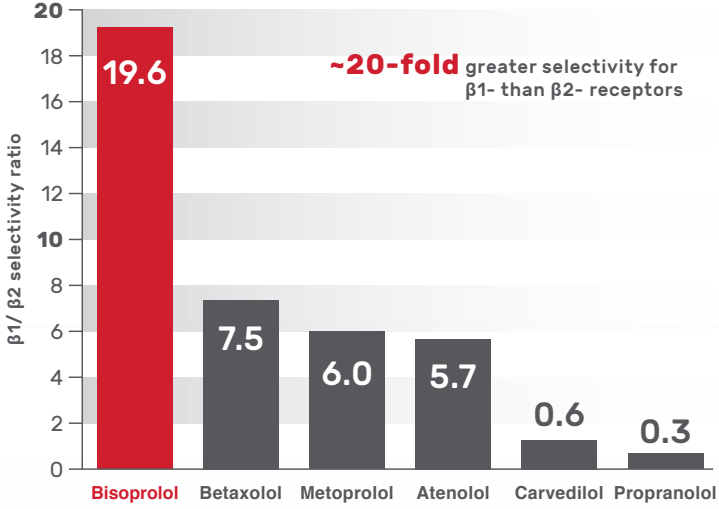
β-1 selectivity

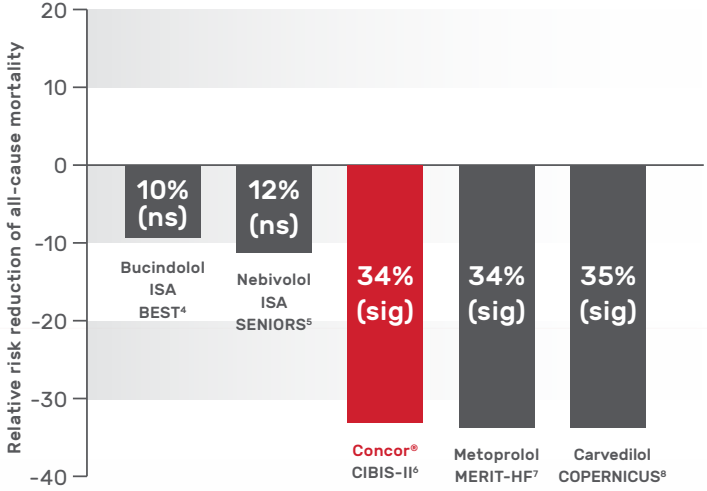
The high β-1 cardioselective β-blocker without ISA, offers cardio-protection for your patients[1,2]

Concor® Bisoprolol

Concor® has higher β-1 selectivity compared to other beta-blockers[3]

Concor® without ISA, is effective in reducing all-cause mortality[2*]





* In addition to standard of care at the time of study. Patient populations varied between trials; therefore relative risk reduction cannot be directly compared.

ISA = Intrinsic Sympathomimetic Activity; HR = Heart Rate; BP = Blood Pressure; ns = non-significant; sig=significant

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Guidelines

Concor® Bisoprolol

International guidelines recommend β-blocker for CVD such as angina, post MI and CHF[9,10]

Concor® is specifically recommended for resistant hypertension[10]

Guidelines	Recommendation
AHA (2017)[9]	Cardioselective β-blockers are preferred in IHD or HF patients. Concor® is preferred in patients with HFrEF
ESC (2018)[10]	All antihypertensive drug including β-blocker has demonstrated effective reduction of BP and CV events in RCTs, and thus indicated as the basis of antihypertensive treatment strategy
	Bisoprolol (Concor®) is recommended as an additional agent to existing treatment for **resistant hypertension**

CVD = Cardiovascular disease; MI= Myocardial Infarction; CHF = Congestive Heart Failure; ACC = American College of Cardiology; AHA = American Heart Association; IHD=Ischemic Heart Disease; HF = Heart Failure; HFrEF =HF with reduced ejection fraction; ESC = European Society of Cardiology; BP = Blood Pressure; CV = Cardiovascular; RCTs = Randomised Clinical Trials

References: **1.** Egan, B. M., Basile, J., Chilton, R. J., & Cohen, J. D. (2005). J. Clin. Hypertens, 7(7), 409–416; **2.** Cruickshank, J. (2007), Int. J. Cardiol., 120(1), 10–27; **3.** Smith, C., Teitler, M. (1999), Cardiovasc Drugs Ther, 13(2), 123–126; **4.** Beta-Blocker Evaluation of Survival Trial Investigators, Eichhorn EJ, Domanski MJ et al, (2001), N. Engl. J. Med., 344(22), 1659–1667; **5.** Flather MD, Shibata MC, Coats AJ, et al.,(2005), Eur Heart J., 26(3), 215–25; **6.** The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial, Lancet, (1999), 2;353(9146), 9-13; **7.** Effect of metoprolol CR/XL in chronic heart failure, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), Lancet, (1999) 12;353(9169):2001-7; **8.** Packer M, Coats AJ, Fowler MB, et al.,(2001), N Engl J Med, 31;344(22):1651-8; **9.** Whelton PK, Carey RM, Aronow WS, et al., J Am Coll Cardiol (2018) 15;71(19):e127-e248; **10.** Williams B, Mancia G, Spiering W, et al. (2018) European Heart Journal 00, 1-98.

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Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT) syncope, reduced tear flow, hearing disorders, allergic rhinitis, hypersensitivity reactions such as itching, flush, rash; hepatitis, potency disorders, nightmares, hallucinations. Very rare: conjunctivitis, alopecia; beta-blockers may provoke or worsen psoriasis or include psoriasis-like rash. Most common signs of overdose: bradycardia, hypotension, bronchospasm, acute cardiac failure, hypoglycemia. **Date of product information:** July 2016

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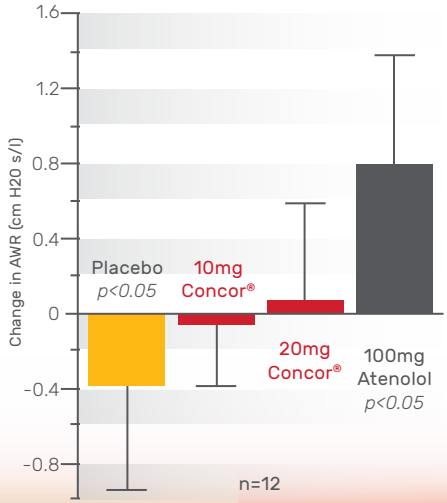
Safety

The high β-1 selective β-blocker with excellent safety profile[1-13]

Concor® Bisoprolol

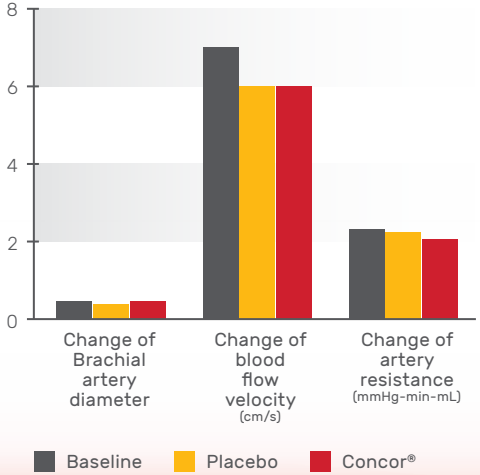
Minimal effect on lung function in COPD patients[1,2]

Concor® has no significant effect on lung function as compared to atenolol[3]



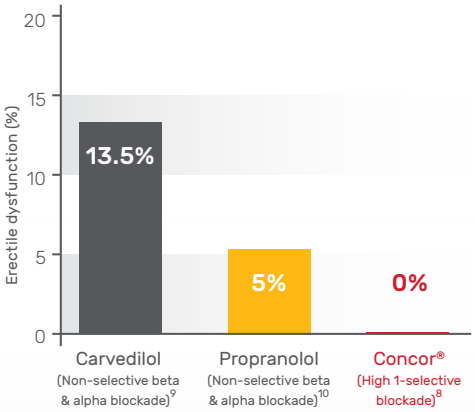
Minimal effect on peripheral circulation[4-7]

Concor® maintained peripheral circulation as placebo[4]



Minimal effect on Sexual function[8]

No detrimental effects on sexuality of male patients with hypertension



Data collected from different studies; not meant for a head-to-head comparison

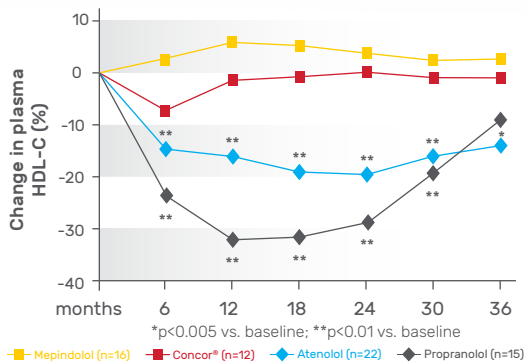
Safety

Concor® Bisoprolol

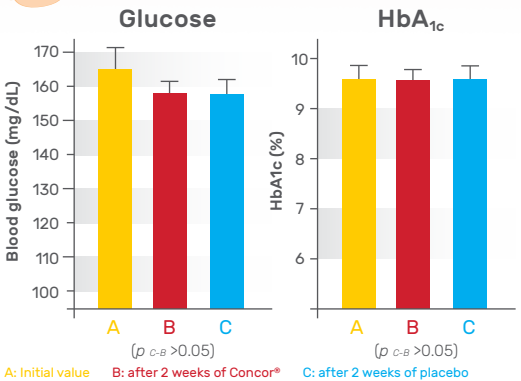
with high β-1 selective offers cardio-protection with minimal side effects[1-13]

Minimal effect on Lipid and Glucose metabolism[11-13]

Concor® lowered cardiovascular risk without posing an impact on the lipid profile[11]



Concor® did not change blood glucose metabolism[12]



HbA1c = Haemoglobin A1c; AWR=Airway resistance; HDL-C=High-density lipoprotein cholesterol; HR=Heart rate

References: 1. Dorow P., Bethge H. & Tönnesmann, (1986), U., Eur J Clin Pharmacol, 31, 143-147; **2.** Cruickshank JM (2011) The Modern Role of Beta-Blockers in Cardiovascular Medicine Fig 1-8, page 9; **3.** Chatterjee SS, (1986), J Cardiovasc Parmacol, 8, Suppl 11, S74-77; **4.** Asmar RG, Kerihuel JC, Girerd XJ et al., (1991), Am J Cardiol, 68 (1), 61-64; **5.** Chang PC, et al. (1988) J. Cardiovasc. Pharmacol 12:317-322; **6.** Chang, P.C., et al. (1986) J of cardiovascular pharmacology, 8, Suppl 11, S58-60; **7.** Bailliart O, et al. (1987) Eur Heart J, 8 (Suppl M):87-93; **8.** Broekman CP, Haensel SM, Van de Ven LL et al., (1992), J Sex Marital Ther, 18(4), 325-331; **9.** Fogari R, Zoppi A, Poletti L, et al., (2001), Am J Hypertens, 14(1), 27-31; **10.** Medical Research Council Working Party, (1981), Lancet, 2(8246). 539-543; **11.** Fogari R, Zoppi A, Tettamanti F et al., (1990) J Cardiovasc Pharmacol, 16 Suppl 5, S76-80; **12.** Janka HU, Ziegler AG, Disselhoff G e t al. (1986), J Car diovasc Pharmacol, 8 Suppl 11, S96- 99; **13.** Cruickshank JM (2011) The Modern Role of Beta-Blockers in Cardiovascular Medicine Table 6-12 & Fig. 6-13, page 230-1.

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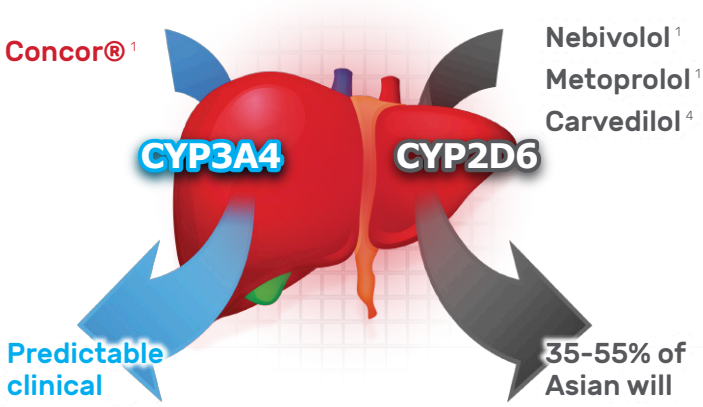
Pharmaco-kinetics

The high β-1 selective β-blocker with favourable pharmacokinetic profile[1-6]

Concor® Bisoprolol

1 Predictable Clinical Response

Unlike other β-blockers relying on CYP2D6[1,2]

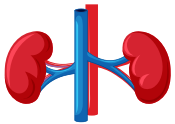


Adverse drugs reactions or altered drug responses could be caused by a CYP2D6 allele variation (e.g. CYP2D6*10), which affects the speed of metabolism in individuals

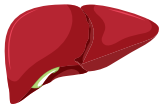
2 Organs Balanced Clearance[5]

No dose adjustment is needed for mild-to-moderate hepatic or renal impairment patients

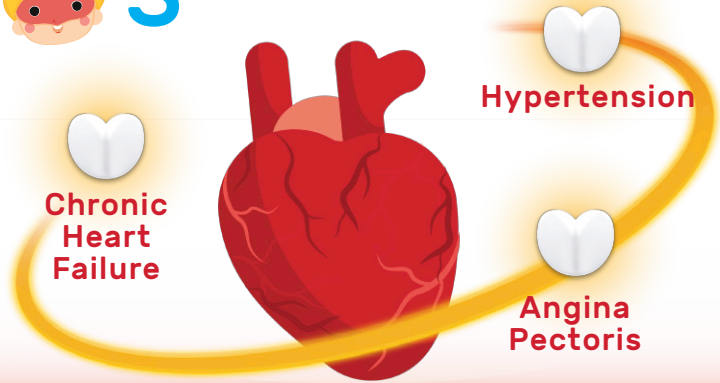
50% Renal Excretion



50% Hepatic Metabolism



3 Indications[5]



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Comparison

Concor® Bisoprolol

High β-1 selective Concor® simplifies treatment with once-daily dosing[5]

Criteria	Concor®[5,6]	Nebivolol[7,8,9]	Metoprolol[6,10]	Atenolol[6,11]	Carvedilol[6,12]
β1/β2 Selectivity	High	High	Medium	Medium	Low
Bioavailability (%)	90	12-96*	77	50	25
Plasma elimination half-life (hours)	10-12	8-27	3-7	6-7	~6.5
Active metabolites	-	+++	-	-	+
Balanced clearance	+	- (Liver)	- (Liver)	- (Renal)	- (Liver)

Oral bioavailbility averages 12% in fast metabolizers and virtually complete in slow metabolizers
* Bioavailability and plasma elimination half-life highly varies due to CYP2D6 Gene Polymorphism. Oral bioavailability averages 12% in fast metabolisers and 96% in slow metabolisers.

References: **1.** Jankovic SM (2014) Expert opinion on drug metabolism & toxicology 10(9):1221-9; **2.** Deroubaix X, Lins RL, Lens S, et al. (1996) International journal of clinical pharmacology and therapeutics 34(2):61-70; **3.** Zhou SF (2009) Clinical pharmacokinetics 48(11):689-723; **4.** Bae JW, Jang CG, Lee SY (2007) The FASEB Journal 21:LB78-LB; **5.** Concor® HK Prescribing Information. Approved Jul 2016; **6.** Tomlinson B, Dalal JJ, Huang J, et al. (2011) Curr Med Res Opin 27(5):1021-33; **7.** Brixius K, Bundkirchen A, Bölck B, et al. (2001) British J. Pharmacol. 133(8):1330-8; **8.** Maack C, Tyroller S, Schnabel P, et al. (2001) British J. of Pharmacol;132(8):1817-26; **9.** Moen MD, Wagstaff AJ. (2006) Drugs 66(10):1389-409; **10.** Toprol-XL® US Prescribing Information. Approved May 2014; **11.** Tenormin® US Prescribing Information. Approved Oct 2012; **12.** Dilatrend® NZ Prescribing Information. (Approved July 2014).

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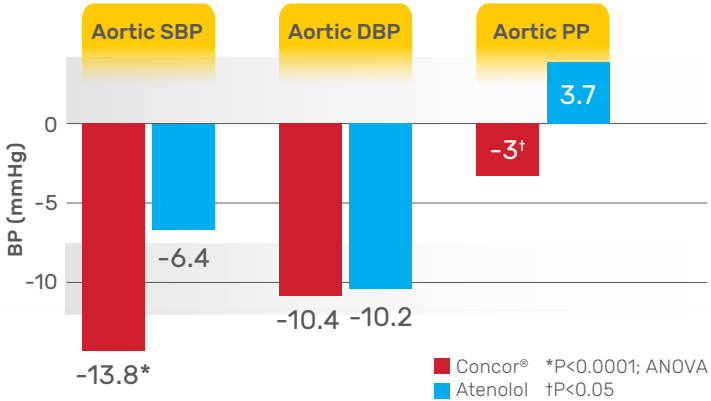
BP Reduction

The high β-1 selective β-blocker with strong efficacy[1,2]

Concor® Bisoprolol

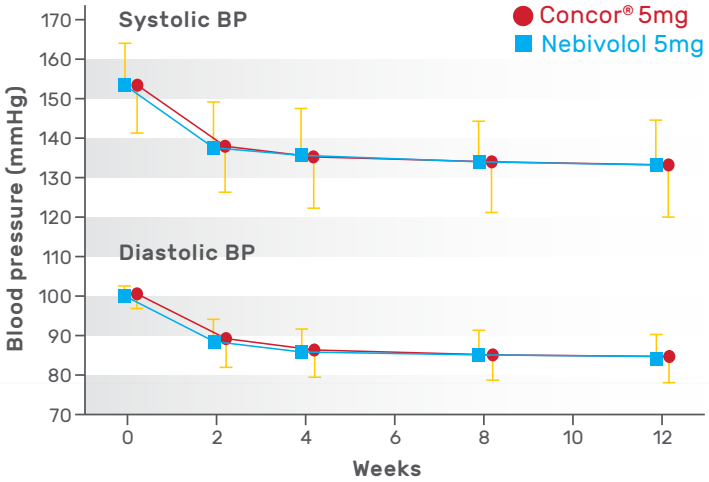
Superior & potent central BP reduction that is beneficial to cardioprotection and stroke prevention[1]

Mean change from baseline hemodynamic variables



Study design : This was a prospective, randomized, controlled study in 109 never-treated hypertensive subjects randomized 1:1 to receive either bisoprolol 5 mg or atenolol 50 mg for 4–8 weeks. Central BP and related parameters were determined using the SphygmoCor device (pulse wave analysis).

Concor® has a similar BP reduction effect as Nebivolol over a 12-week treatment[2]



Study design : Multicenter, single-blind, randomized, parallel-group 16-week study involved a 4-week placebo run-in, follow by a 12-week treatment with Concor® or nebivolol to evaluate antihypertensive efficacy in 273 patients

BP = Blood Pressure; HR = Heart Rate; CV =Cardiovascular;
SBP= Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PP = Pulse Pressure

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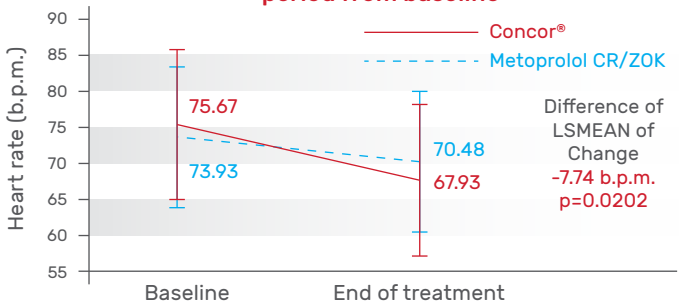
HR Reduction

Concor® Bisoprolol

Shows reduction in RHR and composite cardiac outcome in Asian patients with CAD[3]

Concor demonstrated a better HR reduction compared to metoprolol[4]

Mean heart rate in the last 4 hours of the treatment period from baseline*

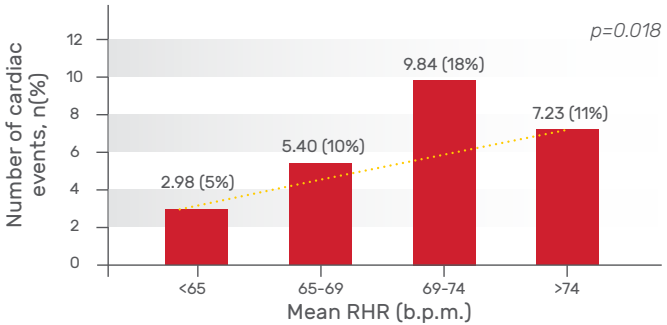


* Gender was used as an covariance in the analysis.

LSMEAN = Least Squares Means

HR was positively correlated with composite CV event rate in BISO-CAD trial[3]

Incidence of composite cardiac endpoint with different RHRs



BP = Blood Pressure; HR = Heart Rate; bpm = beats per minute; CV = Cardiovascular; RHR = Resting Heart Rate

References: **1.** Zhou WJ, Wang RY, Li Y, et al. (2013) Plos one 8(9):e72102; **2.** Czuriga I, Riecansky I, Bodnar J, et al. (2003) Cardiovasc Drugs Ther 17(3):257-63; **3.** Chen Y, Yang X, Nguyen Pham V, et al. (2018) Curr Med Res Opin, 34(2), 217-225; **4.** Yang T, Jiang Y, Hao Y, et al. (2017) Hypertens Res. 40(1):79-86.

Products: Concor 2.5mg, Concor 5mg film-coated tablets for oral use containing 2.5mg & 5mg bisoprolol fumarate, respectively. **Indications:** Treatment of hypertension, coronary heart disease (angina pectoris), stable chronic heart failure (CHF) with reduced left ventricular systolic function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides. **Posology:** for hypertension or angina pectoris the dosage is 5mg bisoprolol fumarate once daily which may be increased to 10mg once daily if necessary. Maximum recommended dose is 20mg once daily. Treatment of stable CHF requires a titration phase, starting with a low dose (1.25mg once daily) and with gradual up-titration (2.5, 3.75, 5, 7.5, 10mg once daily at weekly consideration basis) according to tolerability. Maximum recommended dose for CHF is 10mg bisoprolol fumarate once daily. Special populations: In severe renal impairment (creatinine clearance <20ml/min) or severe liver function disorders a daily dose of 10mg bisoprolol fumarate should not be exceeded for treatment of hypertension of angina pectoris and dose titration in patients with these functional impairments for CHF should be made with particular caution. Use in children is not recommended. Treatment with bisoprolol must not be stopped abruptly, since this might lead to a transitory worsening of heart condition. If transient worsening of heart failure, hypotension or bradycardia occurs during or thereafter the titration phrase, recommend to reconsider the dosage of concomitant medication, or temporarily lower the dose of bisoprolol, or discontinuation. Reintroduction and/or, uptitration of bisoprolol should always be considered when patient becomes stable again. **Contraindications:** acute heart failure or during episodes of heart failure decompensation, cardiogenic shock, second or third degree AV block, sick sinus syndrome, sinoatrial block, symptomatic bradycardia or hypotension, severe bronchial asthma, severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome, untreated phaechromocytoma, metabolic acidosis, hypersensitivity to bisoprolol or to any of the excipients. **Warnings and precautions for use:** Use with caution in: bronchospasm (bronchial asthma, obstructive airways disease; concomitant bronchodilating therapy recommended); diabetes mellitus; symptoms of hypoglycemia can be masked; strict fasting; ongoing desensitization therapy; first degree AV block; Prinzmetal's angina; peripheral arterial occlusive disease; allergic reactions; phaeochromocytoma. Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after a careful balancing of benefits and risks. Symptoms of thyrotoxicosis may be masked. In patients undergoing general anesthesia, the anesthesist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be gradually and completed about 48 hours before anesthesia. Initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. There is no therapeutic experience in Concor in patients with heart failure and concomitant insulin dependent type I diabetes mellitus, severely impaired kidney function, severely impaired hepatic function, restrictive cardiomyopathy, congenital heart disease, hemodynamically significant organic valvular disease. Age>80 years, myocardial infarction within 3 months. **Ability to drive and use machines:** may be impaired, particularly at start of treatment, upon change of medication, or in conjunction with alcohol. **Interactions:** Combinations not recommended: class I antiarrhythmic drugs (CHF), calcium antagonists of the verapamil and diltiazem type, centrally-acting antihypertensive drugs. Combinations to be used with caution: class I antiarrhythmic drugs (hypertension or angina pectoris), calcium antagonists of the dihydropyridine type, class III antiarrhythmic drugs, parasympathomimetic drugs, topical beta-blockers (e.g. eye drops), insulin and oral antidiabetic drugs, anesthetic agents, digitalis glycosides, non-steroidal anti-inflammatory drugs (NSAIDs), sympathomimetic agents, antihypertensive agents and other drugs with blood pressure lowering potential. Combination to be considered: mefloquine, monoamine oxidase inhibitors. **Pregnancy and lactation:** Use of bisoprolol not recommended. **Adverse reactions:** Very common: bradycardia (in CHF patients). Common: worsening of pre-existing heart failure (in CHF patients), dizziness, headache, gastrointestinal complaints such as nausea, vomiting, diarrhea, constipation; feeling of coldness or numbness in the extremities, hypotension (especially in CHF patients), asthenia (in CHF patients), fatigue. Uncommon: AV-conduction disturbances, bronchospasm in patients with bronchial asthma or a history of obstructive airway disease, muscle weakness, muscle cramps, depression, sleep disorders; in patients with hypertension or angina pectoris (worsening of pre-existing heart failure, bradycardia), asthenia. Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT) syncope, reduced tear flow, hearing disorders, allergic rhinitis, hypersensitivity reactions such as itching, flush, rash; hepatitis, potency disorders, nightmares, hallucinations. Very rare: conjunctivitis, alopecia; beta-blockers may provoke or worsen psoriasis or include psoriasis-like rash. Most common signs of overdose: bradycardia, hypotension, bronchospasm, acute cardiac failure, hypoglycemia. **Date of product information:** July 2016

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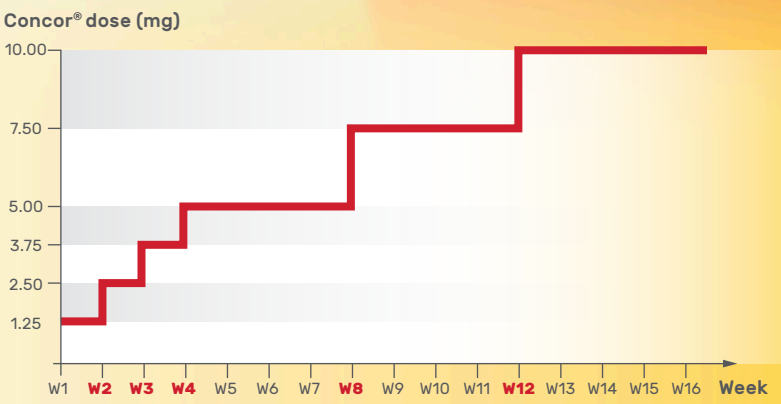
Concor®
Bisoprolol

Titration Scheme of Concor® in treatment of stable chronic heart failure[1]

Close Monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening **heart failure** is recommended during the titration phase.



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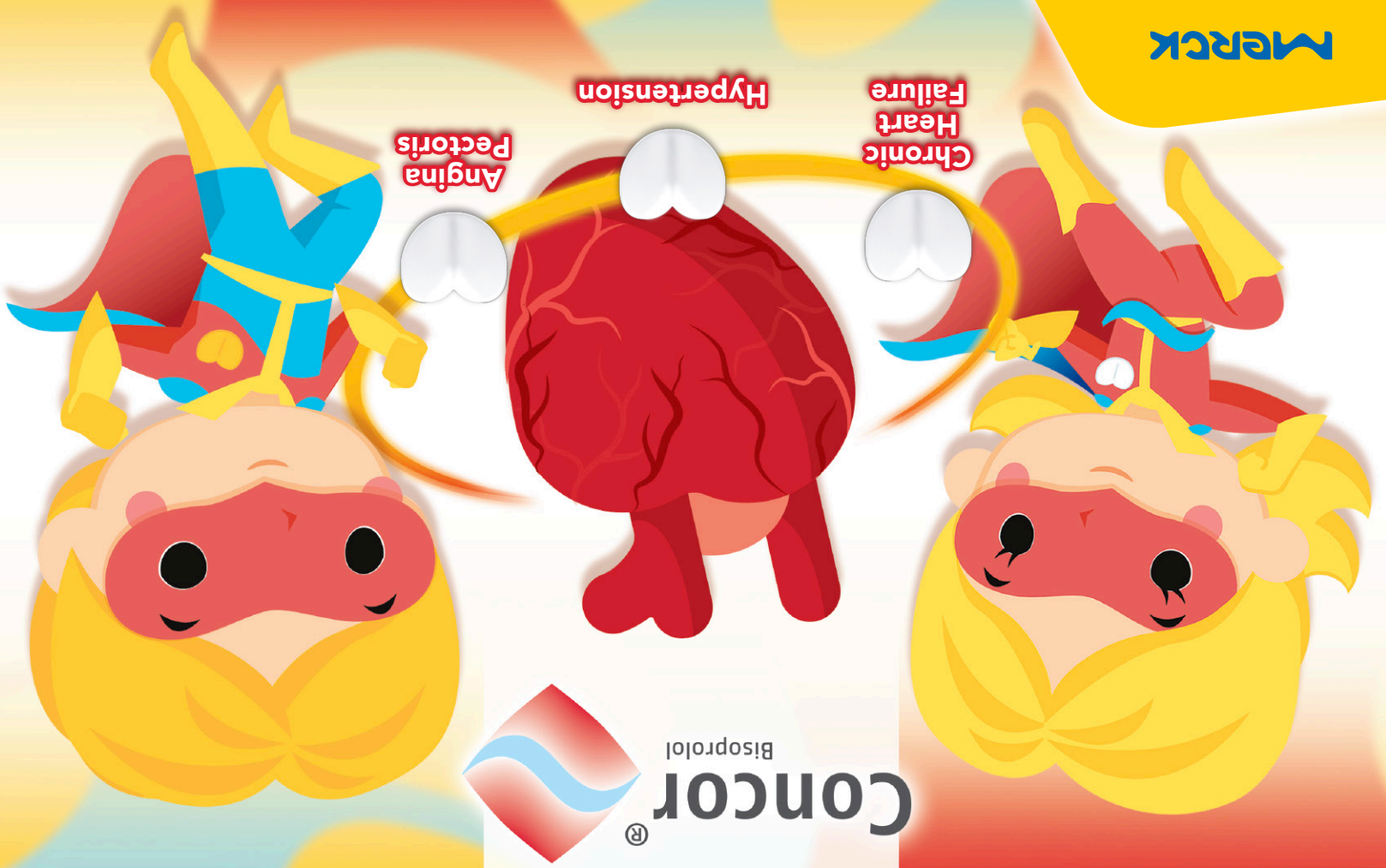

Concor®
Bisoprolol