6); Black men 10.6 (8.9 - 12.7); and White men 12.5 (11.5 - 13.7).

Incidence rates (95% CIs), using a definition for CHD that excluded revascularisation procedures, were as follows: Black women 4.9 (4.6 - 6.0); White women 2.9 (2.5 - 3.4); Black men 9.2 (7.6 - 11.1); and White men 7.9 (7.0 - 8.8) [R11-2180]. The incidence of CHD increased with age across all races and was seen to be greatest in Black men (see SI.Table 17).

SI.Table 17 Incidence of CHD per 1000 person-years by age, race, and sex, US, 1987-2001

Age	**White men**	**Black men**	**White women**	**Black women**
[years]	**[per 1000 person-years]**			
35 - 44	1.1	1.5	0.3	0.8
45 - 54	3.4	4.2	1.1	2.2
55 - 64	7.2	8.1	2.8	5.8
65 - 74	11.9	14.0	6.4	9.3

Data source: [R09-0397]

Temporal trends

The incidence of CHD has decreased over time in developed countries. In the US, the age-standardised incidence of CHD decreased from 13.3 to 11.4 cases per 1000 persons per year of follow-up from 1971 to 1982 (10 869 patients) and from 1982 to 1992 (9774 patients) [R11-2178]. This decline was significant only among white men and women.

Regarding prevalence, the 2010 AHA Heart Disease and Stroke Statistics update reported that 17.6 million individuals in the US have CHD, including 8.5 million with a diagnosis of MI and 10.2 million with angina pectoris. The reported prevalence of CHD increases with age for both genders. On the basis of data from the US NHANES, between 2003 and 2006, an estimated 17.6 million Americans ≥20 years of age have CHD. The total CHD prevalence is 7.9% in US adults ≥20 years of age.

Stroke

In the US, each year approximately 795 000 people experience a new or recurrent stroke. Approximately 610 000 of these are first attacks, and 185 000 are recurrent attacks. Of all strokes, 87% are ischaemic, 10% are intracerebral haemorrhage, and 3% are subarachnoid haemorrhage [R09-0397]. The age-standardised incidence of stroke in the WHO MONICA project was 1.01 per 1000 to 2.85 per 1000 for men, and 0.47 to 1.98 per 1000 in women.

The incidence of stroke from between the ages of 55 and 64 to between 75 and 84, increases with advancing age across both genders (see SI.Table 18). In the US, the age-adjusted incidence rate (per 1000 person-years) of all strokes was higher among men (4.84 vs. 3.69) [R09-0397].

SI.Table 18 Incidence of stroke per 1000 person-years by age and sex, US, 2003

Age [years]	Men	Women	Total
	[per 1000 person-years]		
55 - 64	4.3	2.2	3.23
65 - 74	11.1	7.0	8.49
75 - 84	19.6	17.1	18.01
85 - 94	16.2	27.1	24.2
Age-adjusted	4.84	3.69	4.48

Data source: [R09-0397]

An estimated 6.4 million Americans ≥20 years of age have had a stroke (extrapolated to 2006 using NCHS/NHANES 2003 to 2006 data). Overall, stroke prevalence estimates in the US have varied mainly due to the changing definition of stroke, the prevalence of risk factors and the age groups studied. The age-adjusted prevalence of stroke in 2000 was an estimated 0.85% in the 33 to 45 age group, 4.14% in 1998-2002 for the ≥35 age group, 1.69 between 1987-1989 in the 45 to 64 age group, and 8.82 in 1999 in the ≥70 age group.

Peripheral artery disease

Peripheral artery disease affects 12 to 20% of Americans ≥65 years of age. Overall, it affects approximately 8 million Americans and is associated with significant morbidity and mortality [R11-2177]. In the US between 1987 and 1989, the age-adjusted prevalence of PAD (ages 45 to 64) was 2.6%, higher in Black men than in White men (4.4% vs. 2.4%), and higher in Black women than in White women (3.0% vs. 2.1%) [R09-0397].

The age-adjusted incidence of PAD (age 65) is higher, overall, in men: 5.1 in White men, 7.8 in Black men, 3.0 in White women and 5.6 in Black women. The age-adjusted prevalence is 2.6%, and the incidence of PAD (ages 45 to 74) is similar in men and women, and in Blacks and Whites [R09-0397].

Diabetes mellitus

A total of 1.6 million new cases of DM were diagnosed in people ≥20 years of age in 2006. DM incidence in adults varies markedly by race. Over 5 years of follow-up in 45- to-84-year-olds in the MESA, 8.2% of the cohort developed DM. The cumulative incidence was highest in Hispanics (11.3%), followed by Black (9.5%), Chinese (7.7%), and White (6.3%) participants [R11-2177].

Data from the Framingham study indicates a doubling in the incidence of DM over 30years, most dramatically so during the 1990s. Among adults of between 40 and 55 years of age in each decade of the 1970s, 1980s, and 1990s, the age-adjusted 8-year incidence rates of DM were 2.0%, 3.0%, and 3.7% among women and 2.7%, 3.6%, and 5.8% among men, respectively. Most of the increase in absolute incidence of DM occurred in individuals with a BMI ≥30. The incidence of DM increases with age up to 13.9 per 1000 in men and 12.0 per 1000 in women aged between 65 and 79 years (see SI.Table 19).

SI.Table 19 Incidence of diagnosed DM per 1000 population aged 18-79 years in the US by age and sex (USA 2007)

	Men	Women
Age [years]	**[per 1000 population]**	
18 - 44	4.1	4.2
45 - 64	12.9	10.7
65 - 79	13.9	12.0

Data source: [R11-2155]

SI.2.2 Prevalence

The population prevalence of DM (per 100) varies by ethnicity, gender and age. In 2007, approximately 5.9% of the US population reported that they had DM. The crude and age-adjusted percentages of the population with diagnosed DM were similar from 1980 through to 2007, indicating that most of the increase was not due to changes in the population age

structure. From 1980 through to 2007, the crude percentage of the population with diagnosed DM increased by 136% [R11-2544].

In general, regardless of race/ethnicity and gender, the percentage of population with diagnosed DM tended to be highest among persons aged 65 years or older and lowest among persons younger than 45 years of age. Black females tended to have the highest age–specific percentages. The prevalence varies by race/ethnicity, gender and age. The prevalence is, therefore, presented in the RMP stratified for age, race and gender in the US, and is shown in SI.Table 20.

SI.Table 20 Age-specific prevalence of DM in the US by ethnicity and gender, 2009, (%)

Race	Gender	Age [years]			
		0 - 44	45 - 64	65 - 74	≥75
White	Male	1.7	12.2	19.5	19.8
	Female	1.5	10.8	17.0	14.9
Black	Male	1.8	16.5	32.6	25.3
	Female	2.1	18.7	32.4	27.7
Asian/Pacific Islander	Male	1.6	10.6	26.0	20.9
	Female	1.6	8.8	18.6	20.3

Data source: [R11-2156]

Metabolic syndrome

A study incorporating 11 prospective European cohort studies (6156 men and 5356 women without DM aged between 30 and 89 years) between 1971 and 2001, used a modification of the WHO definition of metabolic syndrome (MetS) and found an overall prevalence in non-diabetic adult Europeans of 15%. Non-diabetic individuals with metabolic syndrome have an increased risk of death from all causes, in addition to an increased risk of CVD (432 of 1119 deaths were due to CVD) [R08-4742].

SI.Table 21 Prevalence of metabolic syndrome and its components (WHO criteria) (Europe multinational study 1971-2001)

	Obe-sity	Hyper-tension	Dys-lipi-daemia	IGR	Any 2 or more	Any 3 or more	HI plus 2 or more	HI plus 3 or more
Men					[%]			
40 - 49	13.4	33.6	38.8	15.5	27.1	9.5	12.8	6.3
50 - 59	15.8	49.1	42.0	22.6	39.3	14.3	16.1	7.6
60 - 69	13.4	56.2	36.8	26.3	39.8	13.8	18.0	8.3
≥70	10.1	64.0	34.0	26.2	38.0	13.0	17.9	9.8
Total	14.0	48.5	39.1	22.2	36.3	12.9	15.9	7.7
Women					[%]			
40 - 49	14.3	22.7	15.2	10.9	15.9	5.2	7.9	3.1
50 - 59	18.8	43.5	25.4	13.9	27.6	9.4	12.5	5.8
60 - 69	22.0	59.6	34.1	22.7	41.8	16.5	20.9	10.0
≥70	21.8	69.2	29.3	28.2	46.8	16.8	21.1	9.3
Total	18.9	45.2	25.7	17.0	30.4	11.0	14.5	6.6

Data source: [R08-4742]

The US NHANES follow-up of 6255 individuals in the US between1976 and 1992 also showed a high prevalence of MetS (see SI.Table 22; National Cholesterol Education Program [NECP] criteria), and an association of metabolic syndrome with mortality (see SI.Table 22) [R08-4749].

SI.Table 22 Prevalence of metabolic syndrome and its components (NECP criteria) in the US (1976-1992). (6255 individuals, age: 30 to 75 years), NHANES II follow-up

Disease (%)	%	IGT (>6.1)	Low HDL-C (NECP)	High Tri-glycerides (NECP)	Hyper-tension (>130/85)	Obesity (BMI≥30)
All groups	100	9.0	46.9	21.8	54.8	20.1
No MetS, DM, or CVD	54.1	4.6	25.4	9.6	31.5	3.5
MetS (all)	26.0	18.5	85.0	48.2	90.5	56.2
MetS (no DM)	19.2	21.0	92.6	52.6	94.9	63.9
DM	6.7	100.0	63.4	35.9	78.0	34.2
CVD (all)	19.7	8.6	59.3	23.3	77.1	20.7
Pre-existing CVD	16.7	8.6	57.3	20.4	74.8	17.8
DM and CVD	3.0	100.0	70.9	40.1	90.0	37.4

Data source: [R08-4749]

Metabolic syndrome is associated with a 1.5- to 2-fold increase in the risk of CVD (meta-analysis 1966-2005) [R08-4750], (US 1987-1999), and also extends to people with MetS who do not have DM (Finland, Sweden, Netherlands, UK, and Italy, pooled analysis 1971-1994), (review article), as well as those without baseline CVD (Finland 1984-1998) [R08-4751, R08-4742, R08-4752, R08-4753].

In a Finnish study, between 1986 and 1999, an association of MetS with death due to CVD (WHO definition, HR adjusted for age and gender: 1.56; 95% CI 1.22 - 2.00) was also observed [R08-4745]. Subclinical target organ damage, most of which is recognised as significant independent predictors of adverse cardiovascular and renal outcomes, can explain the association of MetS with a higher cardiovascular and renal risk (review article) [R08-4744].

SI.2.3 Demographics of the population in the CV prevention indication and risk factors for the disease

There is a strong association between hypertension and the emergence of CVD. The demographic profile of this target population is, therefore, comparable to that of patients with hypertension. The 2006 US CDC publication of the Health Survey in the US highlighted the following prevalence rates for CHD, hypertension, stroke, and for the combination of all 3 factors (see SI.Table 23) [R08-4699].

SI.Table 23 Age-adjusted prevalence (%) of CHD, hypertension, and stroke (US 2006)

US Health Survey 2006	CHD	Hypertension	Stroke	All three
Sex		**[%]**		
Male	8.0	21.5	2.4	12.5
Female	5.2	22.5	2.5	11.1
Age groups [years]				
18 - 44	1.0	7.3	0.4	4.3
45 - 64	7.4	31.2	2.2	13.6
65 - 74	19.0	49.6	6.2	26.8
≥75	25.4	54.8	12.5	36.6

Data source: [R08-4699]

The rates for cardiovascular and cerebrovascular events for older age groups, corresponding to the target population from the UK MSGP4 between 1991 and 1992, are shown in SI.Table 24 [R08-4723]. These appear lower than those figures found in the US.

SI.Table 24 Consulting rate per 100 person-years for ischaemic heart disease, angina pectoris, MI, and cerebrovascular disease in the UK in 1992 (UK 1991-1992)

	Number of patients who consulted at least once during the year for a defined condition per 100 person-years at risk			
Age [years]	**IHD**	**AP**	**MI**	**Cerebrovascular disease**
Men				
45 - 64	4.0	2.6	0.7	0.7
65 - 74	9.2	5.8	1.6	2.7
75 - 84	9.2	5.9	1.9	5.5
≥85	8.8	5.1	1.7	7.5
Women				
45 - 64	1.8	1.3	0.2	0.5
65 - 74	5.0	3.6	0.7	1.8
75 - 84	6.8	4.7	1.2	4.2
≥85	6.0	3.6	1.1	7.2

Data source: [R08-4723]

Potential health risks of patients with manifest atherothrombotic CVD include: acute MI and ischaemic stroke (see potential health risks in Section. SI.1.4).

Diabetes mellitus

Patients with DM are at high risk of CHF, particularly in the presence of comorbid hypertension, coronary artery disease, smoking, and left ventricular hypertrophy [P07-03010].

Type 2 DM is one component of MetS. The term "metabolic syndrome" refers to a cluster of metabolic derangements that cause affected subjects to have an increased risk of developing DM and CVDs associated with insulin resistance. All national and international institutions agree on the core components of the syndrome (obesity, abdominal or visceral), glucose intolerance, insulin resistance, characteristic dyslipidaemia (low high-density lipoprotein cholesterol and high triglycerides) and hypertension, but not necessarily on the clinical criteria [R08-4741, R08-4744].

The current definitions of MetS are provided by criteria according to the WHO, EGIR, the NCEP, the American College of Endocrinology, the IDF, and the AHA (updated NCEP).

SI.Table 25 Death rates per 1000 person-years by presence of metabolic syndrome and its components (NECP criteria) in the US (1976-1992)

Deaths/1000 person-years	CHD mortality	CVD mortality	Total mortality
Neither MetS nor DM	2.6	5.3	14.4
MetS without DM	4.3	7.8	17.1
MetS with DM	4.8	8.6	21.1
DM only	6.3	11.5	26.1
Prior CVD	10.9	16.7	30.9
Prior CVD and DM	17.0	28.1	44.1

Data source: [R08-4749]

Despite its high prevalence, MetS is rarely listed as a discharge diagnosis (ICD9 277.7), with only 16 mentions as the 3rd to 7th listed diagnosis found in 319 530 records of the 2003 US NHDS datasets (US 1999-2002) [R08-4746]. This severely restricts the use of such datasets for MetS research.

More than 85% of those with MetS, even in the absence of DM, have hypertension, which is the leading MetS risk factor that predisposes to increased cardiovascular morbidity and mortality, and is, furthermore, an important risk factor for development of CKD in the presence of obesity, metabolic syndrome, and microalbuminuria [P07-12565].

SI.2.4 The main treatment options

Cardiovascular disease

The prevalence of medication use, particularly of cardiovascular medications, among other factors depends on the sevaerity of the underlying disease and on the prevalence of comorbid

conditions. The main drug groups used in the high-risk multi-national 2003 to 2006 REACH population are shown in SI.Table 26 (Multinational 2003-2006) [R08-4695].

SI.Table 26 Prevalence of medication use (%) in a population at high risk of CVD (Multinational 2003-2006) (REACH registry)

Prevalence of medication use	Total	North America	Western Europe	Eastern Europe	Asia	Australia	Japan
Patients included	64 977	25 999	17 142	5622	5671	2847	5021
Mean age, SD	69 (10)	70 (10)	69 (10)	63 (9)	65 (10)	73 (9)	70 (9)
Medication use				[%]			
≥1 antiplatelet agent	78.7	77.1	78.0	86.4	81.6	74.8	73.9
Aspirin	67.3	71.4	62.1	75.1	63.6	64.5	54.5
Other antiplatelet agent	24.6	20.0	27.3	26.1	30.8	19.8	31.7
Aspirin + other antiplatelet agent	13.2	14.2	11.1	14.8	12.8	9.5	12.3
Oral anticoagulants	12.3	14.2	12.3	11.5	6.5	12.5	12.5
NSAIDs	11.5	18.2	7.6	4.5	4.1	23.4	2.9
≥1 lipid-lowering agent	75.1	83.8	75.4	62.3	67.1	80.3	50.8
Statins	69.3	77.1	70.0	57.6	60.9	78.9	44.1
Other lipid-lowering agents	12.0	18.0	7.9	7.0	9.4	2.5	9.9
≥1 cardiovascular agent	91.3	93.8	90.8	95.1	89.8	88.3	79.6
Calcium channel blockers	34.0	32.8	30.4	27.2	40.0	30.5	56.0
Beta-blockers	47.5	50.6	50.6	63.2	40.5	37.3	18.6
Nitrates	24.5	19.1	23.7	42.4	28.2	31.5	27.5
Diuretics	40.3	48.1	42.4	47.2	23.5	28.4	12.7
ACE inhibitors	45.2	47.1	45.9	72.8	32.4	42.1	18.1
Angiotensin II receptor blocker	22.8	25.4	21.1	3.8	27.8	22.8	32.0
Other antihypertensives	9.4	11.4	8.9	8.1	8.4	8.4	4.8
PAD claudication medications	6.5	4.8	8.8	13.9	5.1	0.2	5.3
≥1 antidiabetic agent	39.7	46.2	35.4	23.5	44.9	26.8	37.9
Insulin	11.8	14.2	12.2	6.6	7.9	6.7	11.3
Biguanides	18.5	22.2	16.5	9.1	25.5	17.5	6.2
Sulfonylureas	19.7	22.9	14.9	11.0	28.6	12.6	21.3
Thiazolidine-dione	7.7	15.8	2.0	0.5	5.4	0.7	3.1
Other	5.0	4.0	4.8	3.2	7.1	0.6	13.5

Data source: [R08-4695]

The proportions of concomitant drugs used by patients included in clinical trials are roughly similar to the REACH registry.

SI.Table 27 Drug uses (%) in a clinical trial population at high risk of CVD (Multinational study 1993-1999)

Patients (n = 9297)	
Medications	**%**
Beta-blockers	39.5
Aspirin or other antiplatelet agents	76.1
Lipid-lowering agents	28.6
Diuretics	15.3
Calcium-channel blockers	47.1

Data source: [R00-0562]

SI.2.5 Natural history of the indicated condition in the CV prevention population, including mortality and morbidity

Coronary heart disease

In 2007 in the US, CHD caused approximately 1 of every 6 deaths. At that time, CHD mortality was 406 351 and MI mortality was 132 968 [R11-2136].

CHD is the largest major health-related killer of Americans. A study of 1275 HMO enrolees between 50 and 79 years of age who had cardiac arrest showed that the incidence of out-of-hospital cardiac arrest was 5.98/1000 person-years in subjects with any clinically recognised heart disease, compared with 0.82/1000 person-years in subjects without heart disease. In subgroups with heart disease, the incidence of out-of-hospital cardiac arrest was 13.69/1000 person-years in subjects with prior MI anvd 21.9/1000 person-years in subjects with heart failure [R11-2181].

Coronary heart disease is the leading cause of death in adults in the US, accounting for about one-third of all deaths in subjects aged over 35. The 2010 AHA Heart Disease and Stroke Statistics update reported that the overall death rate from CVD in 2006 was 262.5 per 100 000.

The CHD death rate is higher in men than in women (3 times higher between the ages of 25 and 34, falling to 1.6 times higher between the ages of 75 and 84), and in Blacks as compared to Whites, an excess that disappears by the age of 75 years. Among the Hispanic population, coronary mortality is not as high as it is among Blacks and Whites.

Any cardiovascular death may be related to hypertension, as there is a strong association between hypertension and the emergence of CVD. The death rates for the population of individuals aged 65 years and older, which has a closer correspondence to the target

population, are shown in SI.Table 28. There are large increases in mortality for all conditions in the older age groups relative to the total population.

In the US, the crude death rate of CHF has been reported to be 559.1 per 100 000 for persons aged ≥85 years, 5-fold higher than the rate for persons aged between 75 and 84 years (124.7) and 18-fold higher than that for persons aged between 65 and 74 years (31.6).

In the high-risk population observed in the REACH registry (Multinational 2003-2006) [R08-4695], the annual all-cause mortality ranges from 2.5% (i.e. 2450 per 100 000) for those with single- to 5.4% (5370 per 100 000) for those with a combination of CHD/CVD and PAD; the range for cardiovascular death is 1.6% and 3.9 %, respectively (see SI.Table 28).

SI.Table 28 Mortality in patients with high atherothrombotic risk per 100 person-years (Multinational 2003 - 2006)

Outcome by disease type	**Overall single disease**	**CHD**	**CVD**	**PAD**	**CHD+ CVD**	**CHD+ PAD**	**CVD + PAD**	**CHD+ CVD + PAD**	**Overall poly-vascular disease**
Patients	42 716	28 867	10 603	3246	5339	3264	939	1132	10 674
Events per 100 PY									
All-cause morality	2.5	2.4	2.6	2.4	3.6	4.6	3.6	5.4	4.1
CV death	1.6	1.6	1.6	1.4	2.4	3.2	2.2	3.9	2.8
Non-fatal MI	1.1	1.4	0.5	1.0	1.7	1.5	1.1	1.8	1.6
Non-fatal stroke	1.5	0.9	3.6	0.8	3.5	1.2	4.9	4.4	3.1
CV death, MI, or stroke	4.1	3.6	5.5	3.1	7.4	5.5	7.8	9.2	7.1
All above + hospital	12.6	13.0	9.9	17.4	19.8	23.1	22.0	26.3	21.7

Data source: [R08-4695]

The rates of cardiovascular death by country in this aforementioned study range from 0.7% in Japan to 2.9% in Eastern Europe [R08-4695]. The corresponding estimated annual cardiovascular death rate from clinical trials is approximately 1.4% (Multinational 1993-1999) [R00-0562].

Stroke

Stroke accounted for approximately 1 of every 18 deaths in the US in 2006. Approximately 53% of stroke deaths in 2005 occurred out of the hospital setting [R11-2137]. When

considered separately from other vascular diseases, stroke ranks third among all causes of death, behind diseases of the heart and cancer (NCHS mortality data). Among persons between 45 and 64 years of age, 8% to 12% of ischaemic strokes and between 37% and 38% of haemorrhagic strokes result in death within 30 days, according to the Atherosclerosis Risk in Communities (ARIC) study of the National Heart, Lung, and Blood Institute (NHLBI) [R11-2174].

In a study of the population aged 65 years and over recruited from a random sample of Health Care Financing Administration Medicare Part B eligibility lists in 4 US communities, the 1-month case fatality rate was 12.6% for all strokes, 8.1% for ischaemic strokes, and 44.6% for haemorrhagic strokes [R11-2173].

More women than men die of stroke each year due to the larger number of elderly women. The women accounted for 60.6% of US stroke deaths in 2006.

From 1996 to 2007 in the US, the annual stroke death rate decreased by 33.5%, and the actual number of stroke deaths declined by 18.4%. In 2007, overall death rate for stroke was 42.2 per 100 000. Death rates were 40.2 for White males, 67.1 for Black males, 39.9 for White females, and 55.0 for Black females [R11-2183].

PAD

PAD tends not to be a direct cause of death. Pooled data from 11 studies across 6 countries found that PAD was a marker for systemic atherosclerotic disease. The age and sex-adjusted relative risk of all-cause death was 2.35; 3.34 for CVD mortality; and 2.13 for CHD fatal and nonfatal events combined. The study findings for stroke were slightly weaker, but still significant, with a pooled relative risk of 1.86 for fatal and non-fatal events combined [R11-2130].

Diabetes mellitus

Diabetes mellitus was the sixth leading cause of death listed on US death certificates in 2007 and is ranked as the 5th leading cause of death worldwide. It is a major risk factor for various cardiovascular and renal disorders. Mortality among diabetics is high, though the cause of death is often due to CVD. At least 65% of people with DM die of some form of heart disease or stroke. Heart disease death rates among adults with DM are 2 to 4 times higher than the rates for adults without DM.

DM mortality in the US in 2007 was 70,905, with ‘any-mention’ mortality being 231 000. The 2006 overall underlying-cause death rate due to DM was 23.3 per 100 000. Death rates per 100 000 persons were 25.4 for White males, 49.7 for Black males, 17.9 for White females, and 41.6 for Black females [R11-2177].

In a cohort of patients receiving at least one cardio-protective medication, the mortality rate was between 8 and 11 %. In national statistics generally, death due to DM is likely under-reported, as death record studies have found DM mentioned in only 30 to 45% of decedents with this condition. The mortality rates for DM for various countries are highlighted in SI.Table 29.

SI.Table 29 Age standardised death rates from DM in various countries in 2002

Diabetes mellitus	Germany	France	Italy	Japan	Canada	UK	US
				per 100 000			
Men	17.7	13.8	17.8	7.6	24.3	9.1	23.7
Women	15.2	9.6	15.0	4.4	15.9	6.3	18.7
Total	16.6	11.4	16.4	5.9	19.6	7.5	20.9

Data source: [R11-2134]

SI.2.6 Important co-morbidities

Important comorbidities are outlined in the HOPE study (see SI.Table 30), and in the REACH registry observational cohort of high-risk patients (see SI.Table 31).

The HOPE study was conducted across the US, Canada, Argentina, Brazil, Mexico, and 14 European countries between 1993 and 1995. It outlined the risk profile for this target population, its main features, and comorbidities (e.g. prevalence of previous MI, stroke, CHF and other risk-defining conditions and interventions).

The proportions of patients with a previous history of atherosclerotic disease from the REACH registry are shown in SI.Table 31. Although slightly lower in each category, the prevalence rates are comparable to those found at baseline in the HOPE trial. Regional variations may be due to true differences or due to differences in regional diagnostic and treatment capabilities [R00-0562].

SI.Table 30 Target population as specified in 3 clinical trials (Multinational study, 1993-1999) (HOPE 2000)

	HOPE
Patient characteristics	
Total patients in study	9297
Age (mean)	66
BMI (kg/m^2)	28
Patient characteristics (%)	
Female sex	26.7
History of CHD	80.4
MI	52.6
Stable angina pectoris	55.5
Unstable angina pectoris	25.5
CABG	25.8
PTCA	17.8
Stroke or transient ischemic attacks	10.9
PAD	43.6
Hypertension	46.8
DM	38.5
Documented elevated total cholesterol	65.9
Documented low HDL cholesterol	18.5
Current cigarette smoking	14.2
LVH	8.4
Microalbuminuria	21.0

Data source: [R00-0562]

SI.Table 31 Prevalence (%) of atherothrombotic conditions among patients in the REACH registry (Multinational 2003-2006)

Prevalence of conditions	Total	North America	Western Europe	Eastern Europe	Asia	Australia	Japan
Previous history				**[%]**			
Coronary artery disease	59.4	60.7	58.1	70.6	51.9	73.6	44.9
Stable angina	30.0	27.6	30.0	51.0	25.5	36.0	23.6
Unstable angina	12.7	11.3	12.1	21.5	13.8	11.7	8.4
MI	31.7	31.7	32.9	39.3	23.3	37.6	22.5
Percutaneous Intervention (PTCA)	25.2	27.8	25.0	15.9	22.6	24.9	24.9
Coronary bypass	20.4	26.9	18.0	10.8	10.4	30.1	11.3
Cardiovascular disease	27.7	21.0	26.4	38.8	42.7	23.4	39.1
Transient ischaemic attack	13.0	12.4	15.2	15.9	11.8	12.6	7.5
Stroke	20.3	14.0	17.0	30.2	37.5	14.9	35.2
Peripheral vascular disease	12.2	9.2	19.8	12.5	5.4	9.0	12.0
Claudication and ABPI <0.9	13.8	9.1	21.9	15.5	7.9	3.6	20.7
Peripheral angioplasty, etc.	6.5	5.4	10.8	4.0	1.9	6.9	7.4
Claudication, history of amputation	1.8	1.8	2.2	1.7	1.4	0.8	0.9
Any symptomatic atherothrombosis	81.9	75.0	84.1	95.0	87.0	89.3	83.5
3 risk factors only	18.1	25.0	16.0	5.0	13.0	10.7	16.6

Data source: [R08-4695]

LVSD is a precursor of symptomatic CHF, has an estimated prevalence of between 3% and 6%, and is at least as common in the community as systolic heart failure (Review 1975-2002) [P03-05124]. In Australia between 2002 and 2003, the prevalence of diastolic dysfunction was reported to be 34.7% and that of moderate to severe diastolic dysfunction was 7.3% [R08-4700].

The prevalence of CHF in the general population 55 years and older was observed to be approximately 6% in Denmark between 1993 and 1995 [R08-4692], 4% in the Netherlands between 1990 and 1993 [R08-4696], and 4% in Germany between 1994 and 1995

[R08-4701], increasing with advancing years, but without significant differences between the genders. In the US between 1997 and 2000, the prevalence of validated CHF was estimated at 2.7% in men and 1.7% in women, showing no statistically significant difference between the genders [R08-4694].

Other important comorbidities among patients with manifest atherothrombotic CVD are (1) CHF, (2) CKD and ESRD, and (3) DM. These comorbidities are described in Section SI.1.5.

SI.3 REFERENCES

SI.3.1 Published references

P97-7764 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhaeger WH, Bulpitt CJ, Leeuw PW de, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 350 (9080), 757 - 764 (1997)

P02-05531 Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 335 (12), 827 - 838 (1990)

P03-05124 Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of asymptomatic' left ventricular systolic dysfunction: implications for screening. Ann Intern Med 138 (11) , 907-916 (2003)

P07-03010 Held C, Gerstein HC, Yusuf S, Zhao F, Hilbrich L, Anderson C, Sleight P, Teo K, ONTARGET/TRANSCEND Investigators. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation published online Mar 5, 2007, DOI: 10.1161/CIRCULATIONAHA.106.661405 Circulation 115 (11) , 1371-1375 (2007)

P07-12565 Franklin SS. Hypertension in the metabolic syndrome. Metab Syndr Relat Disord 4 (4), 287-298 (2006).

P10-08649 Mancia G, Grassi GTitle: Management of essential hypertension. Source: Br Med Bull; 2010; 94(1); 189-199.DB Entry Date: 2010-07-23

P11-05366 Roger VL. Heart disease and stroke statistics - 2011update: a report from the American Heart Association. Circulation 123, e18 (2011)

P13-06683 Mancia G,et al. ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34, 2159 – 2219 (2013).

R00-0562 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342(3):145-153.

R03-1247 Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA 287 (8), 1003 - 1010 (2002)

R04-4255 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360, 1903 - 1913 (2002)

R05-0336 Hsu C, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 165, 923 - 928 (2005)

R05-1391 Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. Lancet 1999;353:1547-1557.

R05-2299 Jackson R, Lawes CMM, Bennett DA, Milne RJ, Rodgers A Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet 365, 434 - 441 (2005).

R07-2817 Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 2006;1:43-51.

R08-0838 Lawes CM, Bennett DA, Feigin VL, Rodgers A. Correction: blood pressure and stroke: an overview of published reviews. Stroke 35, 1024 - 1033 (2004)

R08-4685 U.S. Renal Data System (USRDS). USRDS 2007 annual data report: atlas of chronic kidney disease and end-stage renal disease in the united states. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2007.

R08-4692 Nielsen OW, Hilden J, Larsen CT, Hansen JF. Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. Heart (Lond) 2001;86:172-178.

R08-4694 Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289(2):194-202.

R08-4695 Steg PG, Bhatt DL, Wilson PWF, D'Agostino R, Ohman EM, Roether J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297(11):1197-1206

R08-4696 Mosterd A, Hoes AW, Bruyne MC de, Deckers JW, Linker DT, Hofmann A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population: the Rotterdam Study. Eur Heart J 1999. 20(6):447-455

R08-4697 Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodríguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289(18):2363-2369.

R08-4698 Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988 - 2000. JAMA 2003;290(2):199-206.

R08-4699 Pleis JR, Lethbridge-Cejku M. Summary health statistics for U.S. adults: National Health Interview Survey, 2005 (National Center for Health Statistics). Vital Health Stat (10) 2006(232).

R08-4700 Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. Heart (Lond) 2006;92:1259-1264.

R08-4701 Fischer M, Baessler A, Holmer SR, Muscholl M, Broeckel U, Luchner A, et al. Epidemiologie der linksventrikulaeren systolischen Dysfunktion in der Allgemeinbevoelkerung Deutschlands: Ergebnisse echokardiografischer Untersuchungen einer grossen Bevoelkerungsstichprobe. Z Kardiol 2003;92(4):294-302.

R08-4720 Dannenberg AL, Garrison RJ, Kannel WB. Incidence of hypertension in the Framingham Study. Am J Public Health 1988;78(6):676-679.

R08-4721 Vargas CM, Ingram DD, Gillum RF. Incidence of hypertension and educational attainment: the NHANES I epidemiologic followup study. 4th Int Conf on Preventive Cardiology, Montreal, Jun 1997 Am J Epidemiol 2000;152(3):272-278.

R08-4722 Rywik SL, Williams OD, Pajak A, Broda G, Davis CE, Kawalec E, et al. Incidence and correlates of hypertension in the Atherosclerosis Risk In Communities (ARIC) study and the monitoring trends and determinants of cardiovascular disease (POL-MONICA) project. J Hypertens 2000;18(8):999-1006.

R08-4723 McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice: fourth national study 1991 - 1992. (Office of Population Censuses and Surveys; series MB5 no 3) London: HMSO 1995.

R08-4724 Radi S, Lang T, Lauwers-Cances V, Chatellier G, Fauvel JP, Larabi L, et al. One-year hypertension incidence and its predictors in a working population: the IHPAF study. J Hum Hypertens 2004;18:487-494.

R08-4727 Rosamond WD, Folsom AR, Chambless LE, Wang CH, ARIC Investigators. Coronary heart disease trends in four United States communities: The Atherosclerosis Risk In Communities (ARIC) study. Int J Epidemiol 2001;30:S17-S22.

R08-4741 Daskalopoulou SS, Athyros VG, Kolovou GD, Anagnostopoulou KK, Mikhailidis DP. Definitions of metabolic syndrome: where are we now? Curr Vasc Pharmacol 2006;4(3):185-197.

R08-4742 Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066-1076.

R08-4743 Robert Koch-Institut (RKI). Bundes-Gesundheitssurvey 1998 (Maerz, 2007; von Webpage: gbe-bund.de.). 2007

R08-4744 Mule G, Cottone S, Nardi E, Andronico G, Cerasola G. Metabolic syndrome in subjects with essential hypertension: relationships with subclinical cardiovascular and renal damage. Minerva Cardioangiol 2006;54(2):173-194.

R08-4745 Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007;28:857-864.

R08-4746 Ford ES. Prevalence of the metabolic syndrome defined by the international diabetes federation among adults in the U.S. Diabetes Care 2005;28(11):2745-2749.

R08-4749 Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110(10):1245-1250.

R08-4750 Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006;119(10):812-819.

R08-4751 McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28(2):385-390.

R08-4752 Chew GT, Gan SK, Watts GF. Revisiting the metabolic syndrome. Med J Aust 2006;185(8):445-449.

R08-4753 Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288(21):2709-2716.

R09-0397 Incidence and prevalence: 2006chartbook on cardiovascular and lung diseases (May 2006, for administrative use). National Institutes of Health, National Heart, Lung, and Blood Institute (2006)

R09-2420 Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension 52 (5), 818 - 827 (2008)

R10-4752 Sekikawa A, Hayakawa T. Prevalence of hypertension, its awareness and control in adult population in Japan. J Hum Hypertens 18, 911 - 912 (2004).

R11-2126 Tourdjman M, Jacobi D, Petit P, Vol S, Tichet J, Halimi JM. Ten-year incidence of high blood pressure in the general population: incidence of clinical parameters, and implication for screening strategies. Incidence a 10 ans de l'HTA dans la population generale: role des parametres demographiques et cliniques, et implication pour la surveillance des normotendus. Arch Mal Coeur 100 (8), 615 - 619 (2007).

R11-2127 Pastor-Barriuso R, Banegas JR, Damian J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med 139, 731 - 739 (2003)

R11-2128 Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA 294 (4), 466 - 472 (2005)

R11-2129 Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. JAMA 275 (20), 1557 - 1562 (1996)

R11-2130 Heald CL, Fowkes FGR, Murray GD, Price JF, Ankle Brachial Index Collaboration Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. Atherosclerosis 189, 61 - 69 (2006).

R11-2131 Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 141 (3), 334 - 341 (2001)

R11-2134 The European health report 2005: public health action for healthier children and populations: summary. Website: euro.who.int/__data/assets/pdf_file/0020/98300/E87399.pdf (access date: 29 April 2011) ; Copenhagen: World Health Organization, Regional Office for Europe (2005)

R11-2135 MultipleRiskFactorInterventionTrial (MRFIT) Research Group Mortality after 16 years for participants randomized to the Multiple Risk Factor Intervention Trial. Circulation 94 (5), 946 - 951 (1996)

R11-2136 Kochanek KD, Xu J, Murphy SL, Minino AM, Kung HC. Deaths: preliminary data for 2009.Natl Vital Stat Rep; 2011; 59(4)

R11-2137 Worktable 307. Deaths from 39 selected causes by place of death, status of decedent when death occurred in hospital or medical center, and age: United States, 2005 (12/4/07). website: cdc.gov/nchs/data/dvs/MortFinal2005_Worktable307.pdf (access date: 29 April 2011) (2007)

R11-2138 Selected health conditions and risk factors: United States, selected years 1988 - 1994 through 2007 - 2008. website:cdc.gov/nchs/data/hus/hus10.pdf#066 (access date: 2 May 2011); Hyattsville: National Center for Health Statistics (2011)

R11-2154 Wilson PWF. Establishedriskfactorsandcoronaryarterydisease: theFraminghamstudy. Am J Hypertens 7 (7, Part 2), 7S - 12S (1994)

R11-2155 Incidence of diagnosed diabetes per 1,000 population aged 18 - 79 years, by sex and age, United States, 1997 - 2009. Website: cdc.gov/diabetes/statistics/incidence/fig5.htm (access date: 3 May 2011) ; Atlanta: Centers for Disease Control and Prevention (2011)

R11-2156 Age-specific percentage of civilian, noninstitutionalized population with diagnosed diabetes, by age, race and sex, United States, 2009. Website: cdc.gov/diabetes/statistics/prev/national/fig2004.htm (access date: 3 May 2011); Atlanta: Centers for Disease Control and Prevention (2011)

R11-2157 Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 102, 470 - 479 (2000).

R11-2158 Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, Klag MJ. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the Third National Health and Nutrition Examination Survey (1988 - 1994). Arch Intern Med 161, 1207 - 1216 (2001)

R11-2173 El-Saed A, Kuller LH, Newman AB, Lopez O, Costantino J, McTigue K, Cushman M, Kronmal R. Geographic variations in stroke incidence and mortality among older populations in four US communities. Stroke 37, 1975 - 1979 (2006)

R11-2174 Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 30, 736 - 743 (1999).

R11-2176 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. N Engl J Med 334 (1), 13 - 18 (1996)

R11-2177 Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics - 2010 update: a report from the American Heart Association. Circulation 121, 948 - 954 (2010).

R11-2178 Ergin A, Muntner P, Sherwin R, He J. Secular trends in cardiovascular disease mortality, incidence, and case fatality rates in adults in the United States. Am J Med 117, 219 - 227 (2004)

R11-2179 Whelton PK, He J, Muntner P. Prevalence, awareness, treatment and control of hypertension in North America, North Africa and Asia. J Hum Hypertens 18, 545 - 551 (2004)

R11-2180 Jones DW, Chambless LE, Folsom AR, Heiss G, Hutchinson RG, Sharrett AR, Szklo M, Taylor HA. Risk factors for coronary heart disease in African Americans: the Atherosclerosis Risk in Communities study, 1987 - 1997. Arch Intern Med 162, 2565 - 2571 (2002).

R11-2181 Rea TD, Pearce RM, Raghunathan TE, Lemaitre RN, Sotoodehnia N, Jouven X, Siscovick DS. Incidence of out-of-hospital cardiac arrest. Am J Cardiol 93, 1455 - 1460 (2004).

R11-2183 Mortality by underlying and multiple cause, ages 18+: US, 1981 - 2007 (source: NVSS). Website: cdc.gov/nchs/hdi.htm (access date: 5 April 2011); Centers for Disease Control and Prevention, National Center for Health Statistics (2011)

R11-2544 Crude and age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes, United States, 1980-2009 (page last modified: March 30, 2011). Website:.cdc.gov/diabetes/statistics/prev/national/figage.htm (access date: 6 June 2011) ; Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) 2011

R11-2545 Bekannter Bluthochdruck oder Hypertonie (Anteil der Befragten in Prozent).Gliederungsmerkmale: Jahre, Region, Alter, Geschlecht, Bildungsstand (Blattmerkmal(e) wurde(n) erfolgreich aktualisiert). Website:.gbe-bund.de (access date: 6 June 2011) ; Gesundheitsberichterstattung des Bundes 2011

R12-2500 Thamm M. Blood pressure in Germany - update review of state and trends. Blutdruck in Deutschland - Zustandsbeschreibung und Trends. Gesundheitswesen 61 (Suppl 2), S90 - S93 (1999)

R13-2649 Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 370, 591 – 603 (2007).

SI.3.2 Unpublished references

Not applicable.

ABBREVIATIONS

AII	Angiotensin II
ABPI	Ankle-Brachial Pressure Index
ACE	Angiotensin converting enzyme
ACEI	ACE inhibitor
ACTH	Adrenocorticotropic hormone
AHA	American Heart Association
AP	Angina pectoris
ARB	Angiotensin II receptor blocker
ARF	Acute renal failure
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CABG	Coronary artery bypass graft surgery

CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
COX-2	Cyclooxygenase-2
CV	cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DM	Diabetes mellitus
EGIR	European Group for the Study of Insulin Resistance
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESRD	End-stage renal disease
HDL	high density lipids
HI	Hyperinsulinaemia
HIV	Human immunodeficiency virus
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme-A
HMO	Health Maintenance Organisation
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard rate
ICD	International Statistical Classification of Diseases and Related Health Problems
IDF	International Diabetes Federation
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	Metabolic Syndrome
MI	Myocardial infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
MRFIT	Multiple Risk Factor Intervention Trial
MSGP4	4th National Survey of Morbidity in General Practice
NANSAIDs	Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs
NCEP	National Cholesterol Education Program

NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Surveys
NHLBI	National Heart, Lung, and Blood Institute
OTC	Over-the-counter
PAD	Peripheral artery disease
PTCA	Percutaneous intervention
PY	person-years
RAAS	Renin-angiotensin-aldosterone system
REACH	REduction of Atherothrombosis for Continued Health
RMP	Risk Management Plan
SBP	Systolic blood pressure
UK	United Kingdom
US	United States
WHO	World Health Organisation

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

SII.1.1 Toxicity

The toxicological profile of telmisartan following oral administration has been examined in single dose experiments in rats and dogs, repeat-dose toxicity studies up to 26 weeks in rats and 52 weeks in dogs, reproductive and developmental toxicity studies in rats and rabbits, and lifetime carcinogenicity studies in mice and rats. Intravenous toxicity studies after a single dose in rats and up to 4 weeks in rats and dogs were also performed. Additionally, local tolerance studies were conducted to assure worker safety during transport and manufacture of telmisartan, experimental parameters in the repeat-dose toxicity studies included. Genotoxicity was explored in a standard battery of *in vivo* and *in vitro* experiments. All of these studies conformed to GLP regulations. Results of key studies are outlined below.

Repeat-dose toxicity

Rats and dogs were selected for toxicological evaluation because telmisartan is pharmacologically active in both species, pharmacokinetics and drug metabolism are similar to humans, and the test laboratory had experience with and adequate historical data on these animal models.

Repeated administration of telmisartan resulted in significant and long-lasting hypotension and pharmacodynamically-mediated renal changes, and lesions of the gastro-intestinal tract. Further effects included: reduced body weight gain, heart weight and red blood cell indices, increased potassium as well as AST and ALT, the latter in the absence of morphological evidence of toxicity. Ineffective doses were not identified for all findings, particularly decreased erythroid indices, increased BUN, JG hypertrophy-hyperplasia in dogs and exposure of animals at toxic doses overlapped with or exceeded AUCs measured in human patients treated with therapeutic doses. These changes, also a class effect of ACEIs and other ARBs, do not appear to have clinical significance. Therapeutic margins, or lack thereof, are shown for the two potentially significant adverse events, gastro-intestinal and renal toxicity, in the following tables (SII.Table 1 and SII.Table 2):

SII.Table 1 AUC levels and therapeutic index in repeat-dose toxicity studies in rats after oral administration

Dose (mg/kg)	0.1*	1.0*	**2.0**[#]	4.0*	8.0[#]	10[+]	50*	100[+]	200[+]	500*
AUC (µg•h/mL)	0.10	0.69	1.2	1.7	5.1	4.6	124	223	635	1270
AUC rat/human	0.02	0.16	0.28	0.40	1.2	1.1	29	52	148	295

AUC for humans for 160 mg/day (sexes combined) = 4.3 µg•h/mL (studies 502.112, 502.113, 502.114)
bold letters = no effect level for gastrointestinal toxicity in rats
* = 26-week study
[#] = 13-week study
[+] = 4-week study
Data source: [U97-0222]

SII.Table 2 AUC levels and therapeutic index in repeat-dose toxicity studies in dogs after oral administration

Dose (mg/kg)	5.0*	10[#]	**20**[#]	***40***[+]	50*	160[+]	500*
AUC (µg•h/mL)	2.7	6.6	17.4	39.9	36.1	146	209
AUC dog/human	0.63	1.5	4.0	9.3	8.4	34	49

AUC for humans for 160 mg/day (sexes combined) = 4.3 µg•h/mL (studies 502.112, 502.113, 502.114)
bold letters = no effect level for gastrointestinal toxicity in dogs
bold letters in italics = no effect level for renal toxicity in dogs
* = 52 week study
[#] = 13 week study
[+] = 4 week study
Data source: [U97-0222]

Despite the small or absent safety margin, a review of data from clinical trials demonstrated that telmisartan causes relatively few side effects in human patients treated for hypertension [U97-3132, U98-3026]. Results of repeat-dose toxicity studies in dogs and rats appeared to overestimate adverse events both qualitatively and quantitatively. In clinical studies, incidence and degree of decrease in red blood cell indices and increase in blood urea nitrogen and creatinine were small and clinically insignificant in a majority of patients. Hyperkalaemia was not reported and telmisartan did not appear to have a gastrointestinal ulcerogenic potential.

In dogs, renal tubular dilation and atrophy were observed following telmisartan administration. Gastric mucosal injury (erosion, ulcers, or inflammation) was also noted in rats and dogs. These pharmacologically-mediated side effects, known from pre-clinical studies with both ACEIs and ARBs, were prevented by oral saline supplementation.

Carcinogenicity

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the MRHD of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Mutagenicity

Telmisartan showed no genotoxic potential in several *in vitro* and *in vivo* test systems [U91-0420, U92-0334, U94-2004, U94-2019, U94-2086]. No relevant clastogenic activity was identified in *in-vitro* studies.

Reproductive toxicity

Angiotensin II receptor blockers are known to decrease placental perfusion and to cause renal damage to rat foetuses during late gestation and early lactation. In rats, telmisartan concentrations increased in the foetal compartment during late pregnancy from about 27% on day 12 of pregnancy to about 60% on day 18. Moreover, telmisartan was excreted in milk (rats) at concentrations of 1.5 to 2-fold the maternal plasma concentration 4 - 8 hours post dosing and remained detectable for more than 48 hours.

In humans, ARBs are expected to be foetotoxic and are, therefore, not recommended during the first trimester of pregnancy, and are contraindicated during the second and third trimester of pregnancy.

SII.1.1.1 Relevance to human usage

Results of repeat-dose toxicity studies in rats and dogs appeared to overestimate adverse events both qualitatively and quantitatively, based on experience in humans. Because nearly all toxic effects of telmisartan were linked to its mechanism of action, limited reproducibility of adverse events in humans can be most logically attributed to disruption of RAAS homeostasis in the normotensive models used in toxicology experiments versus improvement or normalisation in hypertensive patients. Findings are, therefore, not considered relevant in relation to human therapeutic use.

As the foetotoxicity reported in humans is considered a class effect of drugs acting on the RAAS, telmisartan, like other ARBs, is contraindicated during the second and third trimesters of pregnancy. Because it is very likely that telmisartan is excreted in human breast milk, telmisartan should not be administered during breastfeeding.

An epidemiological study on antihypertensive medications and the risk of cancer (trial 0502.599) provided evidence that long-term use of ARBs , and of telmisartan in particular, does not increase the risk of cancer overall or of any of the 4 major cancer sites. No evidence for a relationship of malignancies to ARBs was found in meta-analyses by the FDA [P11-06914] and the ARB trialist collaboration: Teo KK *et al* [P11-02779].

There is no clinical evidence for mutagenicity.

SII.1.2 General safety pharmacology

QT interval prolongation

In a clinical study for telmisartan, neither a drug-dependent increase in weighted mean QTcF, maximum QTcF nor any relevant outliers of QTcF, QTcB or uncorrected QT could be seen. No subject's treatment had to be discontinued due to a QT interval prolongation.

SII.1.2.1 Relevance to human usage

Telmisartan in the doses investigated did not reveal any relevant or significant impact on any of the QT interval parameters observed [U03-1077].

SII.1.3 Mechanisms for drug interactions

Telmisartan is exclusively metabolised by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The CYP isoenzymes are not involved in the metabolism of telmisartan nor has telmisartan been shown to be an inhibitor of CYPs contributing to drug metabolism. Telmisartan is not expected to interact with drugs that inhibit CYPs; it is also not expected to interact with drugs metabolised by CYPs.

More recently it has been shown that telmisartan is a substrate and/or inhibitor of drug transporters. In the Caco-2 cell system it was suggested that the intestinal absorption of telmisartan is dependent at least partially on the monocarboxylate transporters (MCTs) and telmisartan can potentially compete with other acidic drugs at this transporter site [P07-02978]. *In vitro* studies have also revealed telmisartan as substrate of OATP/SLCO 1B3 [P06-04458], substrate P-gp/ABCB1 [P07-00439] and inhibitor of P-gp [P07-00439] and OATP 1B1 (SLCO1B1) [P06-08011]. In addition, the biliary excretion of telmisartan-glucuronide seems to be mainly catalysed by MRP/ABCC 2 [P00-02398].

After combination with nisoldipine, the bioavailability of telmisartan was increased [P07-03113]. This effect was suggested to be mediated via P-gp inhibition of nisoldipine.

The increase in ramipril/ramiprilat plasma concentrations [U08-1362-01] as well as the increase in the peak concentration of simvastatin acid [U00-1591] is suggested to be caused by inhibition of OATP1B1 (SLCO1B1, OATP-C) - Ki of telmisartan = 0.44 µM [P06-08011] - thereby preventing the uptake of these acidic drugs into the liver.

SII.1.3.1 Relevance to human usage

Relevant drug interactions are discussed in the SmPC. As with other medicinal products acting on the RAAS, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACEIs, ARBs, NSAIDs,

including selective COX-2 inhibitors, heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACEIs or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

SII.1.4 Other toxicity-related information or data

None relevant.

SII.1.5 Need for additional non-clinical data

Based on the data available and the extensive experience of telmisartan use, it is considered that there is no need for additional non-clinical data related to the use of telmisartan in special patient populations.

SII.2 REFERENCES

SII.2.1 Published references

P00-02398 Nishino A, Kato Y, Igarashi T, Sugiyama Y. Short communication: both cMOAT/MRP2 and another unknown transporter(s) are responsible for the biliary excretion of glucuronide conjugate of the nonpeptide angiotensin II antagonist, telmisartan. Drug Metab Dispos 2000;28(10):1146-8.

P06-04458 Shitara Y, Horie T, Sugiyama Y. Transporters as a determinant of drug clearance and tissue distribution. Eur J Pharm Sci 2006;27(5):425-46.

P06-08011 Hirano M, Maeda K, Shitara Y, Sugiyama Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos 2006;34(7):1229-36.

P07-00439 Chang C, Bahadduri PM, Polli JE, Swaan PW, Ekins S. Rapid identification of P-glycoprotein substrates and inhibitors. Drug Metab Dispos 2006;34(12):1976-84.

P07-02978 Goto Y, Itagaki S, Umeda S, Kobayashi M, Hirano T, Iseki K, et al. Transepithelial transport of telmisartan in Caco-2 monolayers. Biol Pharm Bull 2005;28(12):2235-9.

P07-03113 Bajcetic M, Benndorf RA, Appel D, Schwedhelm E, Schulze F, Riekhof D, et al. Pharmacokinetics of oral doses of telmisartan and nisoldipine, given alone and in combination, in patients with essential hypertension. J Clin Pharmacol 2007;47(3):295-304.

P11-02779 ARB Trialists Collaboration. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138769 individuals. J Hypertens 29 (4), 623 - 635 (2011)

P11-06914 U.S. Food and Drug Administration (FDA). FDA drug safety communication: no increase in risk of cancer with certain blood pressure drugs - angiotensin receptor blockers (ARBs) [06-02-2011]. Website: fda.gov/Drugs/DrugSafety/ucm257516.htm (access date: 3 June 2011) 2011

SII.2.2 Unpublished references

U91-0420 Mutagenicity study on BIBR 0277 SE in the S. Typhimurium/E. coli Mammalian Microsome assay (Ames test). 11 Apr 1991

U92-0334 BIBR 0277 SE: Mutagenicity study in the mouse bone marrow micronucleus assay after oral treatment.11 Jun 1992

U94-2004 BIBR0277SE: mutagenicity study in the V79 (HPRT) forward mutation assay. 11 Jan 1994

U94-2019 BIBR0277SE: mutagenicity study in the S. typhimurium reverse mutation assay (Ames test). 24 Jan 1994

U94-2086 BIBR0277SE: Mutagenicity study for chromosomal aberrations in human lymphocytes *in vitro*. 28 Apr 1994

U97-0222 Application for a marketing authorisation for telmisartan (Micardis) tablets 40 mg/80 mg: toxicological and pharmacological expert report. 29 Jul 1997

U97-3132 Telmisartan tablets, 40 mg and 8 mg (BIBR 277 SE): integrated summary of safety. 24 Jul 1997

U98-3026 Four month safety update report. 19 Jan 1998

U00-1591 Pharmacokinetics of single oral doses of 40 mg simvastatin and its metabolite simvastatin acid with and without concomitant administration of telmisartan 80 mg daily, given orally over 6 days. A randomised, placebo controlled, double blind (for telmisa).12 Jul 2000

U03-1077 A double-blind, randomised, placebo controlled, 6 parallel groups study to assess the influence of telmisartan (40 mg or 160 mg), lacidipine (4 mg or 6 mg) and their combination (telmisartan 40 mg and lacidipine 4 mg) p.o. once daily for seven days on. 05 Dec 2002

U08-1362-01 Steady state pharmacokinetics of 80 mg telmisartan (Micardis), 10 mg ramipril (Delix) or the combination following repeated oral doses to healthy male and female volunteers (an open label, randomised, multiple-dose, three-way crossover study). 21 May 2008

ABBREVIATIONS

ABCC	Adenosine triphosphate-binding cassette transporter, sub-family C
ACE	Angiotensin converting enzyme
ACEI	ACE inhibitor
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
COX-2	Cyclooxygenase 2
CYP	Cytochrome P450
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
JG	Juxtaglomerular
MCTs	Mono-carboxylate transporters
MRHD	Maximum recommended human dose
MRP	Multi-drug resistant protein
NSAIDs	Nonsteroidal anti-inflammatory drugs
OATP	Organic anion transporting polypeptide
P-gp	P-glycoprotein
QTcB	QT interval corrected using Bazett’s formula
QTcF	QT interval corrected using Fridericia’s formula
RAAS	Renin-angiotensin-aldosterone system
SmPC	Summary of Product Characteristics

MODULE SIII CLINICAL TRIAL EXPOSURE

SIII.1 BRIEF OVERVIEW OF DEVELOPMENT

Telmisartan was approved for the treatment of essential hypertension in the EU and in the US in 1998. Currently, telmisartan is marketed in the EU in 20 mg, 40 mg, and 80 mg dose strengths; and the trade names used are Micardis, Pritor, and Kinzalmono.

The IBD for telmisartan is 10 Nov 1998, i.e. the date of registration in the US. The EU marketing authorisations were issued for Pritor on 11 Dec 1998, and for Micardis and Kinzalmono (previously known as Telmisartan Boehringer Ingelheim Pharma KG) on 16 Dec 1998. In the EU, telmisartan tablets were initially authorised in the dose strengths of 40 mg and 80 mg. A further dose strength of 20 mg was approved on 07 Sep 1999 for Micardis and Kinzalmono and on 16 Sep 1999 for Pritor.

The marketing authorisation for Telmisartan Boehringer Ingelheim Pharma KG was transferred to Bayer Pharma AG on 02 Dec 2002, followed by the change of the product name to Kinzalmono. On 22 Oct 2009, the CHMP gave a positive opinion for extending the indication to include the following and amend the SmPC and Package Leaflet accordingly, which was approved:

Cardiovascular prevention.

Reduction of cardiovascular morbidity in patients with:

- Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
- Type 2 diabetes mellitus with documented target organ damage..

SIII.2 CLINICAL TRIAL EXPOSURE

In the following section, patient numbers and exposure are summarised based on completed trials with telmisartan. Separate overviews for each of the topics such as treatment duration, dosage, age and gender, ethnic origin, and special patient populations are provided.

Section SIII.2.1 summarises the randomised, blinded trial population only, without the ONTARGET programme. Data for the following randomised, placebo-controlled clinical trials were included: 0502-0201, 0502-0202, 0502-0203, 0502-0204, 0502-0206, 0502-0207, 0502-0208, 0502-0209, 0502-0210, 0502-0211, 0502-0213, 0502-0214, 0502-0215, 0502-0216, 0502-0218, 0502-0222, 0502-0223, 0502-0224, 0502-0235, 0502-0236, 0502-0237, 0502-0254, 0502-0255, 0502-0261, 0502-0323, 0502-0327, 0502-0329, 0502-0330, 0502-0332, 0502-0343, 0502-0344, 0502-0376, 0502-0396, 0502-0397, 0502-0398, 0502-0413, 0502-0421, 0502-0436, 0502-0439, 0502-0469, and 0502-0476.

Section SIII.2.2 summarises all clinical trial populations, including open label extension programmes, but without the ONTARGET programme. Data for the following open-label follow-up trials were also included for the ‘all clinical trial’ population: 0502-0219, 0502-0220, 0502-0221, 0502-0228, 0502-0238, 0502-0256, 0502-0257, 0502-0258, 0502-0259,

0502-0260, 0502-0316, 0502-0317, 0502-0331, 0502-0339, 0502-0391, 0502-0392, 0502-0399, 0502-0400, and 0502-0516.

Section SIII.2.3 summarises ONTARGET programme (study 0502-0373 including ONTARGET, TRANSCEND), and in addition PRoFESS (study 9.159) for telmisartan. For each patient only the maximum individual treatment duration has been taken into account.

SIII.2.1 Randomised, blinded trial population only, without the ONTARGET programme

Overall 8659 patients studied in randomised, blinded clinical studies (without ONTARGET programme) received at least 1 dose of telmisartan and the total duration of treatment amounted to 2985 person-years. The majority of patients (71.6%) had a treatment duration of at least 1 month.

The exposure was calculated by subgroups for the randomised, blinded trial population including by dose, age and gender, race, ethnicity, and special populations. Information is summarised in the tables below.

SIII.Table 1 By duration of treatment

Duration of exposure (at least)	Persons (N)	Person time [person-years]
1 day	8659	2985
1 month	6203	2851
3 months	2308	2195
6 months	1465	1889
12 months	688	1213
Total	8659	2985

Data source: BI Project Database

SIII.Table 2 By dose

Dose of exposure	Persons (N)	Person time [person-years]
10 mg	81	17
20 mg	843	85
40 mg	5704	881
60 mg	6	0.1
80 mg	5288	1889
100 mg	6	0.1
120 mg	273	36
160 mg	406	78
Total	8659	2985

Data source: BI Project Database

SIII.Table 3 By age group and gender

Age group	Persons (N)		Person time [person-years]	
	Male	Female	Male	Female
18 - <41 years	425	222	92	41
41 - <65 years	3520	2288	1216	662
≥ 65 years	1274	930	615	360
Total	5219	3440	1923	1062

Data source: BI Project Database

SIII.Table 4 By ethnic origin

Racial origin	Persons (N)	Person time [person-years]
Missing	53	8
White	6571	2043
Black	709	139
Asian	1112	766
Other	2	0.2
Not asked	212	29
Total	8659	2985

Data source: BI Project Database

SIII.Table 5 Special populations

	Persons (N)	Person time [person-years]
Pregnant women	Not applicable	Not applicable
Lactating women	Not applicable	Not applicable
Renal impairment		
Serum creatinine not given	733	101
Serum creatinine <1.5 mg/dL	7508	2586
Serum creatinine ≥1.5 mg/dL	418	298
Hepatic impairment (specify or categorise)	Not applicable	Not applicable
Cardiac impairment*	30	28
Sub populations with genetic polymorphism (specify)	Not applicable	Not applicable

Data source: BI Project Database

*Patients with concomitant diseases (MedDRA PT level) including atrial fibrillation, cardiac failure, cardiac failure congestive, cardiac failure chronic, cardiomegaly, cardiomyopathy, conduction disorder, congestive cardiomyopathy, diastolic dysfunction, dilatation ventricular, hypertensive cardiomyopathy, hypertrophic cardiomegaly and ischaemic cardiomyopathy

SIII.2.2 All clinical trial populations, including open extension, without the ONTARGET programme

In the telmisartan clinical development programme (All clinical trial populations, including open extension without ONTARGET programme), overall 13 462 patients received at least 1 dose of telmisartan and the total duration of treatment amounted to 6635 person-years. The majority of patients (76.3%) had a treatment duration of at least 1 month.

The exposure was calculated by subgroups for all clinical trial populations inclusive of open extension, including by dose, age and gender, race, ethnicity, and special populations. Information is summarised in the tables below.

SIII.Table 6 By duration

Duration of exposure (at least)	Persons (N)	Person time [person-years]
1 day	13 462	6635
1 month	10 270	6453
3 months	4714	5519
6 months	2879	4912
12 months	1692	3924
Total	13 462	6635

Data source: BI Project Database

SIII.Table 7 By dose

Dose of exposure	Persons (N)	Person time [person-years]
10 mg	81	17
20 mg	843	85
40 mg	9333	2944
60 mg	6	0.1
80 mg	9406	3473
100 mg	6	0.1
120 mg	273	36
160 mg	459	81
Total	13 462	6635

Data source: BI Project Database

SIII.Table 8 By age group and gender

Age group	Persons (N)		Person time [person-years]	
	Male	Female	Male	Female
Age 18 - <41 years	666	359	248	127
Age 41 - <65 years	5401	3456	2459	1556
Age ≥65 years	1966	1614	1175	1070
Total	8033	5429	3882	2753

Data source: BI Project Database

SIII.Table 9 By ethnic origin

Racial origin	Persons (N)	Person time [person-years]
Missing	127	28
Caucasian	10 590	5477
Black	981	257
Asian	1464	807
Other	5	1
Not asked	295	65
Total	13 462	6635

Data source: BI Project Database

SIII.Table 10 Special populations

	Persons (N)	Person time [person-years]
Pregnant women	Not applicable	Not applicable
Lactating women	Not applicable	Not applicable
Renal impairment:		
Serum creatinine		
not given	2047	381
<1.5 mg/dL	10 906	5935
≥1.5 mg/dL	509	319
Hepatic impairment (specify or categorise)	Not applicable	Not applicable
Cardiac impairment. Patients with concomitant diseases (MedDRA PT level) including atrial fibrillation , cardiac failure, cardiac failure congestive, cardiac failure chronic, cardiomegaly, cardiomyopathy, conduction disorder, congestive cardiomyopathy, diastolic dysfunction, dilatation ventricular, hypertensive cardiomyopathy, hypertrophic cardiomegaly, ischaemic cardiomyopathy	35	35
Sub populations with genetic polymorphism (specify)	Not applicable	Not applicable
Children and adolescent patients (6 to <18 years old) with hypertension	77	6

Data source: BI Project Database

SIII.2.3 ONTARGET programme (including ONTARGET, TRANSCEND, and PRoFESS)

In the telmisartan clinical development programme, (ONTARGET, TRANSCEND and PRoFESS studies) overall 21 638 patients received at least 1 dose of telmisartan and the total duration of treatment amounted to 67 134 person-years. Over half of patients (57.3%) had a treatment duration of at least 3 years.

The exposure was calculated by subgroups for TRANSCEND, ONTARGET, and PRoFESS studies including by dose, age and gender, race, ethnicity, and special populations. Information is summarised in the tables below.

SIII.Table 11 By duration

Duration of exposure (at least)	Persons (N)	Person time [person-years]
1 day	21 638	67 134
365 days (1 year)	19 066	66 370
730 days (2 years)	16 372	61 914
1095 days (3 years)	12 401	52 162
1460 days (4 years)	10 318	45 080
1825 days (5 years)	3100	14 691
2190 days (6 years)	37	176
Total	21 638	67 134

Data source: BI Project Database

SIII.Table 12 By dose (only ONTARGET and TRANSCEND – multiple entries)

Dose of exposure	Persons (N)	Person time [person-years]
40 mg	104*	Not applicable
80 mg	11 392	Not applicable

*Number of patients who had reported a telmisartan dose of 40 mg at least on one visit.
Data source: BI Project Database

SIII.Table 13 By age group and gender

Age group	Persons (N)		Person time [person-years]	
	Male	Female	Male	Female
<65 years	6664	2729	21 311	8314
≥65 - <75 years	5698	2930	18 640	8998
≥75 years	2130	1487	5930	3940
Total	14 492	7146	45 881	21 253

Data source: BI Project Database

SIII.Table 14 By ethnic origin

Racial origin	Persons (N)	Person time [person-years]
Missing	3	6
Caucasian	13 988	45 308
Black	673	1732
Asian	5162	13 889
Other	1812	6200
Not asked	0	0
Total	21 638	67 134

Data source: BI Project Database

SIII.Table 15 Special populations

	Persons (N)	Person time [person-years]
Pregnant women	Not applicable	Not applicable
Lactating women	Not applicable	Not applicable
Renal impairment:		
"yes": eGFR <60 mL/min/1.73 m²	8173	21 878
"no": eGFR ≥60 mL/min/1.73 m²	13 466	45 256
Hepatic impairment (specify or categorise)	Not applicable	Not applicable
Cardiac impairment. Patients with concomitant diseases (MedDRA PT level) including atrial fibrillation , cardiac failure, cardiac failure congestive, cardiac failure chronic, cardiomegaly, cardiomyopathy, conduction disorder, congestive cardiomyopathy, diastolic dysfunction, dilatation ventricular, hypertensive cardiomyopathy, hypertrophic cardiomegaly, ischaemic cardiomyopathy	Not applicable	Not applicable
Sub populations with genetic polymorphism (specify)	Not applicable	Not applicable
Children and adolescent patients (6 to <18 years old) with hypertension	Not applicable	Not applicable

Data source: BI Project Database

SIII.3 REFERENCES

SIII.3.1 Published references

Not applicable

SIII.3.2 Unpublished references

Not applicable

ABBREVIATIONS

BI	Boehringer Ingelheim
CHMP	Committee for Medicinal Products for Human Use
eGFR	estimated glomerular filtration rate
EU	European Union
IBD	International birth date
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SmPC	Summary of Product Characteristics
US	United States

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Based on the broad clinical development programme (covering for Micardis 30 297 subjects and for Micardis Plus 6619 subjects in randomised clinical trials and the CV outcome trials (ONTARGET, TRANSCEND and PRoFESS)) as well as the long marketing experience of almost 25 years in more than 100 countries, resulting in a cumulative patient exposure of more than 71 million PY for Micardis it can be concluded that patients with a broad variety of age, ethnicity, concomitant diseases and medications have meanwhile been exposed to telmisartan. Neither during the development programme nor during the long marketing time of Micardis a particular population was detected for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Pregnant women	Not included in the clinical development programme.	Not applicable
Breastfeeding women	Not included in the clinical development programme.	Not applicable
Patients with relevant comorbidities:		
• Patients with hepatic impairment	Not included in the clinical development programme.	Not applicable
• Patients with renal impairment	Not included in the clinical development programme.	Not applicable
• Patients with cardiovascular impairment	Not included in the clinical development programme.	Not applicable
• Immuno-compromised patients	Not included in the clinical development programme.	Not applicable
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.	Not applicable
Population with relevant different ethnic origin	See SIII.Table 4 for information on ethnic origin.	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.	
Other	None	Not applicable

SIV.4 REFERENCES

Not applicable

ABBREVIATIONS

CV	Cardiovascular

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Ex-factory (commercial) sales numbers for Micardis as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for complete months, beginning in November 1998.

The method used to estimate patient exposure to the marketed drug is based on the number of tablets sold (ex-factory sales). It is assumed that all tablets were used by the patients and that each patient was treated with 1 tablet per day (defined daily dose). The total days of medication is calculated by dividing the total number of tablets sold (ex-factory sales) by the number of tablets taken per day. The total number of days of medication is then divided by 365.25 (= days of an average year) in order to calculate the total patient exposure in PY.

SV.1.2 Exposure

The cumulative patient exposure to marketed Micardis is estimated to be 71 759 079 PY for the period from November 1998 to March 2023.

Calculated cumulative exposure is presented by regions in SV.SV.Table 1.

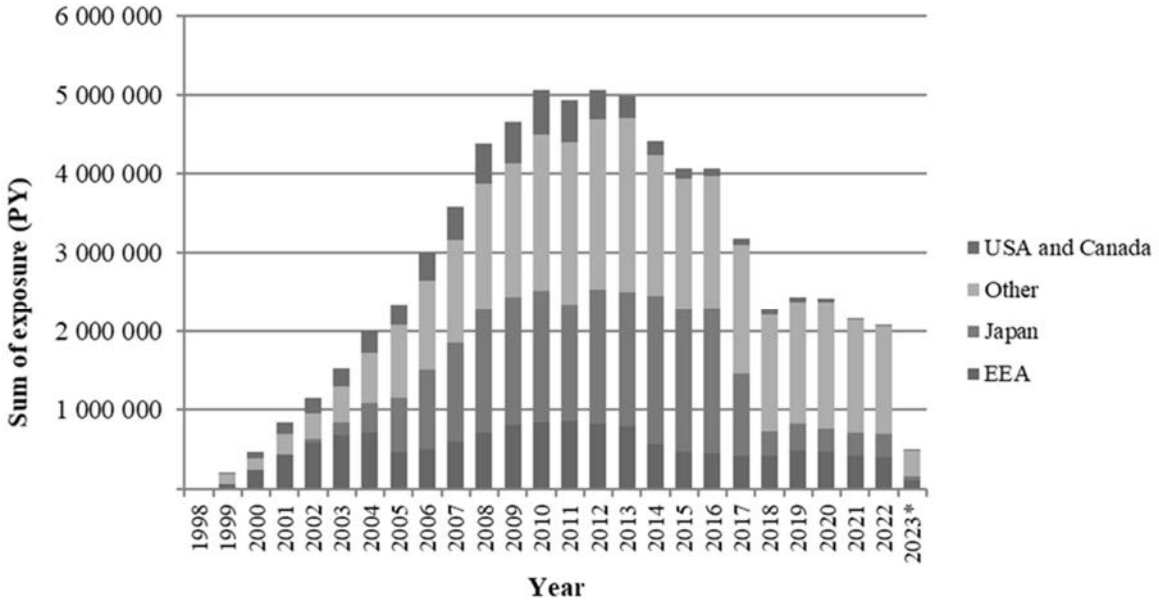
SV.Table 1 Cumulative exposure from post-marketing experience by region for Micardis (November 1998 to March 2023)

Cumulative exposure [PY]				
EEA	**US and Canada**	**Japan**	**Other**	**Total**
13 418 302	5 453 157	21 359 776	31 527 844	71 759 079

Note: all numbers are rounded to the nearest integer
Data source: data on file, ER-018 Micardis exposure (2023 03)

Cumulative post-marketing exposure to Micardis is shown graphically by year and region below.

SV.Figure 1 Cumulative patient exposure to marketed Micardis by year and region



*Exposure for 2023 is available for 3 months only, through 31 Mar 2023.
Data source: data on file, ER-018 Micardis exposure (2023 03)

As there is a single formulation (tablets of different strengths) for the different indications, it is not possible to present post-marketing exposure data by indication. A differentiation of exposure by dose strengths is not considered to be relevant for the safety or benefit-risk balance of Micardis and is therefore not presented. Post-marketing exposure data by age or gender are not available for Micardis.

SV.2 REFERENCES

Not applicable

ABBREVIATIONS

PY	Patient years

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Telmisartan is available as a prescription medicine only. Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive of stimulant, depressant, hallucinogenic, or mood-elevating effects, or other effects that might lead to dependency. There is no known potential for abuse of telmisartan for illegal purposes and it is not expected.

Boehringer Ingelheim will continue to monitor all respective reports received and, based on cumulative experience, will re-evaluate the available evidence.

SVI.2 REFERENCES

Not applicable

ABBREVIATIONS

EU	European Union

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Micardis has been marketed since 1998. An overview of the safety concerns in the initial RMP for Micardis (version 1.0, dated 28 Oct 2008) is presented below.

Important identified risks	Renal dysfunction as a consequence of dual RAAS blockade Sepsis
Important potential risks	Rhabdomyolysis Hypoglycaemia Increase of hepatic related adverse reactions in the Japanese population
Missing information	None

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

With the EU-RMP version 6.1, the list of safety concerns in the Micardis EU-RMP has been revised in line with the recommendations laid down in GVP Module V, Revision 2.

Consequently, the following important identified risks are removed from the list of safety concerns as they are considered adequately characterised and presented in the SmPC (October 2022).

- Renal dysfunction as a consequence of dual RAAS blockade
- Sepsis
- Foetoxicity
- Hypoglycaemia (in diabetic patients)

The following important potential risks are removed from the RMP in accordance with GVP Module V, revision 2, because they are considered adequately characterised and presented in the SmPC and/or are not associated with any additional PV activities or additional risks minimisation measures.

- Rhabdomyolysis
- Increase of hepatic-related adverse reactions in the Japanese population
- Malignancies

Overall, during the long cumulative Telmisartan safety experience of almost 25 years up to this point in time, there was no new information that suggested any change to the current characterisation of these safety concerns. The MAH conducts or plans no further specific

safety studies and no particular milestone data are awaited. Most of the safety concerns are adequately characterised and presented in the SmPC. In addition, there are no additional PV activities or additional risk minimisation measures in place.

The further surveillance of these safety concerns is considered adequate with routine pharmacovigilance and routine risk minimisation measures.

Further details are provided in the corresponding Clinical Overview Statement [c43094432-02].

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

There are no important identified risks, important potential risks or missing information that are associated with any additional pharmacovigilance activities or additional risk minimisation measures.

SVII.4 REFERENCES

SVII.4.1 Published references

None

SVII.4.2 Unpublished references

c43094432-02 Clinical Overview Statement. Supporting the update of Micardis EU-RMP v 6.0 to revise the list of safety concerns in line with GVP Module V revision 2.

ABBREVIATIONS

RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

SVIII.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.4 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no plans for post-authorisation efficacy studies.

PART IV.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

There are no safety concerns in the safety specifications of this Risk Management Plan. Therefore, the following sections are not applicable.

PART V.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable

PART V.4 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR MICARDIS (TELMISARTAN)

This is a summary of the risk management plan (RMP) for Micardis. The RMP details important risks of Micardis, how these risks can be minimised, and how more information will be obtained about Micardis's risks and uncertainties (missing information), if applicable.

Micardis's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Micardis should be used.

This summary of the RMP for Micardis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Micardis's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Micardis is authorised for treatment of essential hypertension and prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease. It contains telmisartan as the active substance and it is given by white, uncoated tablets intended for oral use. Tablets contain 20 mg, 40 mg, or 80 mg telmisartan.

Further information about the evaluation of Micardis’s benefits can be found in Micardis’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Micardis, together with measures to minimise such risks and the proposed studies for learning more about Micardis's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Micardis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Micardis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risks	None
Important potential risks	None
Missing information	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Micardis.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Micardis.

ABBREVIATIONS

RMP

SmPC

APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse drug reaction follow-up forms for Micardis.

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minimisation activities for Micardis.