SCIENTIFIC DISCUSSION

List of abbreviations

AE	Adverse event
AF	Atrial fibrillation
95% CI	95% confidence interval
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ALT	Alanine transaminase, alanine aminotransferase
ASAT	Aspartate aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AWth	Thickening of the anterior wall
b.i.d.	Twice daily
blq	Below limit of quantification
bpm	Beats per minute
BSE	Bovine Spongiform Encephalopathy
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Canadian cardiovascular society
CHMP	Committee of Medicinal Products for Human Use
CL	Total clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phospho kinase
CYP3A4	Cytochrome P450 isoenzyme 3A4
DBP	Diastolic blood pressure
DT	Diastolic time
e.g.	exempla gratia (for example)
EAE	Emergent adverse event
ECG	Electrocardiogram
EMEA	European Medicines Agency
ERG	Electroretinography
ETT	Exercise tolerance tests
F	Absolute bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	Gas Chromatography
GGT	Gammaglutamyltranspeptidase
GLP	Good laboratory practice
HbA_1c	Glycosylated haemoglobin
HCN	Hyperpolarisation-activated cyclic-nucleotide-gated channel
HCV	Hepatitis C virus
HF	Heart failure
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HR	Heart rate
HRR	Heart rate reduction
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
i.e.	id est
i.v.	Intravenous

IOP	Intraocular pressure
IR	Infra red
LC	Liquid chromatography
LC-MS-MS	Liquid chromatography mass detection
LD_{50}	Lethal dose 50
LDL	Low density lipoprotein
LV	Left ventricular
LVD	Left ventricular dysfunction
LVdP/dt	First derivative of left ventricular pressure over time
LVH	Left ventricular hypertrophy
LVWth	Left ventricular wall thickening
MBP	Mean blood pressure
MI	Myocardial infarction
MVO2	Myocardial volume of oxygen consumption
N	Number
NOEL/ NOAEL	No observable effect level
NOS	Not otherwise specified
OSS	Overall oral safety set
p.o.	Per os
PPS	Per Protocol Set
PTCA	Percutaneous transluminal coronary angioplasty
PVC	Polyvinyl chloride
PVD	Peripheral vascular disease
RH	Relative humidity
RPE	Retinal pigment epithelium
RPP	Rate pressure product
SBP	Systolic blood pressure
SD	Standard Deviation
SEAE	Serious emergent adverse event
SPC	Summary of product characteristics
TAO	Time to angina onset
TED	Total exercise test duration
TLA	Time to limiting angina
TLC	Total lung capacity
t_{max}	Time at maximum plasma concentration
ULN	Upper limit of normal range
VDS	Visual disturbance subset
VEP	Visual evoked potential

1. Introduction

Chronic stable angina pectoris is a common disorder: the annual incidence varies between ~0.2% in southern European countries and > 0.6% in northern Europe. In countries with relatively high coronary heart disease rates, the prevalence may be 3–4% of the total population. The term is primarily used for chest discomfort due to myocardial ischaemia associated with coronary artery disease (CAD), although it is recognised that there are other important causes of angina pectoris, such as aortic stenosis and hypertrophic cardiomyopathy. The symptoms occur when there is an imbalance between myocardial perfusion and the demands of the myocardium and the pathological substrate for this is almost invariably atheromatous narrowing of the coronary arteries. In daily life, symptoms typically occur in conditions associated with increased myocardial oxygen consumption, such as during exercise. However, even in stable angina pectoris, symptoms may vary from time to time, depending on such factors as ambient temperature and emotional stress. Prognosis of stable angina pectoris is relatively good in most patients, with an overall mortality rate of 2–3% per annum, although a further 2–3% each year will have a non-fatal myocardial infarction and some subgroups of patients, such as those with impaired left ventricular function, are at much higher risk.

The primary goals in the treatment of stable angina pectoris are (1) to improve prognosis by preventing myocardial infarction and death and (2) to minimize or abolish symptoms. The treatment of angina includes attempts to halt progression of coronary atherosclerosis (e.g. by lifestyle changes), besides drugs and interventional techniques to accomplish these goals. Three main classes of drugs are used to control symptoms in chronic stable angina: nitrates, beta-blockers (e.g. atenolol) and calcium channel blockers (e.g. amlodipine). For symptom relief, generally sublingual short-acting nitrates are used whereas long-acting nitrates are used for intermittent prophylaxis as continuous treatment leads to tachyphylaxis.

It is recognised that heart rate reduction is of paramount importance in the treatment of patients with coronary artery disease and angina. Heart rate reduction decreases oxygen consumption which prevents symptoms and has been shown as an independent factor for reducing morbidity and mortality in patients with CAD. Beta-blockers reduce heart rate and are usually the first-line prophylactic treatment for stable angina in Europe, based on their proven long-term anti-anginal effect as well as positive effects on clinical outcome. Calcium channel blockers are mostly a second-line alternative when beta-blockers are contraindicated or ineffective (or in combination when beta-blockers alone are insufficient). Currently, a new concept for therapeutic class of anti-ischaemic agents with specific negative chronotropic action has been developed, the I_f inhibitors. This new concept involves decreasing the heart rate and thereby prolongation of the duration of diastole, so as to improve the balance between myocardial oxygen supply and demand as well as coronary perfusion.

Ivabradine is a specific heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Within the sinoatrial node, ivabradine is a selective inhibitor of I_f , an important current involved in generating the early phase of spontaneous diastolic depolarisation in pacemaker cells, thereby reducing the frequency of action potential initiation and lowering heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation or coronary vasomotricity.

2. Quality aspects

Introduction

The product is presented as film coated tablets containing 5.390 mg ivabradine hydrochloride corresponding to 5 mg ivabradine base and 8.085 mg ivabradine hydrochloride corresponding to 7.5 mg ivabradine base as active substance. Other ingredients are lactose monohydrate, magnesium stearate,

maize starch, maltodextrin, silica, hypromellose, titanium dioxide (E171), macrogol 6000, glycerol, yellow iron oxide (E172) and red iron oxide (E172).

The tablets are packed in Aluminium/PVC blister strips packed in cardboard boxes.

Drug Substance

Ivabradine hydrochloride is a white to slightly yellow powder. It is freely soluble in water, dimethylsulfoxide, methanol and methylene chloride, it is soluble in ethanol and slightly soluble in acetone. It has the chemical name 3-(3-{[((7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one, hydrochloride. Ivabradine hydrochloride is optically active and corresponds to the S isomer.

Manufacture

Ivabradine hydrochloride is synthesised from azepan and butamine hydrochloride in one manufacturing step. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory. A reprocessing procedure is performed in case of non-compliance of the product.

Batch analysis data is provided on 3 batches produced with the proposed synthetic route, and the batch analysis data show that the active substance can be manufactured reproducibly, and in compliance with the agreed specification.

Specification

The active substance specification includes tests for appearance, solubility, identification (HPLC and IR), assay (99.0-101.0%, Potentiometric titration), related substances (HPLC), water content, sulphated ash, heavy metals, chloride content, chloride identification (Ph Eur), residual solvents (GC), R isomer content (HPLC), specific optical rotation and particle size (Laser Granulometry).

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitably described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Stability

Stability of ivabradine hydrochloride has been shown under long term, intermediate and accelerated conditions according to the ICH/CPMP guidelines and in addition at 30°C/70% RH in the reduced size industrial bulk packaging (cardboard drum) up to 3 years for two pilot scale batches an up to 3 years for one industrial scale batch.

The parameters tested were, appearance, water content, IR-spectrum, assay of the active substance (HPLC and potentiometry), related substances and R-isomer content.

The specifications were met for all batches at all storage conditions. No noticeable signs of degradation and no increase of impurities were observed. Based on these results the proposed re-test period is acceptable when stored in the original container closure system.

Drug Product

Pharmaceutical Development

The main goal was to develop a rapid dissolution finished product to be administered orally.

A compatibility study involving the drug substance and a number of excipients was carried out to select the excipients in the finished product. Wet granulation was chosen as manufacturing process.

During clinical development several formulations were manufactured and administered to subjects and patients. The minor differences in the compositions of the formulations used in the clinical phase studies were adequately explained.

During the development the test methods were set up to the control: the manufacture of the granulate, the compression of the core tablets and the properties of film-coated tablets.

The choice of excipients was initially oriented by the above mentioned compatibility study. The formulation was thereafter modified to take into account the properties of each excipient to produce a robust pharmaceutical dosage form, from the production perspective, and to yield a drug product with immediate release characteristics. All the excipients used in the finished product comply with the Ph.Eur except the two coating agents, red and yellow iron oxides, which comply with the European Directive 95/45/EC.

Lactose monohydrate is the only excipient of animal origin used and it is in compliance with the European Commission Decision 2001/2/EC regulating the use of material presenting risks as regards transmissible spongiform encephalopathy and the public statement "Lactose prepared using calf rennet: risk assessment in relationship to bovine spongiform encephalopathies (BSE)" (EMEA/CPMP/571/02).

The tablets are packed in a heat-sealed blister pack composed of polyvinyl chloride sheet (PVC) and aluminium foil. The blisters are packed in a cardboard box. The compatibility of the finished product with the primary packaging was demonstrated in the stability studies.

Manufacture of the Product

Wet granulation was chosen as manufacturing process.

The in process controls are adequate for this film coated tablet preparation.

The batch analysis data presented show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specifications, which is suitable for control of this oral preparation.

Product Specification

The product specifications include tests by validated methods for appearance, identification of ivabradine (HPLC, TLC), average mass, disintegration time (Ph Eur), microbiological quality, drug substance content (HPLC, 95-105% of the label at release, 94-105% at shelf life) degradation products (HPLC), content uniformity (Ph Eur).

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data are presented for two full scale batches and six pilot scale batches of 5 mg tablets and for two full scale batches and seven pilot scale batches of 7.5 mg tablets. The presented data confirm consistency and uniformity of the product from batch to batch.

Stability of the Product

Stability data of 3 pilot batches of each strength packed in the proposed marketing immediate packaging was provided. The batches were stored under ICH conditions at 40ºC/75% RH for 6 months, at 30ºC/60% RH for 12 months and 25ºC/60% RH, and at 30ºC/70% RH for 36 months.

The parameters investigated were appearance, odour, average mass, uniformity of mass of tablet halves (for 5 mg tablets only), disintegration time, microbiological quality, assay, degradation products, uniformity of content.

Stress towards temperature and photostability stability testing were performed in one 5 mg and 7.5 mg pilot batch packed in heat-sealed aluminium/polyvinyl chloride blister. For photostability testing, the tablets were directly exposed. Based on the results, it was concluded that extreme temperature had no effect on the quality of the tablets and no light resistant packaging was needed.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product.

3. Non-clinical aspects

Introduction

The standard safety pharmacology studies complied with the ICH S7A guideline and were performed according to the applicant under GLP. In addition, a small number of investigational studies necessitated specialised expertise (e.g. mechanistic studies and exploration of visual system); these usually were not performed according to GLP. Particular emphasis was placed on the cardiovascular system, because it is the target system, and on the visual system, due to visual symptoms reported in clinical trials. Pivotal toxicological studies were carried out according to the applicant under GLP except for one complementary embryofoetal development rabbit study.

Pharmacology

Primary pharmacodynamics (in vitro/in vivo)

In vitro

Inhibition of the cardiac pacemaker *f*-current (I_f) reduces the slope of spontaneous diastolic depolarisation, thereby increasing the time required to reach the voltage threshold for action potential initiation and slowing the spontaneous firing and therefore heart rate. *In vitro*, ivabradine was a selective inhibitor of I_f, which was concentration-, use- and current-dependent. In isolated rat right atria, ivabradine reduced the spontaneous atrial beating rate; a similar rate reduction of 20% was observed after either ~3 h exposure to 0.1 µM ivabradine or after 30 min incubation at 1 µM. In isolated rabbit sinoatrial node, a similar (9-12%) firing-rate reduction was achieved after 3h at 0.1 µM or after 40 min at 1 µM. At all concentrations (0.03-1µM) tested, only the slope of slow diastolic depolarisation was reduced, while maximal diastolic potential or threshold potential of activation remained unaffected.

The I_f patch-clamp studies in rabbit sinoatrial node cells demonstrated a concentration-dependent block of I_f with an IC50 in the range of 1.5 to 3 µM. I_f is carried by hyperpolarisation-activated, cyclic

nucleotide-gated channels (similar channels carrying hyperpolarisation-activated I_h currents have been identified in photoreceptors of retina and ganglion cells).

The selectivity of ivabradine for I_f in pacemaker cells was assessed. In rabbit sinus-node cells, ivabradine blocked I_f with a high degree of selectivity, since at concentrations close to the IC50 for I_f inhibition (i.e. 1.5 to 3 µM), no effect was observed on $I_{Ca,L}$, $I_{Ca,T}$ and I_K. Thus, the effect of ivabradine on the diastolic depolarisation slope resulted from a selective inhibition of I_f.

In vivo:
In vivo pharmacodynamic studies were carried out to study the effects of ivabradine in rats, dogs and pigs. Studies in rats were conducted under both acute and sub-acute (up to 10 days) conditions, using either oral (gavage), sub-cutaneous or intravenous routes. In pigs and dogs, intravenous administration was mainly used. The electrocardiographic and cardiac haemodynamic effects of ivabradine were assessed both at rest (rats, pigs and dogs) and during treadmill exercise (pigs and dogs).

In Wistar rats, ivabradine administered as single i.v. (0.5 to 2 mg/kg) or oral doses (1.5 to 6 mg/kg) produced a dose-dependent heart-rate reduction (maximal reduction: i.v.: 20-30%; p.o.: 14-22%) lasting at least 6 h at the highest doses, without modifying the mean blood pressure. After oral administration of ivabradine at 3 mg/kg/d, a similar daily heart rate (HR) profile was observed from Day 1 through Day 10, without any effect on mean blood pressure and no residual heart-rate reduction 24 h after the last administration. In conscious Long-Evans rats, single i.v. bolus administration of ivabradine at the high dose of 10 mg/kg induced 57% heart-rate reduction, with no sign of negative inotropic effect. At these dose-levels, the heart rate reduction (HRR) was associated with an increase in stroke index.

In anaesthetised open-chest pigs, successive i.v. doses of ivabradine (0.1, 0.3 and 1 mg/kg) exerted a potent and dose-dependent HR lowering effect (16-37%), without affecting myocardial contractility, ventricular repolarisation (QTc) and atrioventricular conduction (PR-interval). Ivabradine did not modify blood pressure, peripheral and vascular resistance, left ventricular (LV) contractility, and prevented the spontaneous fall of stroke volume observed with vehicle (due to anaesthesia).

The kinetic profile for heart-rate reduction was similar in rats and pigs after oral administration with peak effect generally reached within 3 to 4 h and lasting 8 to 12 h. After intravenous bolus administration (rats, pigs or dogs), heart-rate reduction occurred significantly more rapidly, within 5 min after dosing, peak effect being reached after 15-20 min.

In conscious micropigs, a single oral 5 mg/kg dose of ivabradine reduced HR (~20%) at rest and during exercise for at least 5 h. Ivabradine did not change the exercise-induced rise in myocardial contractility, supporting the absence of negative inotropic effect and the increase in cardiac output induced by exercise, through an increase in stroke volume. Ivabradine had no effect on SBP and MBP at rest and during exercise. A slight but significant decline in resting DBP was noted (-6.7±7.2 vs. +7.2±2.5% with vehicle, 3 h post-dose).

In male mongrel dogs ivabradine induced a dose-related HRR, significant at rest from 0.5 mg/kg i.v. (-16 and -23% at 0.5 and 1 mg/kg, respectively) and during exercise from 0.3 mg/kg i.v. (~ -10 and -30% at 0.3 and 1 mg/kg, respectively). Ivabradine did not change the increase in mean coronary blood flow velocity and the decrease in coronary vascular resistance observed during control exercise. Epicardial coronary artery diameter was not affected at rest and its increase during exercise was attenuated by ivabradine. Ivabradine did not significantly decrease LVdP/dt throughout exercise. Despite HRR, ivabradine maintained the exercise-increased cardiac output by increasing stroke volume. All coronary and haemodynamic effects of ivabradine were abolished by atrial pacing.

Effects on myocardial oxygen balance were assessed in male mongrel dogs treated with a single i.v. dose of ivabradine (1 mg/kg). During treadmill-exercise ivabradine reduced HR (~ -30%) and LV mean ejection wall stress was not altered. LVdP/dtmax was not reduced. Diastolic time (DT) was increased vs. saline (233±11 ms vs. 123±4 ms). Myocardial oxygen demand (MVO2) was significantly lower

under ivabradine vs. saline (6.7±0.6 vs. 8.1±0.6 ml/min). Under atrial pacing, DT and MVO2 were similar between ivabradine and saline.

In mongrel dogs at rest ivabradine (i.v. doses of 0.25, 0.5 and 1 mg/kg) did not increase the time constant of isovolumic relaxation. During exercise at 1 mg/kg ivabradine limited exercise-induced tachycardia and had no effect on isovolumic relaxation.

The effects of ivabradine were also assessed in the ischaemic setting in pig- and dog-models of exercise-induced ischaemia, mimicking exercise-induced angina pectoris in humans. The pig model involved a fixed partial stenosis of the left anterior descending coronary artery, and the dog model used a partial stenosis of the left circumflex coronary artery applied by an occluder to suppress the increase in coronary blood flow during exercise. In pigs, ivabradine (0.5 mg/kg i.v. or 5 mg/kg p.o.) prevented exercise-induced regional myocardial ischaemia, as demonstrated by a limitation of ST-segment elevation and a protection of the regional contractility in myocardium area perfused by the stenosed artery. Ivabradine did not reduce left ventricular contractility nor prolong atrioventricular conduction time. Ivabradine improved myocardial contractile function in the ischaemic zone. In the dog model, ivabradine (1mg/kg i.v. bolus, 0.5mg/kg i.v. over 6h) limited exercise-induced myocardial ischaemia. During exercise under saline, left ventricular wall thickening (LVWth) was reduced (from 29±4% to 2±1%); when administered before exercise, ivabradine attenuated LVWth depression during exercise (from 35±6% to 10±3%) and limited the subsequent myocardial stunning vs. saline. Atenolol further blunted LVWth depression during exercise (from 29±4% to 17±4%) but had no effect on stunning vs. saline.

The heart rate-lowering activity of several ivabradine metabolites was assessed, *in vitro* in rat right atria and *in vivo* in rats after a single i.v. (2 mg/kg) or oral dose (6 mg/kg). Results showed that the cleaved compounds were all inactive in these models, while all uncleaved compounds tested showed a heart rate-lowering activity, similar to the parent compound. The contribution of each active metabolite to heart-rate reduction in rat and dog was likely to be limited, considering their low plasma levels relative to the parent compound (<1% - 14%).

Secondary pharmacodynamics

The effect of ivabradine on LV function in chronic heart failure (HF) was studied in coronary artery ligated rat model. One week after coronary artery ligation, male Wistar rats received vehicle (control) or ivabradine at the doses of 0.3, 1, 3 or 10 mg/kg/d for 3 months. Ivabradine caused sustained HR reduction and limited left ventricular systolic dysfunction and remodelling.

In a chronic 9-month contractile dysfunction study male Wistar rats were subjected to abdominal aortic banding to induce pressure-overload cardiac hypertrophy in the absence of necrosis. The combination of ivabradine and dobutamine prevented dobutamine-induced tachycardia, maintained positive inotropic effect of dobutamine and increased stroke volume.

In another study anaesthetised male Wistar rats were subjected to ischaemia (I; left coronary artery occlusion) followed by reperfusion (R). 30 min after the start of R, rats received either: vehicle, ivabradine (2 mg/kg i.v.) or dobutamine (2.5 µg/kg/min iv for 90 min) and 30 min after onset of dobutamine, vehicle or ivabradine (2 mg/kg) for 60 min. I/R lead to a marked stunning, as assessed by a marked and persistent decrease in systolic thickening of the anterior wall (AWth) during R, which was reversed by dobutamine. Dobutamine increased HR (from 265±19 to 374±14 bpm) and fractional shortening (+85%), without significant effect on stroke volume. Ivabradine abolished dobutamine-induced tachycardia (232±15 bpm) and did not change the effect of dobutamine on stunning (AWth: 90±5%). Fractional shortening and stroke volume were increased.

Safety pharmacology

Receptor binding studies

Studies performed on 18 cell surface receptors and binding sites showed the lack of affinity of ivabradine for adrenergic, serotonin, central benzodiazepine, dopamine, adenosine, histamine, GABAA, μ-opioid, muscarinic cholinergic receptors and dihydropyridine binding site of the calcium channel. Low affinity for the phenyl-alkyl-amine binding site of the L-type Ca^{2+} channel and for the voltage dependent Na^{+} channel was observed in these isolated open-membrane systems but was not confirmed in more specific electrophysiological studies (microelectrode/patch-clamp).

Heart

Ivabradine and S 18982 were evaluated for their potential to prolong ventricular repolarisation (QT-prolongation) independently of that related to heart-rate reduction.

In vitro

In guinea-pig papillary muscle, ivabradine slightly (<10% at the high concentration of 10 μM) prolonged action potential duration. In rabbit cardiac Purkinje fibres action potential increased slightly (by 14 to 46%) at 3 and 10 μM (~150-fold the mean Cmax achieved in patients with ivabradine 7.5 mg twice daily). In dog cardiac Purkinje fibres, action potential was unaffected up to 10 μM. No proarrhythmogenic effect was observed. Results from HERG-channel assay indicated a concentration-related block of I*Kr*, with an IC50 of 4.85 and 15.8 μM for ivabradine and S 18982, respectively (~70- and 900-fold the mean plasma Cmax for ivabradine and S 18982, respectively, in patients treated with ivabradine 7.5 mg twice daily). When accounting for unbound plasma fraction (30%), these ratios go up to ~244- and ~3000-fold, respectively. Ivabradine had no effect on I*Ks*.

In vivo

An electrocardiographic analysis in unrestrained beagle dogs over repeated oral administration of ivabradine for 5 days at doses ranging from 0.5 to 15 mg/kg twice daily revealed no significant effect on QTc nor on QT/RR-relationship up to the highest dose associated with mean plasma Cmax 134-fold greater than in patients with ivabradine 7.5 mg twice daily.

The reversal of cardiovascular effects that could occur following accidental overdose with ivabradine was evaluated in chronically instrumented conscious dogs. The overdose (mean plasma Cmax 178-fold greater than in patients at 7.5 mg twice daily) induced transient increases in systolic arterial pressure, LV systolic and diastolic pressures, and LVdP/dtmin that spontaneously normalised within 20 to 60 min. Bradycardia was the only long-duration effect, although HR was never below 50 bpm. Heart-rate reduction was 25% at maximum. Heart-rate reduction was effectively and rapidly reversed with either isoprenaline or dobutamine. Atropine was not able to consistently reverse ivabradine-induced bradycardia.

Eyes

Ocular safety was assessed *in vitro* and *in vivo* (by excess of pharmacological doses of 100-fold for *in vitro* studies and ~40-fold *in vivo* up to 4 weeks duration) with no evidence of functional or structural alterations of any of the retinal cell layers. The ion permeability function of the retinal pigment epithelium (RPE) and the integrity of the tight junctions, upon which barrier function is highly dependent, were not affected. There was no deregulation of apoptosis (programmed cell death, TUNEL assay) in retinal or glial cells and no ultrastructural change in rats after oral ivabradine at 6 and 60 mg/kg/d for 4 weeks. Although these data were obtained in albino rats, which do not take into account the melanin binding of ivabradine and its distribution in the pigmented uveal tract, they were consistent with electron microscopy results in the highly pigmented dog eyes after high dose administration for 1 year. Using the voltage-clamp technique, ivabradine induced a concentration-dependent inhibition of the retinal current encoded by mHCN1 with an IC50 of 16 μM.

CNS

Single oral doses of ivabradine up to 80 mg/kg did not affect spontaneous locomotor activity, hexobarbital-induced sleeping time, the latencies for reaction to pain (hot plate test), and did not induce proconvulsant activity in Wistar rats. Single oral doses of ivabradine up to 59 mg/kg did not induce

any physiological or behavioural effects. In the rat (Irwin test) moderate sedation and slight hypothermia were observed within 30 min after dosing at 119 and 238 mg/kg.

Respiratory system
Single oral doses of ivabradine at 5 mg/kg did not affect the respiratory functions in rats. At the higher doses of 20 and 80 mg/kg, ivabradine elicited a transient increase in respiratory rate (max +17%), but did not alter any other respiratory parameters.

Gastrointestinal
Gastrointestinal effects were assessed in rats given single oral doses of ivabradine ranging from 5 up to 30 mg/kg. There was no effect on gastric secretions in pylorus-ligated Wistar rats. Gastrointestinal transit time was slightly delayed in Wistar rats that had no access to drinking water; the effect was dose-dependent across all doses. At the highest single oral dose of 30 mg/kg, some ulcerogenic activity was noted but infusion of 28 mg/kg/d over 14 days did not affect the gastric mucosa.

Renal
Urine output, electrolyte balance and glomerular filtration rate were measured in saline-loaded rats given single oral doses of ivabradine at 5, 15 and 30 mg/kg. There was a dose-related increase in urine volume, and a significant concomitant increase in sodium excretion at the two highest doses, which was of similar magnitude at both doses. Also, renal function was closely monitored in chronic toxicity studies up to 1 year duration; there were no other effects on renal function or on kidney weight or histopathology in any study, where exposure levels were up to 336-times higher than in patients at 7.5 mg twice daily.

Pharmacodynamic drug interactions
Pharmacodynamic interactions were carried out in normal animal models, as single dose studies. In rats, there was no interaction with aspirin (assessed by platelet aggregation and ulcerogenic activity) or on the anticoagulant effect of warfarin. In dogs, there was no significant interaction with diltiazem or digoxin; ivabradine limited the tachycardia induced by isosorbide dinitrate and verapamil and the prolongation of PR-interval elicited by verapamil.

Pharmacokinetics
The pharmacokinetics and metabolism of ivabradine was examined in the mouse, rat and dog, species used in safety assessment, as well as *in vitro* using animal and human tissues. Since oral administration was the intended route for human use, the pharmacokinetics of ivabradine was investigated following oral administration to animals. Pertinent pharmacokinetic parameters were also obtained from intravenous administration. S 18982 (N-desmethyl ivabradine) was the main active primary metabolite in human plasma and thus its pharmacokinetics was characterised after ivabradine administration in animals.

The pharmacokinetics of ivabradine was characterised using non-compartmental (model-independent) and compartmental (model-dependent/combined) approaches, while that of S 18982 was assessed using a non-compartmental approach only. Population analysis was applied to both the rat and dog data.

The bio-analytical methods used for the determination of unchanged drug (ivabradine or S 16257) and its N-desmethylated metabolite S 18982 involved high performance liquid chromatography (HPLC), with either native fluorescence (LC-Fluorescence) or mass spectrometry (LC-MS-MS) detection.

All analyses of samples from regulatory toxicology studies, including prior analytical validations, were carried out according to the principles of GLP according to the applicant.

Absorption- Bioavailability

After oral administration over a large range of doses, ivabradine was rapidly and almost completely absorbed with moderate bioavailability of around 40%, due to a first-pass effect. Peak plasma

concentrations were reached after 20 min in rats and 1 h in dogs. Kinetics was linear over a large range of doses, without time effect. A gender effect was evidenced only in rats, with females being on average 3-fold more exposed than males, which is consistent with the first-pass effect, with male rats having higher CYP3A4 activity than females.

Distribution

Ivabradine and/or its metabolites were rapidly and extensively distributed throughout the body in the rat and to a lesser extent in the dog. The volume of distribution at steady state was ~3.4 l/kg in the rat and ~1 l/kg in the dog.

Plasma protein binding of ivabradine was moderate across animal species (~50 to 70%). Minimal saturation was observed in rat, rabbit and dog plasma at higher concentration (>250 ng/ml). The protein binding of S 18982 was also moderate (60-80%) in all animal species.

The most exposed tissue was the uveal tract. A slower elimination from pigmented structures was observed (mainly iris, ciliary body and choroid), suggesting melanin binding. Microautoradiography of the chorio-retina in rats showed localisation in the choroid and not in the neuroretina, a structure devoid of melanin. Assay for ivabradine in the eyes of dogs exposed for one year confirmed the distribution of the compound in the anterior and posterior ocular segments, including iris and choroid. A similar pattern was observed for the metabolite S 18982. This binding was reversible.

Ivabradine was also distributed into amniotic fluid as assayed in amniotic fluid of pregnant rats and was excreted in maternal milk of rats. Therefore, together with the indication of potential reproductive toxicity, ivabradine should not be given during pregnancy and breast-feeding, which is reflected in the SPC (4.6.).

In the heart, ivabradine and/or derived compounds rapidly equilibrated with plasma. Ivabradine and S 18982 were not retained in cardiac tissues as shown by blq (below limit of quantification) levels in the dog heart one day after cessation of a one-year exposure to plasma levels up to 50 times those in patients at high therapeutic dose of 7.5 mg twice daily.

In the liver, ivabradine and S 18982 did not accumulate over time, as assayed in the rat after single and 26-week repeated oral administration. In the brain, passage was very low, as shown by radioactivity levels representing at most 3% of plasma exposure following single dose in rats.

Metabolism

Ivabradine was extensively metabolised in all animal species tested by oxidation *via* CYP450. The absence of bioconversion of ivabradine (*S*-enantiomer) into the *R*-enantiomer was demonstrated in rats and dogs.

Ivabradine was neither an inducer nor an inhibitor of main drug-metabolising enzymes.

Excretion

Total plasma clearance at steady state was moderately high in rats (males: 66 to 32 ml/min/kg from 2.3 to 37 mg/kg/d; females: ~40 ml/min/kg) and in dogs (~15 ml/min/kg) and the renal clearance contributed to ~5% of the total plasma clearance. Elimination of ivabradine mainly occurred *via* hepatic metabolism.

In the rat, the main half-life (terminal phase) ranged from 6 h in males to 14 h in females, consistent with a total lower clearance in females, and was not associated with any accumulation in repeat-dose studies. In the dog, the main half-life (first exponential phase) was less than 2 h.

Faeces was the major route of excretion of unchanged ivabradine and metabolites in rats and dogs. In both species, most of radioactivity (85-94%) was eliminated within 48 h. In plasma, faeces, bile and urine, most of the radioactivity (78-100%) comprised metabolites, with only minor amounts of unchanged compound.

Drug interactions

No pharmacokinetic drug interaction studies were performed in animals.

Toxicology

Single dose toxicity

Acute toxicity studies were conducted in mice, rats and dogs.

In mice and rats, the observed effects were behavioural changes in association with high plasma concentrations, and death (Observed minimal lethal doses: mice: ≥742 mg/kg p.o., ≥56 mg/kg i.v.; rats: ≥557 mg/kg p.o., ≥74 mg/kg i.v.). In dogs, the observed effects were neurobehavioural changes (Maximum tolerated dose: comprised between 11 and 22 mg/kg p.o. in a dose-escalation study, 9.3 mg/kg i.v.).

Repeated-dose toxicity

The main repeated-dose toxicity studies were conducted in rats and dogs. In rats 6 main studies were conducted with oral doses (2.8-223 mg/kg/d; three 4-week studies, one 13-week study, one 26-week study and one 1-year study), and one study with iv-dose (2.3-37 mg/kg/d; 4-week study). In dogs 4 main studies were carried out with oral doses (2-42 mg/kg/d; one 4-week study, one 13-week study, one 26-week study and one 1-year study), and two studies with iv-doses (1.9-70 mg/kg/d; 4-week studies).

Heart
Heart rate reduction, the pharmacological effect of ivabradine, was evident from the lowest dose in the studies where it was measured.

In the heart of rats, focal myocardial lesions were observed.

NOEL/NOAEL was 6-7 mg/kg/day in 4-, 13- and 26-week studies. The exposure at these dosages was about 2 times (males) and 9 times (females) the human exposure at the maximum therapeutic dose of 7.5 mg twice daily. In the 1-year rat study, no NOEL/NOAEL could be established, since effects were already visible at the lowest dose of 6 mg/kg/day, corresponding to 4 times (males) and 10 times (females) the maximum therapeutic exposure.

In dogs, the main treatment-related findings were sinus bradycardia, sinoatrial block, sinoatrial arrest, first-degree atrioventricular block and second-degree atrioventricular block. These ECG changes were seen at dose levels associated with mean plasma Cmax 20-fold above that in human at 7.5 mg twice daily (3 mg/kg/d; 13-week study). There were also some ventricular escape complexes and atrial or ventricular premature complexes at doselevels associated with mean plasma Cmax at least 80-fold greater than in human at 7.5 mg twice daily. No treatment-related ECG changes were noted at the end of the recovery periods. There was no effect on QT-interval duration corrected for heart rate at Cmax levels.

Eyes
Electroretinography (ERG) examinations were included in the 12-month repeated dose study in dogs (2, 7 or 24 mg/kg/d). At 6 and 12 months, there were ERG changes in the cone system at exposures similar to the expected human therapeutic exposure; these were reversed at one week after treatment cessation

and at the following treatment-free periods (up to 11 weeks). In the rod system, dark adaptation was only affected in the first few minutes. Shorter time intervals than 6 months were not evaluated. The electroretinography changes did not worsen as treatment progressed, and were reversible generally within a week after the end of the dosing period. There were no ophthalmoscopic changes and no pathological changes detected by light microscopy or by transmission electron microscopy in dogs exposed for one year to up to 70-fold and 50-fold higher than those in patients treated with 5 mg and 7.5 mg twice daily. Furthermore, there were no other ophthalmological effects and, particularly, no histopathological effects in the eyes of any species in any study.

Other organs

In rats and dogs, the repeated-dose studies showed a number of other minor effects. These effects were not relevant for human at therapeutic exposures.

Thymus atrophy and/or decrease in lymphocyte counts were occasionally reported. These changes were infrequent, inconsistent (observed only in 1 out of 12 rat studies, and in 2 out of 9 dog studies), appeared at high multiples of the exposure levels achieved in patients at the high therapeutic dose, were not confirmed in studies of longer duration, and were not associated with functional immunotoxicity.

Toxicokinetics: Toxicokinetic studies after oral administration in rats showed that the exposure of females to the drug was markedly higher than that of the males (Cmax and AUC on average 3-fold higher in females). The metabolite S18982 was lower (AUC and Cmax) in females than in males. After IV administration no marked gender difference was observed.

Genotoxicity *in vitro* and *in vivo*

No evidence of mutagenicity or relevant clastogenic activity was observed from an exhaustive review and analysis of the data from a battery of *in vitro* and *in vivo* genotoxicity tests performed in accordance with ICH guidelines.

Carcinogenicity

The tumorigenic potential of ivabradine was investigated in mice and rats over 104 weeks.

There was no evidence of ivabradine-related carcinogenic effects in mice and rats.

Reproductive and developmental studies

Reproductive and developmental toxicity studies were performed by the oral route of administration in rats and rabbits.

Ivabradine did not affect fertility in male or female rats.

Ivabradine was embryotoxic and teratogenic in rats and rabbits. Embryotoxic effects in rats comprised increased intrauterine and post-natal mortality, and teratogenic effects occurred in the heart at systemic exposure levels close to those in patients receiving therapeutic doses of ivabradine. Adverse effects in rabbits comprised three foetuses from three litters in two out of three separate studies, which had ectrodactylia; these were from dams exposed to 21 times the mean human AUC. Intrauterine and neonatal mortality could also have been associated with potentially lethal cardiac malformations, as indicated by some pups that died neonatally and had septal defects. In light of these data, and considering the potential of ivabradine to transfer into placenta and to be excreted in milk, ivabradine should not be used during pregnancy or breast-feeding. These findings have been reflected in the SPC (section 4.3, 4.6, and 5.3).

Local tolerance

Local tolerance was assessed in the intravenous studies, where the injection sites were examined at gross and microscopic examinations; there was no indication of local toxicity. In addition, the potential effects on red blood cells were evaluated *in vitro* on human blood. Ivabradine solutions did not present haemolytic risk at concentrations used in formulations for intravenous administration (i.e. 1 or 10 mg/ml).

Immunotoxicity

In a 4-week Wistar rat study (3, 16, 90 mg/kg twice daily), including lymphocyte subset analysis and Plaque-Forming Cell assay using sheep red blood cells, the lack of functional immunotoxicity of ivabradine up to 90 mg/kg twice daily was shown.

Phototoxicity

The potential phototoxicity of ivabradine was assessed using the *in vitro* Neutral Red Uptake test in cultured mouse Balb/c 3T3 fibroblasts. The results showed no cytotoxic effect observed after treatment of cells with ivabradine at concentrations up to 200 µM.

Impurities

The impurities in ivabradine were adequately qualified in a 4-week Wistar rat toxicity study, an *in vitro* Ames test and *in vivo* micronucleus test. No genotoxic potential or differences in safety profile were found.

Antigenicity

The antigenicity of ivabradine was not studied.

Ecotoxicity/environmental risk assessment

As the predicted environmental concentration was above the trigger limit of 0.01 µg/l, the applicant performed a set of studies required in the Phase II A of the assessment partially in accordance with the current draft CHMP guideline (CPMP/SWO/4447/00). The results showed that no adverse environmental impact from use of ivabradine in soil compartment or in sewage treatment plants was expected. Bioaccumulation was also considered of no concern. However, the environmental risk assessment for the aquatic compartment could not be completed due to missing data. Therefore the applicant committed to perform a post-marketing follow-up measure to address this issue.

Discussion on the non-clinical aspects

Pharmacology

The nonclinical pharmacology programme characterised ivabradine as a selective inhibitor of the cardiac pacemaker I_f-current, involved in the regulation of heart rate. This action resulted in a specific heart-rate reduction that affords effective cardioprotection on both ischaemic and stunned myocardium in experimental models.

The cardiac effects of ivabradine were specific of the sinus node, with no effect on left ventricular contractility and relaxation, cardiac conduction (atrioventricular or intraventricular) or ventricular repolarisation. In contrast to beta-blockers, ivabradine efficiently limited exercise-induced tachycardia while preserving the adaptations of myocardial contractility, cardiac output, mean coronary blood flow velocity and vascular resistances observed during exercise.

Ivabradine did not bind to other receptors (including adrenergic, muscarinergic and serotonergic receptors). From preclinical studies at pharmacological doses, there was no indication of safety concern relevant to human on major vital body systems.

Specific studies on the visual system supported that the visual symptoms reported in the clinic did not reflect any toxicity of ivabradine on ocular structures, but rather pointed to a pharmacological effect, secondary to the partial inhibition of I_h in the retina (shares common properties with the cardiac pacemaker current I_f).

In dogs, an overdose of ivabradine was rather well tolerated, and bradycardia was easily and rapidly reversed by beta-stimulating agents such as isoprenaline or dobutamine.

From preclinical studies at pharmacological doses, there is no indication of safety concern relevant to human on major vital body systems, including cardiovascular, visual, CNS, respiratory, gastrointestinal and renal systems.

Pharmacokinetics
The pharmacokinetics of ivabradine was comprehensively described in animal species used for safety evaluation. Ivabradine was rapidly and almost completely absorbed with moderate bioavailability of around 40%, due to a first-pass effect. Plasma protein binding was 60-70%. Kinetics was linear over a large range of doses without time effect. A gender effect was evidenced only in rats, with females being on average 3-fold more exposed than males. Ivabradine and/or its metabolites were rapidly and extensively distributed throughout the body. The most exposed tissue was the uveal tract, especially the pigmented (melanin) and the well-vascularised structures of the eye. The binding of ivabradine and metabolite S 18982 to pigmented structures was reversible, but took a long time, i.e. many weeks. Ivabradine was extensively metabolised by oxidation *via* CYP450. Ivabradine was eliminated with a main half-life of about 2 h in dogs and humans.

Ivabradine distributed into amniotic fluid and was excreted in maternal milk of rats (see 4.3., 4.6. and 5.3. in the SPC).

Toxicology
In the heart of rats, focal myocardial lesions were observed. These lesions were considered to be caused by focal hypoxia, related to the prolonged and/or exaggerated pharmacological effect bradycardia in normal animals, as seen with betablockers. In dogs, the ECG changes were considered an exaggerated pharmacological effect. The QT-interval was not prolonged, when corrected for heart rate reduction.

As a consequence of clinical transient visual symptoms (phosphenes; see clinical safety), electroretinography (ERG) examinations were included in the 12-month repeated dose study in dogs. Some ERG changes were revealed at 6 and 12 months in the cone system at exposures similar to the expected human therapeutic exposure; these were reversed at one week after treatment cessation and at the following treatment-free periods (up to 11 weeks). In the rod system, dark adaptation was only affected in the first few minutes. Shorter time intervals than 6 months were not evaluated. These ERG changes seemed to be related to a reversible pharmacological effect rather than structural toxicity for the following reasons: (1) ERG changes in dogs were reversible, (2) no changes were observed by ophthalmoscopy, histopathology and transmission electron microscopy in the 1-year dog study, (3) no relevant ophthalmological or histopathologic changes were observed in other studies, and (4) HCN channels, which play a role in the mechanism of action of ivabradine, are present in the retina as well as in the heart. This issue has been reflected in SPC (5.3). There was a consistent absence of toxic damage in any ocular structure in association with ivabradine throughout the animal safety programme. Melanin binding did not correlate with retinal function changes in dogs, as ERG changes rapidly reversed upon treatment cessation while significant levels of ivabradine were still present in the ocular structures. The long-term ocular safety of patients exposed to ivabradine has been documented in the development programme up to one year. Additional data on long-term visual safety will be addressed as a post-marketing commitment.

Infrequent thymus atrophy and/or decrease in lymphocyte counts were occasionally reported and were not associated with functional immunotoxicity. Possible changes in immune system will be addressed as a post-marketing commitment.

Cardiac teratogenicity in rats occurred at systemic exposure levels similar to those in patients receiving therapeutic doses of ivabradine. No safety margin could be set and the drug is thus contraindicated during pregnancy and breast-feeding (4.3., 4.6. and 5.3. in the SPC).

Genotoxicity or carcinogenicity studies revealed no clinically relevant changes.

4. Clinical aspects

Introduction

Ivabradine is a heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node, developed for the treatment of chronic stable angina pectoris.

The efficacy and safety of ivabradine in patients with stable angina pectoris were investigated in clinical trials involving nearly 5000 patients, in which ivabradine was administered to more than 3500 patients and healthy volunteers. The main efficacy studies in patients with stable angina pectoris with a randomised, double-blind and parallel-group design included one placebo-controlled, dose-ranging study, two active-controlled double-blind non-inferiority studies versus the standard therapies atenolol and amlodipine, and a double-blind study comparing ivabradine with placebo when both were given in combination with background therapy of amlodipine. In addition, long-term safety studies included a 1-year randomised double-blind study in comparison with atenolol, a 1-year randomised double-blind study comparing two ivabradine doses, and a 1-year open-label extension study in patients from two main efficacy studies. Further, one study was conducted in patients with coronary artery disease for the investigation of the safety of high doses of ivabradine. Possible drug pharmacokinetic and/or pharmacodynamic interactions were investigated in 22 specific studies in healthy volunteers and patients. A few additional studies were ongoing including a 557-patient 5-year open-label extension study from the overall programme with the purpose of documenting the safety of the long-term use of ivabradine.

According to the applicant, all clinical studies were conducted in accordance with the ICH Guideline for Good Clinical Practice, with local regulatory and ethical requirements, and with the Declaration of Helsinki.

Pharmacokinetics

The populations enrolled in the pharmacokinetic studies included healthy volunteers (n=642 in 32 studies), patients with angina pectoris and coronary artery disease with associated diseases (such as diabetes, asthma, hepatic insufficiency, heart failure, renal failure) (n=3102 in 22 studies). *In vitro* studies using human material were performed in order to help the interpretation of pharmacokinetics and metabolic data of ivabradine. Furthermore, population pharmacokinetic meta-analyses were carried out.

Most pharmacokinetic studies used validated specific HPLC fluorescence detection assay for the simultaneous determination of ivabradine and its main circulating active metabolite S 18982. In some studies a more sensitive LC-MS-MS assay (e.g. to quantify other metabolites of ivabradine) was used. An additional method involving solid-phase extraction, LC separation, and fluorescence detection was developed to differentiate between the R and S enantiomer of ivabradine.

Throughout the clinical development of ivabradine, both non-compartmental and compartmental (a population approach using mixed effects model) approaches were used.

Absorption

The absolute bioavailability of ivabradine was around 40%. Absorption was almost complete (around 90%). Both ivabradine and S 18982 (N-desmethyl metabolite of ivabradine) AUC and Cmax values increased linearly with dose after single dose over the dose range of 0.5–24 mg and after multiple doses over the dose range of 2.5–32 mg twice daily. Peak plasma concentrations were reached 0.75-1.5 h after administration. Steady state was achieved within 1 day, and no unexpected accumulation occurred (twice daily dosing). In healthy volunteers, food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30%.

Distribution

The volume of distribution was about 100 L. *In vitro* protein binding studies using human plasma indicated that protein binding was 70% for ivabradine and 70-75% for S 18982. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily was 22 ng/ml. The average plasma concentration was 10 ng/ml at steady-state. Ivabradine was distributed into semen to a negligible content (0.007% of the administered dose).

Metabolism and excretion

Ivabradine was metabolised by oxidation involving O-desmethylation, N-dealkylation (including N-desmethylation and cleavage), and hydroxylation. Metabolism of ivabradine occurred *via* CYP3A4 only. Ivabradine had a low affinity for CYP3A4. Of all metabolites only the N-desmethylated metabolite had sufficiently high plasma concentrations to contribute to the pharmacological effect (exposure about 40% of that of the parent compound); the metabolism of this active substance also involved CYP3A4. The total clearance was 400 ml/min and the renal clearance 70 ml/min. Ivabradine pharmacokinetics was best described by a two compartmental model. The main elimination half-life of ivabradine was close to 2.0 h contributing to approximately 70% of the AUC and the effective half-life was 11 h. The first elimination half-life of S 18982 was close to 2.0 h and the effective elimination half-life was 11 h. Accumulation was minimal. For both compounds, repeated oral dose data were well predictable from single dose data.

All radioactivity in faeces and urine comprised of metabolites with only trace amounts of unchanged compound. Elimination of metabolites was split between faeces and urine (52 and 45% respectively), with essentially the entire dose recovered within 4 days, and greater than 90% of that in urine excreted within 24 hours. About 4% of an oral dose was excreted unchanged in urine; only 2.4-12% of the total radioactivity AUC accounted for by unchanged ivabradine.

Special populations

Population pharmacokinetic analysis of data obtained from nine clinical studies, involving a total of 1010 patients with coronary artery disease, receiving 2.5-20 mg ivabradine b.i.d., revealed that the only significant covariates were age and gender. Exposure for the same dose was 28% higher in females than males. Further analyses have shown that pharmacokinetics (AUC and Cmax) were comparable for $\geq$65, $\geq$70 and >75 year old patient groups. Weight had no influence on pharmacokinetics.

In terms of plasma exposure to ivabradine and metabolites, no relevant difference was observed between patients with chronic renal insufficiency and creatinine clearance above 15 mL/min and the overall population. No data were available in patients with creatinine clearance below 15 mL/min, and therefore ivabradine should be used with precaution in this population (this is reflected in SPC in 4.2 and 4.4).

A study in 12 subjects with mild to moderate hepatic disease (alcoholic cirrhosis of the liver) revealed lower total clearance in these patients than in healthy subjects (24 L/h versus 34 L/h), while renal clearance was increased because of the increased free fraction of ivabradine in subjects with liver impairment. Further, when elevated transaminases (ALT or AST levels >1.5 times normal value) were

used to select patients with hepatic disorders (n=129), no relevant difference in plasma exposure was observed between patients with elevated transaminases and the overall population; in patients with hepatic insufficiency as defined by Child Pugh score up to 7 unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. No data in patients with severe hepatic impairment, and only limited data in patients with moderate hepatic impairment with Child Pugh score >7 were available. Therefore, ivabradine is contra-indicated in patients with severe hepatic failure. (These findings are reflected in SPC in 4.2-4.4).

102 patients with mild to moderate heart failure were enrolled in the clinical studies in the ivabradine group. There was no relevant difference in plasma exposure between patients with heart failure and the overall population. Also diabetes did not have any effect on the pharmacokinetics of ivabradine.

Interactions

In vitro
Pharmacokinetic interactions for ivabradine were extensively studied in *in vitro* studies. Investigations in hepatic microsomal and hepatocyte systems demonstrated that metabolism of ivabradine occurred *via* CYP3A4 only.

As a consequence, the potential for *in vitro* drug-drug interactions was investigated using human liver microsomes incubated with ivabradine (10 µM) and therapeutic agents likely to be co-administered with ivabradine, or substrates and/or inhibitors of CYP3A4.

More than 50 drugs were tested, including alfentanil, alprazolam, amiodarone, amlodipine, cyclosporin A, dexamethasone, diazepam, digitoxin, diltiazem, erythromycin, ethynil estradiol, fluoxetine, josamycin, ketoconazole, losartan, lovastatin, midazolam, nefazodone, nifedipine, paracetamol, quinidine, simvastatin, verapamil and warfarin. Among the tested drugs an *in vitro* interaction was observed for ketoconazole, josamycin, nefazodone, quinidine, cyclosporin A, erythromycin, clarithromycin, verapamil, and diltiazem.

Ivabradine did not inhibit or induce CYP3A4 nor other isoenzymes of P450 in a relevant magnitude.

In vivo

Pharmacokinetic interactions for ivabradine were studied *in vivo* in 15 phase I and 4 phase II studies, in which the co-administered CYP3A4 substrates/inhibitors could be classified as: potent, moderate or weak. In addition, some pharmacokinetic data were collected in phase III trials.

As standard potent inhibitors of CYP3A4, ketoconazole 200 mg once daily for 4 days, and josamycin, 1000 mg twice daily for 4 days led to a 7- 8-fold increase in ivabradine plasma AUC and a 3- 4- fold increase in ivabradine Cmax following single oral administration of ivabradine (10 mg). Exposure to ivabradine's active metabolite, S 18982, was moderately increased (AUC ratio with/without: 1.1 to 1.9). Similar results were obtained following repeated co-administration of ivabradine and ketoconazole. These findings are reflected in sections 4.3 and 4.5 of the SPC.

Verapamil, 120 mg twice daily and diltiazem, 120 mg twice daily are moderate CYP3A4 inhibitors. Co-administration of these drugs caused a 2.1- 3.1-fold increase and a 1.9- 2.4-fold increase of ivabradine plasma AUC and Cmax, respectively, in healthy volunteers. Exposure to S 18982 was also increased (AUC: 1.5- and 1.2-fold increase for verapamil and diltiazem, respectively). In patients, diltiazem caused a ≈3-fold increase for ivabradine plasma AUC and Cmax, and a 1.5- and a 2.3-fold increase for S 18982 AUC and Cmax, respectively. Moderate CYP3A4 inhibition by grapefruit juice caused 2-fold increase in plasma AUC of ivabradine. These findings are reflected in section 4.5 of the SPC.

Lacidipine 4 mg once a day, amiodarone 200 mg once a day, simvastatin 20 mg once a day, sildenafil 50 and 100 mg once a day, omeprazole 40 mg once a day and lansoprazole 60 mg once a day were studied as weak inhibitors and amlodipine 10 mg once a day and warfarin 2-5 mg once a day as a non-inhibitor of CYP3A4. With the exception of lacidipine, which caused a very slight 1.2-fold increase in ivabradine plasma AUC, no modification of ivabradine and S18982 AUC was noted during the co-administration of ivabradine with these drugs. Combination of ivabradine 10 mg twice daily with St John's wort (CYP3A4 inducer) reduced ivabradine AUC by half. These findings are reflected in section 4.5 of the SPC.

Pharmacodynamics

Pharmacology

Heart rate lowering effect

The heart rate reduction was the main pharmacodynamic effect of ivabradine. This was studied in all clinical studies.

In healthy volunteers, the reduction of maximum heart rate at exercise was between 10 to 15% and was sustained between 1 and 12 h. The minimal effective dose was 2-4 mg and substantial incremental reductions in HR were observed with doses up to 16 mg. The relationship between plasma concentration and heart rate decreasing effect plateaued at doses exceeding 10 mg bid.

In patients with stable angina pectoris, a statistically significant dose-dependent absolute decrease in heart rate was present with ivabradine 2.5, 5 and 10 mg b.i.d. relative to placebo, both at peak and trough during rest and exercise (study CL2-009). Results on ivabradine 7.5 mg b.i.d. from studies CL3-017/018/023 in patients with angina pectoris subsequently showed the expected intermediate heart rate reduction relative to the results obtained with 5 and 10 mg b.i.d. The final PK/PD model that used pooled data from 1236 patients with oral doses ranging between 2.5 and 20 mg b.i.d., showed that the heart rate reduction levels off in a dose range of 10-20 mg b.i.d., while substantial incremental relative heart rate reductions were seen when the dosage was increased with intervals of 2.5 mg in a lower dose range of 2.5-10 mg b.i.d. Studies CL2-009 and CL3-019/21/23 in patients with stable angina showed that the maximal decrease in heart rate was achieved within 2-4 weeks after initiation of therapy and indicated no development of pharmacological tolerance in the sinoatrial node. Data on the HR lowering effect of ivabradine in patients are given in Table 3 below.

Table 3: Mean reduction in heart rate at rest and during exercise at peak and trough of drug activity in phase II and III clinical trials

Study and conditions			n	Heart rate reduction (mean ± SD, bpm)						
					Ivabradine (mg b.i.d.)					
				Placebo	2.5	5	7.5	10	15	20
CL2-047	Rest	Peak	51					20.7 ± 12.6	25.6 ± 13.8	30.6 ± 11.9
	ETT	Peak	51					21.0 ± 15.5	25.8 ± 12.9	29.2 ± 14.5
CL2-009	Rest	Peak	256	-2.8 ± 12.7	6.5 ± 11.0*	12.0 ± 13.1*		18.7 ± 10.4*		
		Trough	257	-0.4 ± 10.9	4.5 ± 10.6*	9.5 ± 12.0*		14.2 ± 10.0*		
	ETT	Peak	256	-3.7 ± 9.8	6.5 ± 11.8*	11.0 ± 11.5*		17.7 ± 11.6*		
		Trough	257	-1.6 ± 9.1	5.5 ± 9.8*	8.3 ± 8.9*		13.4 ± 10.5*		
CL3-017	Rest	Peak	444			10.3 ± 12.3	13.5 ± 12.4	16.1 ± 14.6		
		Trough	449			10.2 ± 11.2	14.4 ± 11.9	15.3 ± 13.2		
	ETT	Peak	444			7.5 ± 13.3	9.0 ± 15.0	12.1 ± 15.9		
		Trough	449			7.0 ± 12.6	8.0 ± 13.1	10.6 ± 14.2		
CL3-018	Rest	Peak	513	1.8 ± 13.1		12.2 ± 12.0*	14.7 ± 12.5*			
		Trough	517	5.5 ± 12.0		12.1 ± 11.6*	12.5 ± 11.3*			
	ETT	Peak	511	-1.4 ± 15.3		10.4 ± 16.0*	12.1 ± 14.6*			
		Trough	514	0.1 ± 13.7		10.2 ± 15.0*	10.4 ± 12.8*			
CL3-023	Rest	Trough	637				11.2 ± 12.1	13.0 ± 13.3		
	ETT	Trough	636				13.1 ± 14.1	14.8 ± 14.1		

*Data represent the mean reduction in HR (non-placebo-corrected) between baseline and the end of the study period per dose. Resting HR data were acquired prior to commencement of the ETT. n: sum of the numbers of patients in each row. For CL3-017 (with forced titration from 5 mg to 7.5 mg or 10 mg b.i.d.), n represents the total of the 7.5 mg and 10 mg b.i.d. treatment groups. *: Significantly different from placebo group (CL2-009, Dunnett's test; CL3-018, Student's t-test). ETTs performed on treadmill in CL2-047, CL3-017 and CL3-018 and on bicycle in CL2-009 and CL3-023; HR reduction may thus not be directly comparable among studies.*

Effect on rate-pressure product

The effects on blood pressure of ivabradine were minor and not clinically significant. Its effect on rate pressure product (RPP; heart rate x systolic pressure; "surrogate measure of myocardial oxygen consumption") was largely reflective of its effect on heart rate. Early phase I studies showed evidence of a dose-dependent relationship between ivabradine and RPP at peak exercise.

In patients a clear dose dependent effect of ivabradine on the change in RPP both during rest and exercise was seen. The difference versus placebo was consistently statistically significant at dosages ≥ 5 mg b.i.d. at peak and trough of drug activity. (See the Table 4 below)

Table 4: Mean reduction in RPP at rest and at exercise at peak and at trough of drug activity in phase II and III efficacy trials

Study and conditions			n	Reduction in rate-pressure product (mean ± sd, bpm·mm Hg)				
					Ivabradine (mg b.i.d.)			
				Placebo	2.5	5	7.5	10
CL2-009	Rest	Trough	257	-178 ± 2218	509 ± 1697	1366 ± 1950*	-	1909 ± 1688*
		Peak	254	-167 ± 1952	740 ± 1696*	1740 ± 2059*	-	2621 ± 1672*
	Exercise	Trough	252	-266 ± 3074	737 ± 2950	1142 ± 3354*	-	1543 ± 3526*
		Peak	251	-765 ± 3389	931 ± 3730*	1490 ± 3774*	-	2148 ± 3057*
CL3-017	Rest	Trough	444	-		1328 ± 2007	1918 ± 2191	1992 ± 2310

	Exercise	**Peak**	437	-	1653 ± 2138	2068 ± 2297	2335 ± 2479
		Trough	384	-	785 ± 3420	894 ± 3925	1349 ± 3602
		Peak	388	-	704 ± 3646	882 ± 4189	1429 ± 4212
CL3-018	**Rest**	**Trough**	516	796 ± 2157	1548 ± 1805*	1627 ± 1864*	-
		Peak	512	468 ± 2195	1845 ± 1952*	2113 ± 2087*	
	Exercise	**Trough**	494	301 ± 3727	1645 ± 3970*	1320 ± 3644*	-
		Peak	493	209 ± 4051	1889 ± 3928*	1784 ± 3889*	
CL3-023	**Rest**	**Trough**	637	-	-	1434 ± 2022	1668 ± 2207
	Exercise	**Trough**	632	-	-	2138 ± 3748	2174 ± 4110

*Data (mean ±SD) represent the mean reduction in rate-pressure product (non-placebo-corrected) between baseline and the end of the study period (CL2-009: 14 days; CL3-017: 5 mg b.i.d., 1 month; 7.5 and 10 mg b.i.d. , 4 months (including 1 month on 5 mg b.i.d.); CL3-018: 3 months; CL3-023: 3 months). "n" represents the sum of the numbers of patients in each row. For CL3-017 (which involved forced titration from 5 mg to 7.5 mg or 10 mg b.i.d.) this number represents the total number of patients in the 7.5 mg and 10 mg b.i.d. treatment groups only. * Significantly different from placebo group (CL2-009, Dunnett's test; CL3-018, Student's t-test).*

Effect on cardiac function and haemodynamics

The effects of ivabradine on cardiac and haemodynamic function were mainly assessed in three phase I studies and two phase II studies. These studies showed no clinically relevant effect of ivabradine on cardiac output either at rest, after standing (tilt test), or at exercise, on stroke volume, or on total peripheral resistance.

In 53 patients with congestive heart failure NYHA class II with a left ventricular ejection fraction between 30 and 45% and with a history of coronary artery disease, ejection fraction did not decrease while a decrease of left ventricular systolic and diastolic volumes was observed following repeated administration of ivabradine (10 mg b.i.d.).

Electrophysiological effects

Study CL1-007 (a double-blind placebo-controlled study with treatments randomised in a Latin square design: successive administrations of 3 single oral doses of ivabradine (10 mg, 20 mg, 30 mg) and placebo: was carried out in 12 healthy volunteers using quantitative electrocardiography. This study found no evidence of a deleterious effect of ivabradine on sinus node function, and no effect of treatment on P wave duration, PQ interval, and QRS duration. Heart rate, RR interval, QT interval, and QTcB were the only parameters that showed a significant effect of ivabradine treatment: heart rate was lowered, RR interval increased, uncorrected QT increased, and QTcB (QT corrected according to Bazett's formula) decreased.

The studies CL2-010/014/015 used invasive electrophysiological testing: in these studies a single intravenous dose of ivabradine (0.2 mg/kg) was administered to a total of 35 subjects with a history of cardiac pathology, all of whom required an electrophysiological study or treatment by radiofrequency catheter ablation, but who had a normal or near-normal baseline electrophysiological examination at the time of the study. The administration of ivabradine resulted in a statistically significantly increased corrected sinus node recovery time (SNRTc) of 87-120 ms and 118-123 ms, after 30 and 60 min, respectively. The increase in sinoatrial conduction time (SACT) ranged from 12 to 20 ms after 30 and 60 minutes, but was never statistically significant.

Other effects

The anti-arrhythmic effects of ivabradine were investigated in two phase II studies carried out in patients with atrial fibrillation (AF). The efficacy of a single intravenous infusion of ivabradine (0.2 mg/kg, administered over 1 hour) on either time to restoration of sinus rhythm or 20% reduction in ventricular rate in patients suffering from AF after cardiac surgery was studied. The second study investigated the efficacy of 10 mg ivabradine b.i.d. in preventing paroxysmal AF. These studies did not show any effect of ivabradine on the treatment of post-surgical AF, or on the prevention of paroxysmal AF. There is no evidence of risk of (excessive) bradycardia on return to sinus rhythm when

pharmacological cardioversion is initiated in patient treated with ivabradine. However, in the absence of extensive data, non-urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Neurohumoral reaction to HR lowering effect of a single 30 mg dose was also investigated. Ivabradine had no effect on plasma levels of adrenalin and noradrenalin at rest, and did not influence the rise in plasma levels of these hormones that normally occurs after standing (tilt test) or during exercise.

Pharmacodynamic drug-drug interactions

See also Clinical aspects/ Pharmacokinetics/ Interactions/ *In vivo*.

A large number of interaction studies were conducted with ivabradine 10 mg b.i.d. The co-administration of ivabradine and potent inhibitors of CYP3A4 led to additional heart rate reductions compared to ivabradine monotherapy at rest and a contraindication has now been included in the SPC (4.3). The co-administration of ivabradine and heart rate lowering agents that are moderate inhibitors of ivabradine metabolism such as diltiazem and verapamil showed a somewhat more than additive effect on heart rate.

In an interaction study in healthy volunteers, no pharmacokinetic interaction with atenolol was observed. However, concomitant administration of ivabradine (10 mg b.i.d.) with atenolol (50 mg o.d.) resulted in an additive HR lowering effect both at rest and during exercise. Concomitant administration of ivabradine in patients already treated by amiodarone did not result in a PK interaction and showed that the reduction in heart rate after co-administration was in the expected range (12 to 15 bpm) when results are compared to those obtained on ivabradine monotherapy in stable CAD patients. No pharmacokinetic or -dynamic interaction was observed when ivabradine and digoxin were administered concomitantly.

No clinically significant pharmacodynamic interaction was observed when ivabradine was given concomitantly with imipramine or thioridazine. In a study using repeated doses of both aspirin and ivabradine, no significant effect on the platelet anti-aggregant properties of aspirin were reported.

In two studies, no QTc prolonging effect was observed when ivabradine was used as monotherapy or co-administered with amiodarone, imipramine or thioridazine. Similarly, QT data from co-administration studies with strong CYP3A4 inhibitors using three correction methods (Bazett's, Fridericia's and a population-derived correction) showed no evidence for a QTc prolonging effect of ivabradine at supratherapeutic plasma levels, especially not at the peak of drug activity.

In 12 patients with stable coronary artery disease with no angina pectoris at rest, the concomitant use of sildenafil 50 to 100 mg once daily did not alter heart rate -decreasing effect of ivabradine 10 mg twice daily during this 10-day study.

No long-term efficacy and safety data on the combination of ivabradine with beta-blockers were available. In the phase III clinical trials the following drugs were not restricted and therefore were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, diuretics, dihydropyridine calcium channel blockers, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet agents.

Clinical efficacy

The anti-anginal and anti-ischaemic efficacy of repeated oral doses of ivabradine was evaluated using standardised exercise tolerance tests (ETT) in four efficacy studies in patients with chronic stable angina pectoris (see the Table 5 below). Additionally, the efficacy of ivabradine in preventing angina

symptoms was also evaluated in three long-term (1-year) safety studies. A 5-year open-label extension safety study (CL3-044) was on-going at the time of submission.

The clinical phase II-III development was designed and conducted in accordance with available CHMP guidance and Scientific Advice.

Table 5: Main efficacy studies

Study No Report No	Type of study Study design	Test product(s) Dose regimen and route	Included patients
CL2-006	Phase II Randomised, placebo-controlled, parallel group, dose ranging	Single oral doses ivabradine 5, 10, 15 or 20 mg or Placebo	55 patients: 44 ivabradine (11 patients each dose) and 11
CL2-009	Phase II Randomised, placebo-controlled, parallel group, dose ranging, 2 weeks	Repeated oral doses ivabradine 2.5, 5 or 10 mg b.i.d. or Placebo	360 patients: 90 ivabradine 2.5 mg, 91 ivabradine 5 mg, 88 ivabradine 10 mg, 91 placebo
	Open-label period, 2 or 3months	Repeated oral doses ivabradine 10 mg b.i.d.	173 patients
	Randomised, placebo-controlled, parallel group, run-out, 1 week	Repeated oral doses ivabradine10 mg b.i.d. or Placebo	157 patients: 77 ivabradine, 80 placebo
CL3-017	Phase III Randomised, double-blind, controlled, parallel group, non-inferiority study versus atenolol, 4 months	Repeated oral doses: ivabradine 5 mg b.i.d. then 7.5 or 10 mg b.i.d. or atenolol 50 mg o.d. then 100 mg o.d. Run out period : Placebo or atenolol 50 mg o.d. then 25 mg o.d.	939 patients: 315 ivabradine 7.5 mg 317 ivabradine 10 mg 307 atenolol
CL3-018	Phase III Randomised, double-blind, placebo-controlled, parallel group, superiority study on top of amlodipine, 3 months	Repeated oral doses :ivabradine 5 or 7.5 mg b.i.d. and amlodipine 10 mg o.d. or Placebo and amlodipine 10 mg o.d.	728 patients: 232 ivabradine 5 mg 244 ivabradine 7.5 mg 252 placebo
CL3-023	Phase III Randomised, double-blind, controlled, parallel group, non inferiority study versus amlodipine, 3 months	Repeated oral doses : Ivabradine 7.5 or 10 mg b.i.d. or amlodipine 10 mg o.d.	1195 patients: 400 ivabradine 7.5 mg 391 ivabradine 10 mg 404 amlodipine

Methods

Study participants

Across the dose-finding and main efficacy studies the following inclusion and exclusion criteria were used:

Selection criteria
– Male or female of non-childbearing potential (sterile, hysterectomised, or menopausal for more than 2 years).
– 18 years ≤ age ≤ 75 years.
– Written informed consent.
– History of chronic effort angina pectoris for at least 3 months prior to inclusion. (Effort angina was defined as typical or atypical angina pain associated with physical activity, lasting several minutes and disappearing with cessation of physical activity and/or administration of short-acting nitrates);
– Severity: no angina at rest.
– Clinical stability: no significant change in frequency, severity or triggering activity within 1 month preceding inclusion, and no change in nitrates consumption. Clinical stability was assessed by direct questioning of the patient.
– Documented coronary artery disease:

- a history of myocardial infarction (Q wave and/or cardiac enzyme elevation) (≥3 months before inclusion) or;
- a coronary angioplasty (≥ 6 months before inclusion) or;
- a bypass graft (≥ 3 months before inclusion) or;
- a coronary angiography showing a significant stenosis (≥ 50% stenosis in the proximal two third of at least one of the major coronary arteries), the stenosis being read as the relative diameter reduction or;
- a positive scintigraphic test showing exercise-induced reversible ischaemia in patients without left bundle branch block or;
- a positive stress echocardiography showing regional wall motion abnormalities with failure of the normal rise in left ventricular ejection fraction with exercise.

– Analysable ST segment on 12-lead ECG: morphology of ST segment within normal limits, no electrocardiographic state that precluded ST segment interpretation at rest or during exercise, sinus rhythm
– Positive ETT: at selection (end of wash-out period). Positivity is defined below.

Inclusion criteria
– At the end of the run-in period, patients were required to have a second qualifying ETT that met both of the following criteria:

- Positivity criteria: occurrence of limiting angina and significant ST segment depression, defined as ST segment depression of at least 1 mm compared to the value at rest, horizontal or down sloping and persisting for at least 0.08 seconds after J-point, on at least three consecutive complexes. Both events should occur between 3 and 12 minutes following initiation of the exercise test. If the ETT was interrupted before reaching positivity for any reason, the patient will not be included.
- Stability criteria: the stability of the ETT criteria was assessed between the selection and inclusion visits on the parameter "time to 1 mm ST segment depression" recorded at each minute. The values have to be within ± 20% or ± 1 min of each other. If stability could not be demonstrated on the second ETT, a third pre-treatment ETT could be performed after at least 24 h. The patient should then continue to take placebo until this third test is completed. The patient could be included if stability criteria could be verified between any two of the three ETT performed.

– Compliance to placebo: the calculated compliance should be ≥ 80% and ≤ 130%. In addition, the patient should not have missed more than one full daily dose (i.e., the patient should not have missed four or more consecutive capsules).

Non-selection and non-inclusion criteria
Patients with one of the following criteria could not be included in the study:
– Recent acute myocardial infarction, coronary bypass surgery (less than 3 months before inclusion) or coronary angioplasty (less than 6 months before inclusion).
– Unstable angina, Prinzmetal angina or microvascular angina.
– Known high-grade left main coronary artery disease that has not been surgically bypassed or mechanically improved.
– Patient who cannot perform exercise tests
– Clinically significant heart disease other than coronary artery disease
– Congestive heart failure stage III or IV NYHA.
– Symptomatic hypotension.
– Uncontrolled hypertension (systolic blood pressure at rest > 180 mmHg or diastolic blood pressure at rest > 100 mmHg).
– Atrial fibrillation, flutter, pacemaker or cardioverter-defibrillator implantation.
– ECG abnormalities that would confound ETT interpretation
– Hepatic disorders (ALT > 3 times normal value), renal failure (serum creatinine level > 180 µmol/l).

– Electrolyte disorders
– Anaemia (haemoglobin < 100 g/l).
– Thyroid disorders (unless stable and controlled by thyroxin treatment for at least 3 months).
– Any treatment with unauthorised concomitant medication that could not be interrupted for the duration of the study
– Treatment with bepridil within 7 days prior to selection.
– Treatment with amiodarone within 3 months prior to selection.
– Contra-indication to ivabradine:
  - 2nd and 3rd degree atrioventricular block,
  - resting bradycardia with heart rate < 50 bpm or sick sinus syndrome.
– Severe disease likely to interfere with the study in the investigator's judgement.
– Known carrier of HBs antigen, HIV or HCV antibodies (with some exceptions)
– History of severe psychiatric or behavioural disorders likely to interfere with the study
– History of serious abnormal drug reaction.
– Use of investigational drug within 30 days of pre-selection, or concurrent therapy with an investigational drug(s).

Study design

In all the efficacy studies, efficacy was evaluated primarily by standardised ETT using either bicycle or treadmill ergometry. Although there were some variations among studies, the basic study design was as follows:

- Pre-selected patients underwent a 2-7-day "run-in" period on placebo during which previous anti-anginal medication was discontinued.
- At the end of the "wash-out" period, at the selection visit, patients performed a first ETT.
- This was followed by a 1-week, single-blind "run-in" period on placebo, at the end of which, at the inclusion visit, a second ETT was performed.
- Included patients were then randomised to the various treatment groups, and treatment was administered in double-blind fashion.
- At the end of the double-blind treatment period, patients performed an ETT at the trough (at the end of the dosing interval) and, in most studies, at the peak (~4 h after dosing) of the drug activity.

Study treatments
See table "Main efficacy studies" above.

In the main efficacy studies concomitant anti-anginal medication was withdrawn during the run-in period and not permitted throughout the study; only short-acting nitrates were permitted as rescue medication. Drugs that could interfere with the interpretation of ST segment changes (including class I antiarrhythmic agents, digitalis, monoamine oxidase inhibitors) were also not permitted, similarly to agents with known or suspected pharmacokinetic/ pharmacodynamic interaction with ivabradine. Other medications such as angiotensin converting enzyme inhibitors, angiotensin II antagonists, diuretics, short acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet agents could be continued.

Study objectives
See under "Results" for each study.

Outcomes and endpoints
According to the CHMP guideline, the primary anti-anginal efficacy end-point was total exercise duration (TED) in phase III efficacy studies, time to limiting angina (TLA) and time to 1 mm ST segment depression (TST) in the phase IIb dose-ranging study. Time to angina onset (TAO), time to limiting angina (TLA) and time to 1 mm ST segment depression (TST) were also measured. The main analysis was always performed on data gathered during ETT performed at the trough of drug activity

but data were also gathered during ETT performed at the peak of drug activity. Also the occurrence of anginal pain and the concomitant use of short-acting nitrates were documented as secondary endpoints.

Sample size

The number of patients required in each study was calculated to achieve a significant result for the primary efficacy criterion with a power of at least 95% (80% for the phase IIb study).

Procedures for randomisation and blinding

The randomisation was non-adaptive, non-centralised and without stratification; it was balanced between treatment groups and performed using permutation blocks with a fixed size of therapeutic units.

For blinding purposes, the different doses of ivabradine, comparator drugs, or placebo were supplied as units of identical weight, appearance, and taste; packaging and labelling were also identical for all blinded treatments. Central reading of ETT data was performed retrospectively by cardiologists who were independent of the study recruitment and who were blind to the treatment allocation, concomitant treatments, past medical history, selection/inclusion/non-inclusion criteria and investigators' evaluation of ETT parameters. In studies CL3-018 and CL3-023 comparison of ETT data from before and after randomisation was prevented.

Statistical methods

In the dose-ranging study CL2-009 two primary efficacy criteria were specified, i.e. time to limiting angina and time to 1 mm ST segment depression; treatment groups were compared using a one-way analysis of variance, followed by pairwise comparisons versus placebo using Dunnett's procedure. In the phase III efficacy studies the primary efficacy criterion was total exercise test duration; comparisons between each ivabradine dose and the reference were performed using a one-sided Student's test based on the overall general linear model (least-squares norm) with baseline as covariate and country as a random factor. In the phase III efficacy studies, each ivabradine dose was compared with the reference using a hierarchical stepwise procedure.

Results

Study Participants

Patient demographics and characteristics at baseline in the main efficacy studies are given in the Table 6 below. The patient population was sufficiently representative of the target population with chronic stable angina pectoris.

Table 6: Patient demographics and characteristics at baseline in main efficacy studies, randomized sets

	CL2-006 N = 55	CL2-009 N = 360	CL3-017 N = 939	CL3-018 N = 728	CL3-023 N = 1195
Age (years)	56.4 ± 8.0	58.5 ± 9.2	61.2 ± 8.5	60.4 ± 8.0	59.7 ± 8.9
Age range (years)	40 – 72	35 – 86	33 – 79	39 – 80	33 – 83
Age ≥65 years (%)	N/A	28.6	38.9	32.8	30.7
Male (%)	100	89.7	85.0	80.8	86.5
Ethnicity (%)					
Caucasian	100	99.4	81.9	96.4	99.9
Asian	0	0.6	17.5	0.4	0
Black	0	0	0.3	0.3	0
Other	0	0	0.3	2.9	0.1
Supine SBP (mmHg)	134.3 ± 15.6	133.7 ± 16.3	136.2 ± 16.9	132.4 ± 14.0	133.2 ± 16.3
Supine DBP (mmHg)	83.8 ± 7.5	81.3 ± 8.2	81.1 ± 9.1	80.5 ± 7.4	81.5 ± 8.1
Supine HR (bpm)	63.5 ± 9.7	69.7 ± 10.3	74.7 ± 11.2	76.5 ± 11.2	73.0 ± 11.6
Disease duration (months)	N/A	68.1 ± 63.9	79.7 ± 74.0	82.2 ± 73.9	71.3 ± 68.6
Angina grade[a] (%)					
Grade I	N/A	17.8	20.7	9.3	14.2
Grade II	N/A	66.4	70.5	69.1	67.4
Grade III	N/A	15.8	8.8	21.6	18.4
Grade IV	N/A	0	0	0	0
Frequency of angina attacks[b] (attacks/week)	N/A	5.3 ± 7.9	3.39 ± 9.29	3.13 ± 5.21	5.11 ± 7.68
Previous MI (%)	54.6	36.7	53.9	66.8	44.0
Previous CABG (%)	9.1	16.4	18.6	16.6	14.1
Previous PTCA (%)	7.3	18.3	19.8	11.7	11.5
Medical history					
Hypertension (%)	56.4	60.7	52.6	69.6	59.1
Diabetes (%)	1.8	16.1	21.2	23.8	12.6
Hyperlipidaemia (%)	0	40.3	57.2	56.9	44.2
Obesity (%) BMI>30Kg/m2	N/A	18.3	22.2	27.3	17.7
Previous anti-anginal medication (%)					
Organic nitrates	96.4	68.6	85.3	89.1	90.0
β-blockers	58.2	49.7	62.8	58.9	60.8
CCBs	52.7	30.3	26.8	28.3	19.7

[a] *Canadian Cardiovascular Society Functional Classification*
[b] *During run-in period*
CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; DBP, diastolic blood pressure; MI, myocardial infarction; N/A, data not available; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure.

Dose response studies

Study CL2-006: Single-administration phase IIa dose-ranging study. Dose ranging evaluation of the safety and efficacy of 4 single oral doses of S-16257-2 (5 mg – 10 mg – 15 mg – 20 mg) and placebo in 50 hospitalised patients with chronic stable angina pectoris.

The objective of this study was to determine the safety and efficacy of 4 single oral doses of ivabradine compared to placeco in stable effort angina. The study was a randomized, controlled, double-blind, five way, parallel group trial. Fifty-five male patients presenting myocardial ischemia on exercise test were included into the study. The efficacy was evaluated at baseline, 2 hours after dosing and 10 to 11 hours after dosing.

Ivabradine produced a statistically significant heart rate lowering effect during exercise with the doses of 10 and 20 mg after 10 hours in comparison to placebo. The study failed to show any dose effect relationship in lowering heart rate. No consistent dose related changes in any of the exercise tolerance efficacy criteria were seen. A trend for an increase in the time to 1 mm ST segment depression in comparison to placebo at 10 and 15 mg doses was noted.

Study CL2-009: Phase IIb dose-ranging study. Dose ranging evaluation of the anti-anginal efficacy and safety of three oral doses (2.5, 5, 10 mg b.i.d.) of S 16257 in comparison to placebo in 360 patients with stable effort angina pectoris. A 2-week multicentre, parallel group, double blind,

randomised, placebo-controlled trial (P1-P2 period). Followed by a 2 or 3-month safety study of S 16257 (10 mg b.i.d., open design) (P3 period). Followed by a 1-week run-out period (10 mg b.i.d. or placebo in parallel groups, double-blind, randomised) (P4 period).

This phase IIb trial was the first repeated oral dose study in patients. The objective of the first part of this study was to determine a safe and effective oral dose from a range of three doses of ivabradine as compared to placebo during 2 weeks in the treatment of chronic stable angina pectoris, assessed on exercise-induced ischemia.

Ivabradine caused a dose-dependent reduction in heart rate at all doses and showed anti-ischaemic and anti-anginal effects during exercise tolerance test at the trough of drug activity over a 14-day treatment period (see the Table 7 below). The following open and run-out periods confirmed the anti-ischaemic and anti-anginal effects of 10 mg b.i.d. ivabradine and did not show rebound phenomenon and pharmacological tolerance.

Table 7: CL2-009 (P1-P2 double-blind period): main ETT results at the trough of drug activity

		Per-protocol set				
Treatment group	n	Baseline	Change from baseline	Between-group p-value [a]	Estimated difference from placebo (SE)	95% CI [b]
Time to 1 mm ST segment depression (s)						
Placebo	68	369.1 ± 119.0	9.0 ± 63.6			
2.5 mg b.i.d.	64	343.7 ± 120.7	32.0 ± 74.3	0.016	23.0 (12.9)	–7.6; 53.5
5 mg b.i.d.	59	364.1 ± 119.3	44.1 ± 80.1		35.2 (13.2)	**4.0; 66.3**
10 mg b.i.d.	66	370.2 ± 120.8	46.2 ± 78.2		37.2 (12.8)	**6.9; 67.5**
Time to limiting angina (s)						
Placebo	68	417.8 ± 115.6	12.7 ± 51.3			
2.5 mg b.i.d.	64	402.5 ± 121.0	22.5 ± 55.4	0.049	9.8 (10.2)	–14.4; 33.9
5 mg b.i.d.	59	432.8 ± 124.0	27.2 ± 56.8		14.5 (10.4)	–10.1; 39.2
10 mg b.i.d.	66	430.5 ± 125.4	40.8 ± 69.3		28.1 (10.1)	**4.1; 52.0**
Time to angina onset (s)						
Placebo	68	352.8 ± 98.2	24.7 ± 64.2			
2.5 mg b.i.d.	64	330.5 ± 105.4	37.6 ± 57.7	0.003	13.0 (12.2)	–15.8; 41.8
5 mg b.i.d.	59	355.6 ± 110.9	38.8 ± 81.7		14.2 (12.4)	–15.3; 43.6
10 mg b.i.d.	66	351.5 ± 123.1	69.4 ± 74.8		44.7 (12.1)	**16.1; 73.3**

[a] *statistical analysis of treatment effect by one-way analysis of variance.*
[b] *Dunnett's 95% confidence interval, significant results are printed in bold.*

Main studies

Study CL3-017: Non-inferiority study versus atenolol. Evaluation of the anti-anginal efficacy and safety of oral chronic administration of ivabradine (5 mg b.i.d. then 7.5 mg b.i.d. or 10 mg b.i.d.) compared to atenolol (50 mg o.d. then 100 mg o.d.) in patients with stable effort angina pectoris. A 4-month international multicentre, parallel group, double-blind, randomised, controlled trial.

The primary objective of this study was to demonstrate the non-inferiority of ivabradine (7.5 mg b.i.d. or 10 mg b.i.d.) versus atenolol 100 mg o.d. at the trough of drug activity after 4 months of treatment in patients suffering from stable angina pectoris. The efficacy was assessed on the change from baseline to last value of total duration of a treadmill exercise tolerance test at the trough of drug activity considering a clinical non-inferiority limit equal to -35 seconds.

In all treatment groups, the TED increased by approximately 1.5 minutes at the end of the study as compared to baseline after the 4-month treatment period at the trough of drug activity (see the Table 8 below). The non-inferiority of ivabradine 7.5 and 10 mg b.i.d. versus atenolol 100 mg o.d. was demonstrated. TLA and TAO increased by 1.5 minutes and more than 2 minutes, respectively, in the three treatment groups. TST increased by approximately 1.5 minutes in the three treatment groups. At peak of exercise the decrease in HR was greater in patients treated with atenolol (-14.0 bpm) than in

those treated with ivabradine (-8.6 bpm and -10.3 bpm in the ivabradine 7.5 and 10 mg b.i.d. group respectively) showing that ivabradine induced a similar improvement in exercise capacity to atenolol for a comparatively smaller heart rate reduction.

A decrease by two thirds in the mean number of angina attacks/week and in the mean short acting nitrates´consumption/ week at end of the study as compared to baseline was seen in all groups.

During the first month ivabradine was dosed 5 mg b.i.d. and atenolol 50 mg o.d. The anti-anginal and anti-ischaemic effects were significant after 1-month treatment with ivabradine; non-inferiority versus atenolol 50 o.d. was demonstrated in the main analysis [change in TED at through of drug activity 64.2 ± 104.0 sec (SE) in the ivabradine 5 mg bid group; 60.0 ± 114.4 sec in the atenolol 50mg group]. Importantly, regarding the comparison between ivabradine 7.5 and 10 mg b.i.d., at the trough and at the peak of drug activity, no statistically significant differences were observed between 7.5 mg bid and 10 mg b.i.d doses of ivabradine; therefore an ivabradine dose-effect relationship was not observed in this study. The absence of rebound phenomenon after ivabradine discontinuation was confirmed in this study.

Table 8: Study CL3-017 ETT results at trough and peak of drug activity, 4-month period, non-inferiority analyses

		End – baseline (s)	Ivabradine 7.5 mg b.i.d. (N = 300)	Ivabradine 10 mg b.i.d. (N = 298)	Atenolol 100 mg o.d. (N = 286)
TED (s)	At the trough of drug activity	Mean ± SD	86.8 ± 129.0	91.7 ± 118.8	78.8 ± 133.4
		E (SE)[a]	10.26 (9.45)	15.69 (9.46)	
		95% CI[b]	[-8.28 ; 28.80]	[-2.88 ; 34.25]	
		p-value[c]	p < 0.001	p < 0.001	
	At the peak of drug activity	Mean ± SD	93.8 ± 150.9	99.8 ± 132.5	108.9 ± 133.0
		E (SE)[a]	-11.46 (10.06)	-5.39 (10.10)	
		95% CI[b]	[-31.21 ; 8.29]	[-25.21 ; 14.43]	
		p-value[c]	p = 0.010	p = 0.002	
TLA (s)	At the trough of drug activity	Mean ± SD	91.8 ± 131.1	96.9 ± 121.2	85.4 ± 133.7
		E (SE)[a]	9.33 (9.65)	15.07 (9.65)	
		95% CI[b]	[-9.60 ; 28.26]	[-3.86 ; 34.01]	
		p-value[c]	p < 0.001	p < 0.001	
	At the peak of drug activity	Mean ± SD	99.2 ± 150.9	104.9 ± 132.6	117.2 ± 132.5
		E (SE)[a]	-13.56 (10.13)	-7.57 (10.16)	
		95% CI[b]	[-33.45 ; 6.34]	[-27.51 ; 12.38]	
		p-value[c]	p = 0.017	p = 0.004	
TAO (s)	At the trough of drug activity	Mean ± SD	145.2 ± 153.4	139.6 ± 140.6	135.2 ± 154.7
		E (SE)[a]	12.11 (11.51)	10.14 (11.55)	
		95% CI[b]	[-10.48 ; 34.71]	[-12.53 ; 32.81]	
		p-value[c]	p < 0.001	p < 0.001	
	At the peak of drug activity	Mean ± SD	165.1 ± 161.1	162.1 ± 148.6	178.9 ± 151.9
		E (SE)[a]	-10.91 (11.60)	-10.45 (11.66)	
		95% CI[b]	[-33.67 ; 11.85]	[-33.33 ; 12.43]	
		p-value[c]	p = 0.019	p = 0.018	
TST (s)	At the trough of drug activity	Mean ± SD	98.0 ± 153.7	86.9 ± 128.2	95.6±147.5
		E (SE)[a]	4.26 (10.74)	-3.32 (10.75)	
		95% CI[b]	[-16.81 ; 25.34]	[-24.41 ; 17.78]	
		p-value[c]	p < 0.001	p = 0.002	
	At the peak of drug activity	Mean ± SD	108.4 ± 165.8	95.4 ± 133.6	140.5 ± 141.9
		E (SE)[a]	-28.25 (11.00)	-38.56 (11.04)	
		95% CI[b]	[-49.84 ; -6.66]	[-60.24 ; -16.88]	
		p-value[c]	p = 0.270	p = 0.626	

Non-inferiority tests of ivabradine (7.5 mg, 10 mg) as compared to atenolol 100 mg. Non-inferiority limit: -35 s. One-sided type I error rate: 0.025. [a] Estimate (Standard Error) of ivabradine minus atenolol effects: difference between group means adjusted for baseline and country factor,) parametric approach. [b] 95% CI of the estimate (two-sided), in bold lower limit to be compared to - 35s. [c] Student's t test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor.

Study CL3-023: Non-inferiority study versus amlodipine. Evaluation of the anti-anginal efficacy and safety of oral chronic administration of ivabradine (7.5 mg b.i.d. or 10 mg b.i.d.) compared to amlodipine (10 mg o.d.), in patients with stable effort angina pectoris. A 3-month randomised double-blind controlled parallel-group international multicentre trial.

The main objective of the study was to demonstrate the non-inferiority of ivabradine (7.5 mg b.i.d. or 10 mg b.i.d.) in comparison to amlodipine (10 mg o.d.) on the improvement over a 3-month treatment period of TED evaluated by ergometric bicycle ETT at the trough of drug activity. The non-inferiority limit was set at -30 seconds.

Over the 3-month treatment period the improvement in TED was 27.6 s in the ivabradine 7.5 mg b.i.d. group, 21.7 s in the ivabradine 10 mg b.i.d. group and 31.2 s in the amlodipine 10 mg o.d. group at the trough of drug activity (see the Table 9 below). The non-inferiority of both doses of ivabradine compared to amlodipine 10 mg o.d. was demonstrated ($p < 0.001$) within the set equivalence limit. The efficacy was reached within the first month. The improvement in TLA and TAO of 0.5 minute and 1 minute, respectively were similar in the three treatment groups. Regarding the anti-ischaemic effect, TST was also significantly increased by 0.7 minutes in the three treatment groups.

A decrease by two thirds in the mean number of angina attacks/week and in the mean short acting nitrates´consumption/ week at the end of the study as compared to baseline was seen in all groups.

No difference in exercise capacity improvement was observed between ivabradine 7.5 mg b.i.d. and 10 mg b.i.d. doses at the trough of drug activity, except that ivabradine at the dose of 7.5 mg bid significantly increased mean total work while ivabradine 10 mg bid had no statistically significant effect. For a discussion of issues related to non-inferiority criteria in this study and the comparability to amlodipine see discussion on clinical efficacy.

Table 9: Study CL3-023 ETT criteria at the trough of drug activity, summary of non-inferiority analyses

	End – baseline (s)	Ivabradine 7.5 mg b.i.d. (N = 381)	Ivabradine 10 mg b.i.d. (N = 376)	Amlodipine 10 mg o.d. (N = 398)
TED (s)	Mean ± SD	27.6 ± 91.7	21.7 ± 94.5	31.2 ± 92.0
	E (SE)[a]	-1.79 (6.55)	-6.60 (6.58)	
	95% CI[b]	[-14.64 ; 11.06]	[-19.52 ; 6.31]	
	p-value[c]	p < 0.001	p < 0.001	
TLA (s)	Mean ± SD	29.9 ± 93.3	22.9 ± 94.7	32.7 ± 92.1
	E (SE)[a]	-1.20 (6.59)	-6.96 (6.63)	
	95% CI[b]	[-14.14 ; 11.74]	[-19.97 ; 6.04]	
	p-value[c]	p < 0.001	p < 0.001	
TAO (s)	Mean ± SD	64.7 ± 104.9	59.7 ± 110.8	66.6 ± 99.1
	E (SE)[a]	-0.60 (7.44)	-4.6 (7.47)	
	95% CI[b]	[-15.19 ; 13.99]	[-19.26 ; 10.06]	
	p-value[c]	p < 0.001	p < 0.001	
TST (s)	Mean ± SD	44.9 ± 98.6	34.7 ± 104.5	39.7 ± 103.2
	E (SE)[a]	6.51 (7.19)	-1.83 (7.22)	
	95% CI[b]	[-7.6 ; 20.61]	[-16.00 ; 12.34]	
	p-value[c]	p < 0.001	p = < 0.001	

Non-inferiority tests of ivabradine (7.5 mg, 10 mg) as compared to amlodipine 10 mg. Non-inferiority limit: -30 s One-sided type I error rate: 0.025. [a] Estimate (Standard Error) of ivabradine minus amlodipine effect: difference between group means adjusted on baseline and country factor. [b] 95% CI of the estimate (two-sided), in bold lower limit to be compared to - 30s. [c] Student's t test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor.

<u>*Study CL3-018: Study versus placebo on top of amlodipine.*</u> *Evaluation of the anti-anginal efficacy and the safety of oral chronic administration of ivabradine (5 mg b.i.d. or 7.5 mg b.i.d.) versus placebo in association to background therapy with amlodipine (10 mg o.d.) in patients with stable effort angina pectoris. A 3-month international multicentre, parallel group, double-blind, randomised, controlled trial.*

The main objective of the study was to demonstrate that after a 3-month treatment period, ivabradine (5 mg or 7.5 mg b.i.d.) was more efficacious than placebo when given in combination with amlodipine (10 mg o.d.) on the improvement of TED at the trough of drug activity in stable angina patients insufficiently controlled by amlodipine alone, evaluated on a treadmill ETT.

The study showed no significant antianginal and anti-ischaemic effect with ivabradine 5 mg and 7.5 mg b.i.d. as compared to placebo at the trough of drug activity on top of a background therapy with amlodipine (see Table 10 below). At the peak of drug activity, ivabradine at the doses of 5 mg bid and 7.5 mg bid was found to be clinically superior to placebo for TED (30 and 23 s, respectively) and TAO (48 s and 32 s, respectively), and 5 mg bid for TLA (30 s) and time to TST (31 s). Heart rate and rate pressure product significantly decreased with both ivabradine doses as compared to placebo. No significant differences between the 5 mg and 7.5 mg b.i.d. ivabradine doses were found.

Table 10: Main ETT results from study CL3-018

Treatment group	Baseline mean ± SD	Change after treatment mean ± SD	Adjusted difference from placebo (SE)	95% CI[a]	p-value[a]
Trough of drug activity					
Total exercise duration (s)					
Placebo	582.8 ± 142.8	52.5 ± 113.7			
Ivabradine 5 mg b.i.d.	596.8 ± 138.7	62.4 ± 139.7	13.06 (10.88)	–8.29; 34.42	0.115
Ivabradine 7.5 mg b.i.d.	585.0 ± 141.6	58.3 ± 110.9	7.50 (10.79)	–13.69; 28.68	0.244
Time to 1 mm ST segment depression (s)					
Placebo	496.1 ± 164.6	74.9 ± 147.2			
Ivabradine 5 mg b.i.d.	508.3 ± 163.0	84.5 ± 154.7	12.96 (13.15)	–12.87; 38.79	0.162
Ivabradine 7.5 mg b.i.d.	505.8 ± 165.2	81.6 ± 140.2	9.87 (13.00)	–15.66; 35.40	0.224
Time to angina onset (s)					
Placebo	476.6 ± 145.0	89.9 ± 126.3			
Ivabradine 5 mg b.i.d.	491.5 ± 145.2	105.2 ± 166.7	18.70 (12.93)	–6.70; 44.09	0.074
Ivabradine 7.5 mg b.i.d.	475.5 ± 145.6	104.9 ± 138.2	15.41 (12.84)	–9.81; 40.63	0.115
Peak of drug activity					
Total exercise duration (s)					
Placebo	581.2 ± 142.6	58.4 ± 124.0			
Ivabradine 5 mg b.i.d.	595.4 ± 137.6	84.1 ± 150.1	30.15 (11.80)	6.97; 53.32	0.005
Ivabradine 7.5 mg b.i.d.	583.0 ± 141.1	79.0 ± 124.2	23.05 (11.74)	0.01; 46.10	0.025
Time to 1 mm ST segment depression (s)					
Placebo	493.9 ± 163.9	74.1 ± 159.8			
Ivabradine 5 mg b.i.d.	507.7 ± 160.9	100.4 ± 161.7	31.03 (13.93)	3.68; 58.38	0.013
Ivabradine 7.5 mg b.i.d.	502.8 ± 164.8	96.5 ± 152.1	25.74 (13.85)	–1.45; 52.94	0.032
Time to angina onset (s)					
Placebo	476.2 ± 144.5	98.9 ± 144.0			
Ivabradine 5 mg b.i.d.	490.4 ± 144.5	142.6 ± 168.4	47.54 (13.75)	20.55; 74.53	< 0.001
Ivabradine 7.5 mg b.i.d.	473.8 ± 146.2	130.6 ± 144.1	32.21 (13.70)	5.31; 59.11	0.010

[a] *analysed using a superiority test for ivabradine compared with placebo, with a one-sided type I error rate of 0.025.*

Long-term persistence of efficacy

Long-term efficacy of ivabradine was assessed (as a secondary end-point) in three 1-year safety studies, CL3-019, CL3-021, and CL3-022, and in an ongoing 5-year safety study CL3-044.

Study CL3-019: This was a 1-year, randomised, double-blind, controlled, parallel group, multicentre trial comparing ivabradine 10 mg b.i.d. to atenolol 100 mg o.d. in outpatients with stable effort angina pectoris. A total of 318 patients were included; 212 in ivabradine and 106 in the atenolol group. The principal efficacy criterion (defined as a secondary objective) was to compare the anti-anginal efficacy of ivabradine vs. atenolol by assessing the mean number of angina attacks per week and the mean consumption of short acting nitrates per week (based on information reported in the patients' diary).

Study CL3-021: This was a 1-year multicentre, parallel group, double-blind, randomised trial comparing two ivabradine doses (5 mg b.i.d. versus 7.5 mg b.i.d.) in patients with stable effort angina pectoris. A total of 386 patients were included: 198 in the 5 mg b.i.d. group and 188 in the 7.5 mg b.i.d. group. The principal efficacy criterion (defined as a secondary objective) was to assess the clinical anti-anginal activity of ivabradine within each of the 2 dose groups, and to compare the clinical anti-anginal activity of the 2 doses of ivabradine (5 mg b.i.d. and 7.5 mg b.i.d.), by assessing the following parameters that were recorded based on the patient diary: mean number of angina attacks per week, and the mean consumption of short acting nitrates units per week.

Study CL3-022: This was a 12-month international multicentre, open extension study of ivabradine (7.5 mg b.i.d.) in patients with stable effort angina pectoris including patients from studies CL3-017 or CL3-018. A total of 660 patients were included: 391 from study CL3-017, and 269 from study CL3-018. The principal efficacy criterion (defined as a secondary objective) was the mean number of angina attacks per week and mean consumption of short acting nitrates per week (based on the data recorded in the patient's diary and collected at each visit).

The main inclusion criteria in studies 019/021 for patients were in general: age ≥ 18 years, with history of chronic angina pectoris for at least 3 months prior to inclusion and with defined severity (no angina at rest and at least one angina attack per month during the last 3 months or a positive exercise tolerance test within 6 months prior to inclusion) and clinical stability (no significant change in frequency, severity or triggering activity within one month preceding inclusion and no changes in nitrates consumption). Anti-anginal drugs (except for beta-blockers and non-dihydropyridine calcium channel blockers) prescribed prior to study entry could be continued in studies 021/022.

For studies CL3-019 and CL3-021, there were sustained significant reductions with ivabradine treatment in angina attack frequency and short-acting nitrates use between baseline and the end of the studies. Results on angina attacks and short-acting nitrate use are shown in the tables 11-12 below:

Table 11: Angina attack frequency by visit in long-term safety studies CL3-019, CL3-021, and CL3-022

Study, treatment group	n	Baseline	Change from baseline				Difference M12 – baseline		Difference from comparator	
			M3	M6	M9	M12[a]	E (SE)	95% CI	E (SE)	95% CI
CL3-019										
Ivabradine 10 mg b.i.d.	204	1.99 ± 4.19	–1.13 ± 3.48	–1.51 ± 4.01	–1.55 ± 4.36	–1.33 ± 4.27	–1.33 (0.37)	–2.05; –0.61	–0.54 (0.63)	–1.79; 0.71
Atenolol 100 mg o.d.	102	2.04 ± 2.89	–1.12 ± 2.11	–0.83 ± 6.97	–1.51 ± 2.50	–0.79 ± 6.73	–0.79 (0.52)	–1.81; 0.23		
CL3-021										
Ivabradine 5 mg b.i.d.	191	2.87 ± 5.25	–1.52 ± 3.48	–2.04 ± 4.73	–2.01 ± 4.94	–1.91 ± 4.79	–1.91 (0.32)	–2.55; –1.28		
Ivabradine 7.5 mg b.i.d.	179	2.29 ± 3.87	–1.31 ± 3.42	–1.65 ± 3.49	–1.47 ± 3.74	–1.20 ± 4.14	–1.20 (0.34)	–1.86; –0.54	0.71 (0.47)	–0.20; 1.63
CL3-022										
Ivabradine 7.5 mg b.i.d.	647	0.77 ± 2.09	0.08 ± 2.58	–0.07 ± 2.24	–0.07 ± 2.34	–0.10 ± 2.14	–0.100 (0.084)	–0.265; 0.065	–	–

[a] *Visit is M12 for the PPS and last visit under treatment for the FAS; other data for FAS.*

Table 12: Short-acting nitrates use by visit in long-term safety studies CL3-019, CL3-021, and CL3-022

Study, treatment group	n	Baseline	Change from baseline				Difference M12 – baseline		Difference from comparator	
			M3	M6	M9	M12[a]	E (SE)	95% CI	E (SE)	95% CI
CL3-019										
Ivabradine 10 mg b.i.d.	204	0.90 ± 2.19	–0.42 ± 1.71	–0.55 ± 1.95	–0.53 ± 2.23	–0.45 ± 2.36	–0.45 (0.19)	–0.82; –0.08	0.64 (0.33)	–0.01; 1.28
Atenolol 100 mg o.d.	101	1.50 ± 3.58	–0.86 ± 2.99	–1.14 ± 3.45	–1.19 ± 3.37	–1.08 ± 3.26	–1.08 (0.27)	–1.61; –0.56		
CL3-021										
Ivabradine 5 mg b.i.d.	191	2.15 ± 6.09	-1.14 ± 4.04	–1.39 ± 4.13	–1.46± 4.22	–1.17 ± 4.27	–1.17 (0.32)	–1.79; –0.55		
Ivabradine 7.5 mg b.i.d.	179	1.66 ± 3.92	–0.94 ± 3.51	–1.22 ± 3.61	–1.09 ± 3.97	–0.72 ± 4.48	–0.72 (0.33)	–1.36; –0.08	0.45 (0.45)	–0.45; 1.34
CL3-022										
Ivabradine 7.5 mg b.i.d.	647	0.62 ± 1.70	0.17 ± 2.30	–0.00 ± 1.79	0.03 ± 1.93	0.00 ± 1.78	0.003 (0.070)	–0.134; 0.140	–	–

[a] *Visit is M12 for the PPS and last visit under treatment for the FAS; other data for FAS.*

The persistence of efficacy of ivabradine and the possibility of rebound phenomena following abrupt cessation of ivabradine therapy were evaluated during the run-out period of the pivotal efficacy studies CL2-009 and CL3-017, and in the long-term safety study CL3-019. Studies revealed lack of rebound reduction in exercise capacity or increase in angina symptoms following withdrawal of treatment.

Efficacy in special populations

Data from the five main studies showed a therapeutic response (reduction in HR and decrease in the frequency of angina attacks) in females consistent with the overall patient population.

The anti-anginal efficacy of ivabradine was also preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

Additional post-hoc analyses, requested by the CHMP, did not reveal a loss of anti-anginal efficacy in high-risk patient groups [those with HR below 50 bpm, severe angina, left ventricular hypertrophy (LVH) or factors likely associated with left ventricular dysfunction (LVD; history of myocardial infarction documented by Q wave on ECG or use of concomitant diuretics in patients without history of hypertension) and at risk of arrhythmia (all patients having at least one of the following risk factor for drug induced ventricular arrhythmia: female patients, aged ≥ 70 years, history of LVH, history of HF, concomitant treatment with QT prolonging drug, history or AE of atrial fibrillation, hypokaliemia, bradycardia < 45 bpm under treatment, QT prolonged at baseline or under treatment)].

Discussion on clinical efficacy

The clinical efficacy of ivabradine was evaluated using standardised exercise tolerance tests (ETT) in four well conducted, large-scale, repeated-administration, randomised, controlled studies. Three of these compared ivabradine monotherapy with placebo (dose-finding study CL2-009) or with the standard anti-anginal therapies atenolol (CL3-017) or amlodipine (CL3-023). The add-on study CL3-018 compared ivabradine to placebo during background amlodipine treatment. Additionally, the efficacy of ivabradine in preventing angina symptoms was evaluated in three 1-year safety studies; CL3-019/021/022.

Overall, a relevant anti-anginal effect was demonstrated relative to placebo and atenolol. Although the non inferiority to amlodipine was statistically demonstrated at the predefined delta of -30 sec (estimated between group difference with ivabradine 7.5 mg b.i.d. versus amlodipine: 1.8 sec with 95% CI:-14.6; +11.6), the robustness of these results was questioned, considering the effect size (28 sec with ivabradine and 31 sec with amlodipine on TED), and the obtained lower limit of the 95% CI of -14.6 sec. The predefined delta of -30 sec was considered too permissive and the obtained lower limits did not, thus, sufficiently rule out inferiority. Furthermore, non-inferiority studies with other calcium channel blockers, in particular the heart-rate lowering medicinal products verapamil and diltiazem, were not performed. Post-hoc analysis confirmed the non inferiority of ivabradine 7.5 mg twice daily to amlodipine at a delta of 15 sec on all ergometric criteria. Despite difficulties with bicycle exercise testing the clinical efficacy of ivabradine and of amlodipine was found comparable (See benefit-risk assessment).

In a 725-patients randomised placebo controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity (12 hours after oral intake) while an additional efficacy was shown at peak (3-4 hours after oral intake). Therefore, administration of ivabradine in combination with other anti-anginal therapies (apart from nitrates) could not be recommended due to insufficient additional clinical efficacy (amlodipine) or the absence of efficacy and safety data (beta-blockers and the non-dihydropyridine calcium channel blockers diltiazem and verapamil). Taking all this above into account, the place of ivabradine in the treatment of chronic stable angina pectoris, with beta-blockers and calcium channel blockers respectively as established first- and second-line therapies, was discussed by the CHMP (i.e. should ivabradine be used only in patients who have intolerance to beta-blockers and calcium channel blockers, or could a second-line indication for patients who are intolerant or have contra-indication only to beta-blockers be granted). Finally, a second-line indication was considered approvable.

Concerning the dose, the dose-ranging study (CL2-009) showed superiority of ivabradine 10 mg b.i.d. over placebo at trough, whereas 5 mg b.i.d. dose generally failed to show statistically significant improvements at trough, but showed significant improvements at peak. Results from the study CL3-017 that included a forced titration step provided evidence for the non-inferiority of ivabradine 7.5 and 10 mg b.i.d. versus atenolol 100 mg o.d. after 3 months, and also for ivabradine 5.0 mg b.i.d. versus atenolol 50 mg o.d. after 1 month of treatment at trough. The second non-inferiority study (CL3-023) showed non-inferiority of both ivabradine 7.5 and 10 mg b.i.d. compared to amlodipine 10 mg o.d. In both of the forced-titration main non-inferiority studies, ivabradine 10 mg b.i.d. showed no larger mean

change from baseline in the main efficacy parameter compared to ivabradine 7.5 mg b.i.d. It was concluded by the CHMP, that there was insufficient information available to support the 10 mg dose in the treatment of stable angina pectoris.

The 1-year safety studies CL3-019/021 had more permissive inclusion and exclusion criteria and also accepted the use of also other anti-anginal drugs than short-acting nitrates, which resulted in an enhanced representativeness of the study population that contained a larger proportion of females and CSS grade I patients compared to the phase III efficacy trials described above. Along with the open-label extension study CL3-022, these studies indicated the persistence of efficacy with ivabradine, in terms of a sustained reduction in angina attacks and nitrate consumption over 12 months. No exercise testing was, however, performed beyond 4 months of treatment. No rebound phenomena were observed at cessation in these studies.

Regarding post-hoc subgroup analyses, efficacy could be shown in subgroups such as patients with previous MI, CABG, PTCA, diabetes, as well as the elderly and patients with varying CSS angina grade. The efficacy data regarding patients with heart failure, hepatic impairment and the very elderly patients remained inconclusive due to limited amount of patients included in these subgroups; the SPC is reflecting these findings (4.2, 4.3, 4.4).

Overall, these data established the clinical efficacy of ivabradine monotherapy robustly compared to placebo and atenolol, and sufficiently compared to amlodipine in the treatment of stable chronic angina pectoris. However, the efficacy of ivabradine as add-on therapy on top of amlodipine relative to placebo at trough of drug activity was not shown. As a consequence, the CHMP concluded, that sufficient overall efficacy data had been provided for positive benefit-assessment of "Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for beta-blockers"-indication.

No studies in patients < 18 years of age were carried out, and therefore ivabradine is not recommended to be used in patients <18 years of age. This is reflected in the SPC (4.2).

Clinical safety

The safety of ivabradine was investigated in 52 completed and 9 on-going (at the time of the submission) studies.

In addition to studies described in other parts of Clinical aspects section, study CL3-044 was an ongoing, long-term (5-year), open-label, flexible dosing extension study, in which patients from safety studies CL3-019, CL3-021, and CL3-022 who wished to continue ivabradine therapy were included. Patients could join study CL3-044 either immediately after the last visit of previous study for most of patients and after a variable period of time for some patients. The primary objective of the study was to further assess the long-term safety of ivabradine. Investigators had the possibility, based on their judgment on patient's condition, to increase the dose to 7.5 mg and then to 10 mg b.i.d. from the overall starting dose of 5 mg b.i.d.

It is noteworthy, that in the below analyses, a majority (ca 80%) of the patients of the overall safety set in the "placebo-group" came from the study CL3-018 in which background therapy with amlodipine was given. In the overall ivabradine-group, a minority (<20%) of patients received also amlodipine as background therapy.

Patient exposure

Ivabradine was studied in clinical trials involving nearly 5,000 participants. Approximately 3,000 patients were treated with ivabradine.

Table 13 below summarises the number of healthy volunteers, subjects (patients having a disease other than coronary artery disease or stable angina pectoris) or patients who received at least one dose of ivabradine or its main active metabolite S 18982 during the clinical development programme.

Table 13: Number of healthy volunteers, subjects or patients who received at least one dose of ivabradine or metabolite S 18982 during the clinical programme

		Ivabradine				S 18982			
		i.v.	**oral**	**i.v. and oral**	**Total**	**i.v.**	**oral**	**i.v. and oral**	**Total**
Healthy volunteers	Completed studies	88	446	24	558	0	72	12	84
	On-going studies	0	102	0	102	0	0	0	0
Subjects	Completed studies	63	17	12	92	0	0	0	0
	On-going studies	9	39	0	48	0	0	0	0
Patients	Completed studies	17	2953	0	2970	0	0	0	0
	On-going studies	0	570	0	570	0	0	0	0

Several groupings were used in the Integrated Analysis of Safety:
- Overall Intravenous Safety Set
- Overall Oral Safety Set (OSS): all information from studies - except follow-up periods
- Short-Term Oral Safety Set: all information collected during the first month of oral double-blind studies except for study CL2-009 (first 14 days) and for study CL2-047 due to the 3-week sequential dose titration
-Middle-Term and Middle-Term Double-Blind Oral Safety Sets: All information collected during the first 3 months of the controlled double-blind studies, except for CL3-017 (first 4 months)
-Long-Term Oral Safety Set: All information collected over 1 year (excluding run-out) of the studies.

In the Overall Intravenous Safety Set, all patients (N = 111) received a single intravenous dose of either ivabradine (N = 80) or placebo (N = 31). Ivabradine doses ranged from 0.13 to 0.26 mg/kg (mean ± SD = 0.203 ± 0.027 mg/kg) and corresponded to total doses ranging from 7 to 25 mg (mean ± SD = 15.7 ± 3.8 mg).

Number of patients exposed to oral ivabradine/ placebo/ atenolol/ amlopidine at the time of submission is given in the Table 14 below.

Table 14: Treatment duration in the Overall Oral Safety Set - Descriptive analysis by treatment group

		Ivabradine (N = 2907)	**Placebo (N = 313)**	**Atenolol (N = 435)**	**Amlodipine (N = 404)**
N		2902*	313	435	404
Mean ± SD (days)		134.0 ± 109.1	75.5 ± 30.5	156.1 ± 110.1	86.3 ± 13.8
Min – Max (days)		1 – 420	5 – 117	1 – 401	1 – 119
Missing n (%)		5	-	-	-
Estimate of exposure in patient-years		1064.5	64.7	185.9	95.5
< 1 month	n (%)	324 (11.2)	55 (17.6)	47 (10.8)	7 (1.7)
]1 - 3] months	n (%)	974 (33.6)	171 (54.6)	12 (2.8)	275 (68.1)
]3 - 6] months	n (%)	1091 (37.6)	87 (27.8)	285 (65.5)	122 (30.2)
]6 - 12] months	n (%)	297 (10.2)	-	58 (13.3)	-
> 12 months	n (%)	216 (7.4)	-	33 (7.6)	-

N: total number of patients in the group; n: number of assessable patients; %: n/N x 100
Treatment duration: (last administration date – first administration date); SD: Standard Deviation
**: exposure could not be calculated for 5 patients who did not have a last drug-intake date*

Treatment duration in the long-term oral safety set per ivabradine dose is given in the Table 15 below.

Table 15: Treatment duration in the Long-Term Oral Safety Set - Descriptive analysis by treatment group and by ivabradine dose group

		Ivabradine				Atenolol
		5 mg b.i.d. (N = 198)	7.5 mg b.i.d. (N = 188)	10 mg b.i.d. (N = 212)	All (N = 598)	(N = 104)
n		195	187	212	594	104
Mean ± SD (days)		324.9 ± 101.0	307.7 ± 118.7	315.9 ± 114.6	316.3 ± 111.7	325.1 ± 95.3
Min – Max (days)		2 – 420	1 – 411	1 – 402	1 – 420	4 – 401
Missing		3	1	-	4	-
≤ 6 months	n (%)	21 (10.8)	29 (15.5)	31 (14.6)	81 (13.6)	13 (12.5)
]6 – 12] months	n (%)	102 (52.3)	99 (52.9)	96 (45.3)	297 (50.0)	58 (55.8)
> 12 months	n (%)	72 (36.9)	59 (31.6)	85 (40.1)	216 (36.4)	33 (31.7)

N :total number of patients in the group; n: number of assessable patients; %: n/N x 100;
Treatment duration: (last administration date – first administration date); SD: Standard Deviation

During the assessment of the dossier, the number of patients treated for 12 months and more with ivabradine had increased to 713. In the 5 year-extension study CL3-044, the number of patients treated for more than two years was 169.

Adverse events

In the OSS, the number of patients exposed to ivabradine was much higher than the comparator groups. The total exposure duration in the ivabradine group (1064.5 patients-years) was approximately 6 times greater than in the atenolol (185.9), 11 times greater than in the amlodipine (95.5) and 16 times greater than in the placebo groups (64.7). Therefore for comparison of incidences across treatment groups , the rates were also expressed per patient-year to obtain an estimation of the incidence per patient year of exposure.

In the Overall Oral Safety Set excluding study CL2-047 (OSS-047), the overall incidence of adverse events (AE's) was higher in the ivabradine group as compared to the other groups, which was primarily driven by an increased incidence for visual disturbances NOS (16.4% vs 6.6%, 4.5% and 2.9% for atenolol, amlodipine and placebo respectively), and to a lesser extent by an increased incidence of cardiac disorders. (Eye and cardiac AEs are presented in the Table 16a below).

Table 16a: Emergent eye and cardiac adverse events reported by at least 0.5% of patients exposed to ivabradine 5 , 7.5 mg and 10 mg b.i.d. in the Overall Oral Safety set (excluding CL2-047)

System organ class Preferred term	Ivabradine (5 or 7.5 mg bid) (N=1651) PY=635.2			Ivabradine (10 mg bid) (N=1160) PY=424.9			Placebo (N=313) PY=64.7			Atenolol (N=408) PY=184.4			Amlodipine (N=404) PY=95.5		
	n	%	PY	n	%	PY	n	%	PY	n	%	PY	n	%	PY
Eye disorders	**281**	**17.0**	**44.24**	**336**	**29.0**	**79.08**	**10**	**3.2**	**15.46**	**39**	**9.6**	**21.15**	**19**	**4.7**	**19.90**
Visual disturbance NOS	270	16.4	42.51	316	27.2	74.37	9	2.9	13.91	27	6.6	14.64	18	4.5	18.85
Cardiac disorders*	**296**	**17.9**	**46.60**	**219**	**18.9**	**51.54**	**29**	**9.3**	**44.82**	**62**	**15.2**	**33.62**	**53**	**13.1**	**55.50**
Sinus bradycardia	53	3.2	8.34	84	7.2	19.77	3	1.0	4.64	21	5.1	11.39	7	1.7	7.33
Ventricular extrasystoles	50	3.0	7.87	29	2.5	6.83	4	1.3	6.18	5	1.2	2.71	11	2.7	11.52
Angina pectoris aggravated	33	2.0	5.20	21	1.8	4.94	6	1.9	9.27	7	1.7	3.80	4	1.0	4.19
Angina unstable	33	2.0	5.20	14	1.2	3.29	1	0.3	1.55	1	0.2	0.54	5	1.2	5.24
Atrioventricular block first degree	23	1.4	3.62	13	1.1	3.06	3	1.0	4.64	8	2.0	4.34	2	0.5	2.09
Myocardial ischaemia	19	1.2	2.99	17	1.5	4.00	3	1.0	4.64	6	1.5	3.25	2	0.5	2.09
Palpitations	15	0.9	2.36	10	0.9	2.35	0	0.0	0.00	1	0.2	0.54	3	0.7	3.14
Supraventricular extrasystoles	15	0.9	2.36	7	0.6	1.65	4	1.3	6.18	2	0.5	1.08	2	0.5	2.09
Atrial fibrillation	15	0.9	2.36	11	0.9	2.59	1	0.3	1.55	2	0.5	1.08	5	1.2	5.24
Myocardial infarction	13	0.8	2.05	5	0.4	1.18	1	0.3	1.55	2	0.5	1.08	3	0.7	3.14
Ventricular tachycardia	11	0.7	1.73	4	0.3	0.94	0	0.0	0.00	0	0.0	0.00	0	0.0	0.00
Supraventricular tachycardia	8	0.5	1.26	1	0.1	0.24	1	0.3	1.55	0	0.0	0.00	2	0.5	2.09

The undesirable effects most frequently observed with the doses of 5 mg and 7.5 mg are given in the Table 16b below and include luminous phenomena (phosphenes), bradycardia (0.5% of patients experienced bradycardia below 40 beats per minute, ventricular extrasystoles, headaches, dizziness, blurred vision, AV 1st degree block and palpitations.

Table 16b: The most frequently reported undesirable effects (reported by at least 0.1% of patients) with 5 and 7.5 mg bid ivabradine doses (pooled; N=1651); regardless of investigator's causality assessment

Phosphene like events	14.5*
Bradycardia (sinus & NOS)	3.3
Ventricular extrasystoles	3.0
Blurred vision	1.5
AV 1st degree block	1.4
Headache NOS	2.2
Dizziness (exc vertigo)	1.5
Palpitations	0.9
Angina pectoris aggravated	2.0
Eosinophilia (exc pulmonary)	0.7
Hyperuricaemia	1.0
Vertigo NEC	0.4
Supraventricular extrasystoles	0.9
Sinus arrhythmia	0.2
Ventricular tachycardia	0.7
Myocardial ischaemia	1.2
Blood creatinine increased	0.2
Nausea	0.3
Constipation	0.5
Diarrhea NOS	0.3
Muscle cramps	0.4
Dyspnea NOS	0.4

% of patients with undesirable effect.

Ophthalmic safety

Visual symptoms were specifically studied in the Visual Disturbance Subset (VDS): consisting of patients in the phase III efficacy studies 017, 018, and 023, the 1-year safety studies 019 and 021 and the phase II study 030, which together involved 2545 patients treated with ivabradine. In these studies ophthalmic symptoms were collected using standardised charts and were reviewed by an Ophthalmic Safety Committee. The incidence of visual symptoms in the VDS was higher in the ivabradine group (17%) as compared to all other groups (3 to 7%). An ivabradine dose-dependency was noted: 5 mg (14%), 7.5 mg (18%) and 10 mg (29%). The vast majority of visual symptoms with ivabradine were phosphene-like events (luminous phenomena): transient enhanced brightness in a limited area of the visual field. A large majority of events was considered mild to moderate. In patients with only phosphene-like events, the first events usually occurred within 2 months after treatment initiation. These patients showed a large variability in frequency of these events and experienced each separate event for a few seconds to a few minutes. Light variation was the main triggering factor for phosphene-like events. The impact of these visual symptoms on the patients' daily life was low and a large majority (76%) of all phosphene-like events resolved during treatment. In the OSS, the frequency of phosphene like events was 14.5%. and the frequency of patients changing their daily routine or discontinuing the treatment in relation to visual symptoms was less than 1%.

In studies CL3-019/CL2-047, specific ophthalmic testing by electroretinography (ERG) was performed. The only consistent difference between ivabradine and atenolol treatment groups was the increase (2 to 4 ms) in maximal response b-wave latency with ivabradine in a dose-dependent manner. The cone system tests (visual fields, colour vision and visual acuity) and other ophthalmic tests (VEP, anterior segment, ophthalmoscopy, IOP, electro-oculogram) showed no clinically important differences between the ivabradine and atenolol groups.

Cardiac safety

In the OSS, the most frequently noted cardiac AEs with ivabradine were bradycardia (3.3%), ventricular extrasystoles (3.0%) and coronary artery disorders (mainly angina aggravated/ CAD aggravated: 2.0%), of which the rates per patient-year were comparable to amlodipine and higher relative to atenolol, except for bradycardia that showed similar rates per patient-year with ivabradine and atenolol. A clear ivabradine dose-dependency was only seen for bradycardia. The number of cardiac withdrawals per patient-year under ivabradine was comparable to the amlodipine group, but higher compared to the atenolol group in the OSS. Notably, the withdrawal rate for bradycardia was lower with ivabradine compared to atenolol.

Various ECG parameters were studied in specific ECG Safety Sets (studies where ECG data were collected in standardised manner and reviewed by a central reader). The changes noted in the PR interval and the QRS duration with ivabradine were of no clinical concern. The mean changes from baseline in the population corrected QT (QTcP) consisted of small changes in either direction that never exceeded +1.4 ms in the ivabradine group, never attained statistical significance within a treatment group and showed a good agreement between different ECG Safety Sets for each ivabradine treatment group, which was acceptable. Concerning QT changes in individual patients, only 1 patient out of 1140 (0.1%) in the ivabradine group and 1 patient out of 91 patients (1.1%) in the atenolol group had a QTcP value $\geq$ 500 ms in the Middle-Term ECG Safety Set. In the Long-Term ECG Safety Set, the overall proportion of patients with QTcP $\geq$ 500 ms in the ivabradine treatment group was 1.0%, which was primarily driven by 4 patients with QTcP $\geq$ 500 ms in the ivabradine 7.5 mg b.i.d. group. Importantly, there were no patients with a QTcP $\geq$500 ms and change $\geq$ 60 ms in either ECG Safety Set.

Head-to-head comparisons with atenolol and amlodipine

In the head-to-head comparisons of ivabradine and atenolol (CL-017/019-studies) the overall incidence of common AEs was higher with ivabradine compared to atenolol, which was mainly driven by higher rates on visual disturbance and cardiac disorders. Sinus bradycardia was reported under ivabradine and atenolol at frequencies of 5.7% and 5.1%, respectively. The rate of serious coronary artery disorders with ivabradine was higher compared to atenolol (3.8% vs. 1.5%). A further analysis of the subset of beta-blocker naive patients (30% of patients) showed a similar incidence of cardiac disorders with ivabradine and atenolol. The rates of serious arrhythmias with ivabradine and atenolol were 1.3% and 0.7% respectively.

In head-to-head comparisons of ivabradine and amlodipine (CL3-023), the overall incidence of common AEs was higher with ivabradine compared to amlodipine, mainly driven, again, by higher rates on visual disturbance and sinus bradycardia (19.0% vs. 4.5% and 8.5% vs. 1.7%). The rate on the serious coronary artery disorders with ivabradine was somewhat lower compared to amlodipine (1.8% vs. 2.5%). Higher rates were observed with ivabradine versus amlodipine on serious cardiac arrhythmias, but absolute incidences were low in both treatment groups (0.6% vs. 0.2%, resp). No cases of serious sinus bradycardia were observed in either the ivabradine or amlodipine treatment group in the study.

Serious adverse event/deaths/other significant events

In the OSS, 8.1% of the ivabradine group experienced at least one serious emergent adverse event (SEAE), while lower incidences were noted in the other groups (4.7-6.4%). A different pattern was observed when expressed per patient-year: ivabradine 0.22, 'placebo' 0.23, atenolol 0.15, amlodipine 0.20, and amlodipine+'placebo' 0.21, showing a comparable rate in the ivabradine and amlodipine (with or without 'placebo') group, and a higher rate versus atenolol. As expected, the highest incidences on SEAE's were noted for serious cardiac disorders in all groups (1.3-3.7%). The incidence of serious coronary artery disorders with ivabradine was 2.6% compared to 0.6%-2.5% in the other groups. The rates per patient-year were: ivabradine 0.072, 'placebo' 0.031, atenolol 0.038, amlodipine 0.105, and amlodipine+'placebo' 0.075, again showing a comparable rate in the ivabradine and amlodipine (with 'placebo') group, but a higher rate versus atenolol.

Cardiac arrhythmias reported as SEAE's were more frequent in the ivabradine group as compared to the other groups (1.1% vs. 0.2-0.7%; similarly also when the rates were expressed per patient-year of exposure). The combined incidence of serious sinus bradycardia and bradycardia NOS was very low in both the ivabradine (0.2%) and atenolol group (0.4%).

The long-term open extension studies CL3-022/044 were not included in the OSS. The overall incidence of SEAE's in study CL3-022 (ivabradine 7.5 mg b.i.d. only, n=659) and CL3-044 (ivabradine 5, 7.5 or 10 mg b.i.d., n=558, data obtained up to cut-off date 31-10-2003) was higher compared to the OSS (15.8-17.8% vs. 8.1%, respectively), a reversed pattern was observed when rates were normalised to patient exposure (0.17 – 0.12 vs. 0.22). A similar pattern was observed for serious cardiac disorders in these extension studies (0.077 – 0.052 in studies CL3-022/044 vs. 0.10 in the OSS).

In the OSS a total of 32 patients died out of 4059 patients exposed to ivabradine or to one of the comparators: 27/2907 patients in the ivabradine group (0.9% of the exposed patients), 1/435 patient in the atenolol group (0.2%), 2/313 patients in the placebo group (0.6%) and 2/404 in the amlodipine group (0.5%). The incidence of deaths calculated in relation to the number of patient-years of exposure is presented in the Table 17 below:

Table 17: Estimated incidence of deaths for 100 Patient-years - by treatment group - Overall Oral Safety Set

	Ivabradine	**Placebo**	**Atenolol**	**Amlodipine**
N	**2907**	**313**	**435**	**404**
Patient-years	1107.23	65.18	201.86	95.86
Number deaths	27	2	1	2
Incidence	2.439	3.068	0.495	2.086
95% CI	[1.607, 3.548]	[0.368, 11.092]	[0.015, 2.759]	[0.250, 7.542]

N: number of patients by group. Incidence expressed as number of death for 100 patient-years. 95% CI: Two-sided 95% confidence interval of the number of death for 100 patients-years based on Poisson distribution.

Thus, the death rates were higher with ivabradine compared to atenolol and most of the deaths in the OSS under ivabradine were classified as arrhythmic, sudden or unexplained (17/27 = 63%). Death rates in the OSS were comparable with ivabradine and amlodipine. Overall, the death rates with ivabradine and amlodipine were in line with those given by ESC guideline on stable angina pectoris (2-3% mortality per annum in patients with stable angina; Eur Heart Journal 1997;18:394-413), but a lower death rate was reported on atenolol in the OSS.
Death rates in the extension studies (2.09 per 100 patient-years) were comparable to the OSS (2.44 per 100 patient-years).

The majority of cardiovascular deaths under ivabradine in the entire clinical programme (OSS plus the extension studies) was classified as arrhythmic, sudden or unexplained (28/43 = 65.1%), This proportion is similar to the proportion of sudden deaths in developed countries which is estimated to be 65.6% (Zheng et al, Circulation 2001;104:2158-2163), and together represents a pool of arrhythmic deaths at a rate of 1.10 per 100 pt-years. This rate was clearly higher versus atenolol (zero arrhythmic deaths) and somewhat higher compared to amlodipine (1.05-0.0 arrhythmic deaths per 100 pt-years). However, fewer serious coronary artery disorders were reported with ivabradine compared to amlodipine (but not atenolol), rendering the overall death rate comparable between ivabradine and amlodipine.

Laboratory findings
A wide spectrum of biochemical parameters (blood) were analysed: sodium, potassium, calcium, chloride, uric acid, CPK, creatinine, glucose, HbA_1c, ASAT, ALAT, GGT, total cholesterol, LDL cholesterol, triglycerides. Also, various haematological parameters were analysed: red blood cells, haemoglobin, haematocrit, white blood cells, neutrophils, basophils, lymphocytes, monocytes and platelets. For all these biochemical and haematological parameters, the changes noted with ivabradine were generally minor, comparable to other treatment groups and not considered of clinical relevance.

Safety in special populations
Only limited number of very elderly patients (>75 years of age; n=68) were included into the studies. No studies in patients < 18 years of age were carried out. These facts are reflected in SPC (4.2).

Safety was comparable among subgroups (with limited number of patients in many subgroups) according to age or the presence of mild to moderate renal insufficiency, hypertension, mild to moderate heart failure, COPD, asthma, peripheral vascular disease, diabetes, hyperlipidaemia and obesity. The mildly increased frequency of AEs in females that was observed for almost all system organ classes, except for cardiac disorders was not confirmed when rates were normalised for patient exposure.

Twelve subjects with mild to moderate hepatic insufficiency investigated in the study PKH-008 and the ivabradine-treated patients (n = 129 OSS excluding CL2-047) with elevated transaminases (>1.5 times ULN) included in the OSS had an ivabradine plasma exposure close to that of the overall population. No safety concern was raised in this population. No data in patients with severe hepatic impairment were available.

Unstable angina and acute myocardial infarction (MI) were infrequently reported during the clinical program. The Emergent Adverse Event (EAE) unstable angina was reported in 49 patients in the OSS and 14 patients in the extension studies CL3-022 and CL3-044. The EAE MI was reported in 18 patients in the OSS and 29 patients in the extension studies. Following these events, treatment with ivabradine was continued by 23 of the 63 patients having had unstable angina and by 14 of the 47 patients having experienced MI. For both unstable angina and MI, treatment with ivabradine was not a limitation in the appropriate management of the patients nor seemed to influence the outcome of these EAEs. However and since the experience was limited, the use of ivabradine is contra-indicated in patients with unstable angina and during the acute phase of MI. No data on patients with heart failure of NYHA class III-IV, and only limited data on patients with left ventricular dysfunction or NYHA class II heart failure were available. These findings are reflected in SPC (4.3, 4.4).

During the evaluation the CHMP requested additional analyses in high risk patients. There was no evidence of increased frequency of coronary or arrhythmic events as compared to amlodipine either in patients at risk of coronary events and arrhythmia (patients with LVH or with factors associated with LVD) and in the pooled set of patients at risk of arrhythmia (for definition of this subgroup in post-hoc analyses, see Clinical efficacy in special populations). In patients with HR below 60 bpm prior to treatment initiation there was no evidence of an increased risk of excessive bradycardia-related symptoms, coronary events or arrhythmia when comparing the subset to the overall ivabradine-treated patient population and to atenolol-treated patients. The risk of excessive bradycardia (below 40 bpm) was shown to be very low (<0.3% of patients) when treatment was initiated with a heart rate ≥ 60 bpm according to SPC recommendations. Overall this analysis suggested a comparable safety profile of ivabradine and amlodipine in high risk patients.

Discontinuation due to adverse events

The overall rates on treatment discontinuation were substantial across all treatment groups, with the highest rates observed in the ivabradine (7.8%) and atenolol (6.7%) group, and lower rates in the amlodipine (5.2%) and 'placebo' (3.8%) group. This incidence pattern changed when expressed per patient-year of exposure: 0.21 in the ivabradine group relative to 0.16, 0.22, 0.19 and 0.21 per patient-year of exposure in the atenolol, amlodipine, 'placebo' and amlodipine+'placebo' group respectively.

Most treatment discontinuations were due to cardiac and eye disorders in the ivabradine group. The incidence of cardiac disorders leading to treatment discontinuation was 4.1% in the ivabradine group, 3.0% in the atenolol group, 2.5% in the amlodipine group and 1.9% in the 'placebo' group. Once again, this incidence pattern changed when expressed in patient-years of exposure: 0.11 in the ivabradine group relative to 0.07, 0.11, 0.09 and 0.10 per patient-year in the atenolol, amlodipine, 'placebo' and amlodipine+'placebo' group, resulting in comparable rates in the ivabradine and amlodipine (with or without 'placebo') group.

Overall, the rates per patient-year of exposure on discontinuations with ivabradine were comparable to amlodipine (with or without 'placebo') while being higher compared to atenolol.

Other

Study CL1-055 was a randomised double-blind placebo-controlled phase I study in 90 healthy volunteers with the objective to document the effects of high doses of ivabradine (10 and 15 mg b.i.d.) and related visual symptoms on driving performance in a driving simulator. 47 patients receiving ivabradine reported visual symptoms during the study whereas 28 did not. A single subject reported visual symptoms during a driving session, after a series of flashes. No visual symptom was reported in the placebo group. Mean changes from baseline in driving performance criteria were comparable in all groups (receiving ivabradine or placebo; with or without visual symptoms); thus, ivabradine at doses higher than those recommended (10 to 15 mg b.i.d.) and the occurrence of visual symptoms triggered by flashes did not affect driving performance in comparison to placebo. However, the possible occurrence of luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night. This has been reflected in the SPC (4.7.).

Discussion on clinical safety

Ivabradine was studied in clinical trials involving nearly 5000 participants. Approximately 3000 patients were treated with ivabradine in phase II-III trials. At the time of submission 216 patients had been treated over 12 months with ivabradine and 297 for >6 months; at the time of approval 713 had been treated for 1 year.

The most common AEs with ivabradine were dose dependent and related to the pharmacological effect of the medicinal product. The most common AE was "luminous phenomena" (phosphenes), reported by 14.5% of patients and described as a transient enhanced brightness in a limited area of the visual field, usually triggered by sudden variations in light intensity. The onset of phosphenes was generally within the first two months of treatment after which they may occur repeatedly; they were generally reported to be of mild to moderate intensity, and resolved during or after treatment; fewer than 1% of patients changed their daily routine or discontinue the treatment in relation with phosphenes. Overall, thorough ophthalmic investigations did not indicate any clinically significant persisting deleterious effects due to ivabradine exposure on retinal function or morphology. Thus, there was no evidence to suggest that the frequently observed visual symptoms with ivabradine represented a toxic effect of ivabradine on the retina. Further focused surveillance will be conducted within ongoing and planned trials and post-marketing. This is adequately detailed in the submitted pharmacovigilance plan.

Other most common AEs included bradycardia, AV 1st degree block, ventricular extrasystoles, headaches, dizziness and blurred vision.

Compared to atenolol, a direct safety comparison from pooled studies CL3-017/019 showed consistently higher rates of adverse events, serious adverse events, discontinuations and deaths with ivabradine; these findings were in agreement with those obtained in the OSS analysis. The effects of ivabradine on cardiac events were thus less favourable compared to atenolol, although a more definite conclusion would require an outcome study. It should also be recognised that beta-blockers have beneficial effects beyond reduction of heart rate. Pharmacodynamic and clinical studies did not raise suspicion that ivabradine itself would have detrimental effects on cardiovascular morbidity and mortality, but data were limited.

Compared to calcium antagonists the data suggest that the safety profile of ivabradine is comparable to amlodipine, with rather comparable rates on the aforementioned main indicators of safety. However, only one comparator from the heterogeneous group of calcium channel blockers was studied: no definite conclusions could be drawn on this issue.

The data on QTcP changes did not raise safety concerns with respect to ivabradine and the duration of ventricular repolarisation.

Ivabradine was metabolised by CYP3A4, but it did not influence metabolism or plasma concentrations of other CYP3A4 substrates. CYP3A4 inhibitors and inducers, however, could interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction studies established that CYP3A4 inhibitors increased ivabradine plasma concentrations, while inducers decreased them. Thus, the concomitant use of ivabradine with potent CYP3A4 inhibitors is contra-indicated, and with moderate inhibitors or inducers of CYP3A4 ivabradine should be used with caution. (SPC 4.4 and 4.5).

Only limited data were available of the use of ivabradine in the very elderly (>75 years of age), patients with severe renal insufficiency, moderate hepatic insufficiency, and therefore caution should be exercised when used in these patient groups. Ivabradine is not recommended in children or adolescents, as no data were available. Use of ivabradine is contraindicated (or there is a special warning) in several cardiovascular diseases (e.g. acute MI, unstable angina, HF with NYHA functional classification III-IV) and in patients with severe hepatic impairment due to lack of sufficient data. At the time of CHMP Opinion a clinical outcome trial was being carried out in patients with LVD (described in a separate risk management plan), but until more data become available, use of ivabradine in patients with asymptomatic LVD and NYHA class II HF is included into precautions (SPC 4.4).

The heart rate lowering effect of ivabradine was dose dependent at the dose levels of 2.5, 5, 7.5 and 0–10 mg and the heart rate reduction levels off in a dose range of 10-20 mg b.i.d. In patients with angina pectoris, mild to moderate bradycardia (40–50 bpm) is generally not a major safety issue. HR can usually be registered by the patients, and causality to dosage and symptoms recognised. However, use of ivabradine is limited to patients with contraindication or intolerance to beta-blockers, and in this group tendency to excessive, symptomatous bradycardia is not uncommon. Therefore, the applicant committed to perform a clinical risk management plan to further evaluate the issue of bradycardia.

There was no evidence for deleterious effect of ivabradine in patients with AF and patients with AF were successfully converted to sinus rhythm by either amiodarone or DC cardioversion while treated with ivabradine without evidence for excessive bradycardia on return to sinus rhythm. However, there is still theoretical basis for paroxysmal tachyarrhythmias including AF as a sympathetic response to HR-lowering effect of ivabradine. In patients with paroxysmal atrial fibrillation (PAF), ivabradine did not demonstrate any prevention of symptomatic PAF attacks and did not increase the rate of PAF attacks in comparison to placebo. In comparison to beta-blockers (first line drugs in angina) ivabradine has no

anti-arrhythmic efficacy. Further focused surveillance will be conducted within ongoing and planned trials and post-marketing. This is adequately detailed in the submitted pharmacovigilance plan.
It was recommended to regularly clinically monitor ivabradine-treated patients for the occurrence of AF (sustained or paroxysmal), including ECG-monitoring when clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse). (This is reflected in SPC 4.4.)

The applicant commits to conduct a survey to analyse how ivabradine is prescribed in the daily medical practice.

Due to (albeit infrequent) thymus atrophy findings in non-clinical studies, the applicant also committed to pay special attention to possible changes in immune system function that will be addressed as a post-marketing commitment.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

Non-clinical pharmacology and toxicology
The nonclinical pharmacology programme characterised ivabradine as a selective inhibitor of the cardiac pacemaker I_f-current resulting in a specific heart-rate reduction. The cardiac effects of ivabradine were specific of the sinus node, with no effect on left ventricular contractility and relaxation, cardiac conduction (atrioventricular or intraventricular) or ventricular repolarisation.

Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit. Animal studies indicated that ivabradine was excreted in milk. Therefore, ivabradine was contra-indicated during pregnancy and in breast-feeding women.

In dogs given ivabradine (doses of 2, 7 or 24mg/kg/day) for one year, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data were consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I_h currents in the retina, which share extensive homology with the cardiac pacemaker I_f current.

Other long-term repeated dose and carcinogenicity studies revealed no clinically relevant changes.

Overall, the preclinical findings suggested that ivabradine does not pose a significant hazard to humans at therapeutic doses.

Efficacy
Metabolism of ivabradine involved CYP3A4. Ivabradine was neither an inducer nor an inhibitor of main drug-metabolising enzymes. The extensive pharmacokinetic drug-drug interaction programme performed in humans demonstrated the absence of interaction of ivabradine with other CYP3A4 substrates. Conversely, the exposure profile of ivabradine may be affected by strong and moderate CYP3A4 inhibitors or inducers.

The clinical efficacy of ivabradine was evaluated using standardised exercise tolerance tests in four well conducted, large-scale, repeated-administration, randomised, controlled phase IIb-III studies. Three of these compared ivabradine monotherapy with placebo or with the standard anti-anginal therapies atenolol or amlodipine; the add-on study compared ivabradine to placebo during background amlodipine

treatment. Additionally, the effect of ivabradine in preventing angina symptoms was evaluated in three 1-year safety studies.

In the reference-controlled study versus atenolol ivabradine 5 and 7.5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. The efficacy of 5 and 7.5 mg twice daily was relatively consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression).

The clinical efficacy of ivabradine 7.5 mg twice daily was found comparable to that of amlodipine. No further studies comparing ivabradine with other calcium channel blockers were conducted.

Ivabradine efficacy was maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The anti-anginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

Long-term efficacy on angina symptoms was studied as a secondary endpoint in three open-label 1-year safety follow-up studies including patients receiving combined background anti-anginal therapies such as calcium channel blockers and long acting nitrates. A sustained reduction of heart rate and the decrease of angina attacks were demonstrated in these patients. Exercise testing was not performed beyond 4 months of treatment in any of the clinical studies.

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended (see SPC sections 4.4 and 4.5). In a randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity while an additional efficacy was shown at peak.

Safety
Ivabradine was studied in clinical trials involving nearly 5,000 participants. Approximately 3,000 patients have been treated with ivabradine in phase II-III studies.

The most common AEs with ivabradine were dose dependent and related to the pharmacological effect of the medicinal product. The most common adverse effect was “luminous phenomena” (phosphenes), reported by 14.5% of patients and described as a transient enhanced brightness in a limited area of the visual field, usually triggered by sudden variations in light intensity. The onset of phosphenes was generally within the first two months of treatment after which they could occur repeatedly. They were generally reported to be of mild to moderate intensity, and resolved during or after treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes. In non clinical studies, there was no evidence of retinal toxicity with the use of ivabradine. Further focused surveillance will be conducted within ongoing and planned trials and post-marketing. This is adequately detailed in the submitted pharmacovigilance plan.

Other most common AEs included bradycardia, AV 1st degree block, ventricular extrasystoles, headaches, dizziness and blurred vision.

The data on QTcP changes did not raise safety concerns with respect to ivabradine and the duration of ventricular repolarisation.

Several precautions and contraindications were included into the SPC (4.3-4.4) to allow the safe use of ivabradine in the treatment of angina pectoris. The applicant has submitted a relevant pharmacovigilance plan.

Benefit/risk assessment

The main issue in the overall benefit/risk assessment was the potential place of ivabradine in the current treatment of chronic stable angina pectoris, with beta-blockers and calcium channel blockers respectively as established first- and second-line therapies.

Ivabradine shares with beta-blockers similar heart rate reducing effects, which remain one key therapeutic objective in stable angina. Beta-blockers have additional beneficial effects beyond reduction of heart rate and in contrast to beta-blockers, ivabradine is devoid of anti-arrhythmic effect. Ivabradine showed comparable anti-anginal efficacy versus atenolol. Safety data indicated a less favourable safety profile in terms of cardiac events, events leading to treatment discontinuations and deaths. Pharmacodynamic and clinical studies did not raise suspicion that ivabradine itself would have detrimental effects on cardiovascular morbidity and mortality but data were limited. Final conclusions were difficult to draw, as these studies were not designed to show whether ivabradine confers a benefit in terms of morbidity and mortality in patients with coronary artery disease. The benefit/risk ratio of ivabradine was overall considered less favourable compared to atenolol, and therefore ivabradine was considered as an alternative treatment for those patients who have contra-indication or intolerance to beta-blockers.

A second issue was whether further restriction of the indication would be warranted with regard to calcium antagonists. Overall, the benefit/risk ratio of ivabradine was found comparable to that of amlodipine. In contrast to amlodipine, ivabradine had the potential to induce bradycardia (risk factor for arrhythmia), which raised some concern in the absence of anti-arrhythmic efficacy and with the potential for pharmacokinetic interactions. However, the possibility of dosing patients with the ivabradine dose of 10 mg twice daily was withdrawn and heart rate threshold for treatment initiation was raised to 60 bpm, thus minimising the risk of excessive bradycardia. No comparisons with non-dihydropyridine calcium channel blockers such as diltiazem were made.
Overall, the CHMP concluded that ivabradine had demonstrated anti-anginal and anti-ischemic effects in patients with chronic stable angina pectoris, and that ivabradine safety profile was shown comparable to that of amlodipine although no safety advantage was evidenced in the limited comparison of both treatments in study CL3-023.

The CHMP came to the conclusion that sufficient overall data had been provided for granting the MA for a second line indication: symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm , who have a contra-indication or intolerance for beta-blockers. This indication, together with other recommendations and warnings in the SPC (4.2, 4.4), addressed the current lack of evidence for add-on efficacy of ivabradine in patients with insufficient response to either beta-blockers or calcium channel blockers, and also addressed the safety concerns regarding the combination of ivabradine with beta-blockers and non-dihydropyridine calcium channel blockers. It enabled ivabradine to become a treatment alternative when beta-blockers are not suitable

There was no evidence to suggest that the frequently observed visual symptoms with ivabradine (mainly phosphenes) represented a toxic effect of ivabradine on the retina. The long-term ocular safety of patients exposed to ivabradine was documented in the development programme up to one year. The data on QTcP changes did not raise safety concerns with respect to ivabradine and the duration of ventricular repolarisation. The potential of ivabradine to induce bradycardia was minimised in the target population with a treatment initiation heart rate raised to 60 bpm with the recommended therapeutic doses. Furthermore, the applicant submitted a relevant pharmacovigilance plan, detailing how some specific ophthalmic, cardiac or immune system adverse events will be addressed within ongoing or planned trials and within post-marketing pharmacovigilance activities.

In conclusion, ivabradine has sufficient anti-anginal effect and acceptable safety profile, and thus provides a treatment alternative to patients with chronic stable angina pectoris with normal sinus rhythm who have a contra-indication or intolerance for beta-blockers.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Procoralan in the treatment of chronic stable angina pectoris with normal sinus rhythm who have a contra-indication or intolerance for beta-blockers was favourable and therefore recommended the granting of the marketing authorisation.