Public Assessment Report
BETALOC ZOK

INFORMASI PRODUK

Nama obat	:	Betaloc Zok
Bentuk sediaan	:	Tablet lepas lambat
Zat aktif	:	Metoprolol succinate ~ Metoprolol 25 mg & 50 mg
Kemasan	:	Dus, 2 blister @ 14 tablet pelepasan lambat
Pendaftar	:	AstraZeneca Indonesia
Produsen	:	AstraZeneca AB, Sodertalje, Swedia
Kategori Registrasi	:	Registrasi obat baru yang sudah terdaftar dengan indikasi dan posologi baru
Indikasi yang diajukan	:	− *Hypertension* − *Angina pectoris* − *Symptomatic mild to severe chronic heart failure as an adjunct to the other heart failure therapy; to increase survival, reduce hospitalization, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life* − *Maintenance treatment after myocardial infraction*
Posologi yang diajukan	:	*Hypertension* *...* *Angina Pectoris* *...* *Chronic heart failure* *The dose of Betaloc ZOK should be individually adjusted in patients with chronic heart failure stabilized on other heart failure treatment. A recommended initial dose during the first two weeks is a 25 mg tablet once daily. It is recommended that patients with NYHA functional classes III-IV begin with half a 25 mg tablet once daily the first week. It is recommended that the dose then be doubled every second week up to a maximum target dose of 200 mg Betaloc ZOK once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 200 mg Betaloc ZOK once daily (or the highest tolerated dose).* *At each dose level the patient should be carefully evaluated with regard to tolerability. In case of hypotension, decrease in concomitant medication may be necessary. Initial hypotension does not necessarily mean that the dose cannot be tolerated in chronic treatment, but the patient should be kept at the lower dose until stabilized* *Maintenance treatment after myocardial infarction* *...*

PENGANTAR

Betaloc Zok mengandung zat aktif metoprolol dan merupakan betablocker selektif teradap reseptor β. Obat ini telah diterima di Indonesia untuk indikasi : *Hypertension, Angina pectoris, Maintenance treatment after myocardial infraction*

Pengajuan saat ini dalam rangka penambahan indikasi, dengan indikasi yang diajukan sebagai berikut :

Symptomatic mild to severe chronic heart failure as an adjunct to the other heart failure therapy; to increase survival, reduce hospitalization, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life

ASPEK MUTU
NA
Tidak terdapat perubahan terkait aspek mutu obat

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
NA
Tidak terdapat data studi non klinik yang diserahkan untuk mendukung pengajuan ini

Studi Klinik
Evaluasi dilakukan pada 4 studi klinik untuk mendukung khasiat dan keamanan metoprolol tablet pelepasan lambat untuk indikasi gejala gagal jantung kronis ringan hingga berat sebagai tambahan untuk pengobatan gagal jantung lainnya dengan desain *randomised, double-blind, placebo controlled, parallel group* (studi SH-MET-0024, n=3991; studi S-996, n=83; studi S-996 extension, n=83; dan studi SH-AHS-001 RESOLVD, n=262)

Efikasi

Studi SH-MET-0024
Studi ini menilai kemanfaatan klinik dari metoprolol tablet pelepasan lambat 25 mg, 50 mg, 100 mg dan 200 mg, satu kali sehari, sesuai dengan dosis individu pasien vs. *placebo* pada pasien gagal jantung kongestif(NYHA Class II-IV) yang telah menerima pengobatan kombinasi diuretik dan ACE inhibitor. Hasil studi menunjukkan :

- *Risk Reduction* (RR) kematian total sebesar 34%, 145 vs. 217, p=0,00009
- RR kematian dan perawatan di RS karena gagal jantung sebesar 31%, 30 vs. 58, p<0,00001
- perawatan di RS *(hospitalisations*) karena perburukan gagal jantung sebesar 317 vs. 451, p=0,0013

Studi 996 dan S 996 *extension*
Studi ini menilai tolerabilitas / efek pemberian metoprolol tablet pelepasan lambat 12,5 mg, 25 mg, 50 mg, 100 mg dan 150 mg, satu kali sehari vs. *placebo* pada pasien gagal jantung kongestif (NYHA Class III-IV), *left ventricular ejection fraction* (LVEF) < 0,4 yang stabil dalam 30 hari sebelumnya dan telah menerima diuretik/digoxin/vasodilator/ACE inhibitor/kombinasi digoxin+vasodilator/ACE inhibitor. Hasil studi menunjukkan :

- frekuensi kunjungan ke rumah sakit yaitu 4,8% vs. 10,5% (minggu ke-26) dan 9,1% vs. 30,0% (18 bulan)
- perbaikan LVEF pada minggu ke-26 yaitu 0,09 vs. 0,02, p=0,015

Studi 996 dan S 996 extension menunjukkan bahwa Metoprolol memiliki frekuensi kunjungan ke rumah sakit yang lebih sedikit dibandingkan dengan *placebo*. Perbaikan LVEF lebih baik pada kelompok metoprolol

Studi SH- AHS-001 RESOLVD
Studi ini menilai kemanfaatan klinik Metoprolol yang ditambahkan pada terapi Candesartan. Studi dilakukan dengan pemberian metoprolol tablet pelepasan lambat 200 mg, satu kali sehari selama 24 minggu vs. *placebo* pada pasien gagal jantung kongestif (NYHA Class II-IV), LVEF < 0,4 sebagai terapi tambahan yang telah diberikan sebelumnya yaitu candesartan 4 mg, 8 mg atau 16 mg; enalapril 20 mg; atau kombinasi candesartan 4 atau 8 mg dengan enalapril 20 mg selama 17 minggu. Hasil studi menunjukkan :

- 6-*minute walk test distance* (meter) sebanding yaitu 397+84 vs. 400+85 (*baseline*) dan 396+94 vs. 397+103 (minggu ke-46), p=0,909
- Perbaikan nilai Pro-ANP dan BNP yang lebih baik pada kelompok metoprolol, yaitu : nilai Pro-

ANP (pmol/l) sebesar 208+696 vs. -17+657, p<0,001 dan BNP (pmol/l) sebesar 11,3+41,5 vs. 2,0+31,2 p=0,002
- perbaikan skor NYHA(%) dan LVEF(%) pada minggu ke-24 sebanding yaitu 12% vs. 10,2% dan 0,025+0,06 vs. -0,005+0,06, p<0,05

Keamanan
Tidak ada laporan efek samping jenis baru pada semua studi yang diserahkan

Kematian
- Jumlah kematian pada studi SH-MET-0024 sebanyak 145 pasien dimana jumlah tersebut lebih rendah dibandingkan placebo sebesar 217 pasien
- Jumlah kematian pada studi SH-AHS-001 RESOLVD sebanyak 8 pasien (4%) dimana jumlah tersebut lebih rendah dibandingkan placebo sebanyak 17 pasien (8%)

Efek samping lainnya
- Jumlah pasien yang dilaporkan mengalami efek samping serius non- fatal pada studi SH-MET-0024 menunjukkan nilai yang lebih rendah pada kelompok Metoprolol dibandingkan *placebo* (664 vs 751). Efek samping samping yang paling sering dilaporkan adalah *cardiac failure/ aggravated cardiac failure* dan *angina pectoris / aggravated angina pectoris*
- Jumlah pasien yang dilaporkan mengalami efek samping serius non fatal pada studi SH-AHS-0002 (RESOLVD) menunjukkan nilai yang similar antara kelompok Metoprolol dengan placebo. Efek samping yang paling sering dilaporkan adalah *cardiac failure / aggravated cardiac failure*

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, penambahan indikasi dan posologi baru Betaloc Zok tablet pelepasan lambat diterima sesuai posologi yang diajukan dan dengan perbaikan indikasi :
Heart Failure, to reduce the risk of cardiovascular mortality and heart failure hospitalizations in patients with heart failure

Public Assessment Report
BETALOC ZOK

PRODUCT INFORMATION

Name of the drug	:	Betaloc Zok
Dosage form	:	Prolonged release tablets
Active substances	:	Metoprolol succinate ~ Metoprolol 25mg & 50mg
Packaging	:	Box, 2 blisters @ 14 Prolonged release tablets
Registrant	:	AstraZeneca Indonesia
Manufacturer	:	AstraZeneca AB, Sodertalje, Sweden
Registration Category	:	Registration new indication and posology
Proposed Indications	:	– *Hypertension* – *Angina pectoris* – *Symptomatic mild to severe chronic heart failure as an adjunct to the other heart failure therapy; to increase survival, reduce hospitalization, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life* – *Maintenance treatment after myocardial infarction*
Proposed posology	:	*Hypertension* *...* *Angina pectoris* *...* *Chronic heart failure* *The dose of Betaloc ZOK should be individually adjusted in patients with chronic heart failure stabilized on other heart failure treatment. A recommended initial dose during the first two weeks is a 25 mg tablet once daily. It is recommended that patients with NYHA functional classes III-IV begin with half a 25 mg tablet once daily the first week. It is recommended that the dose then be doubled every second week up to a maximum target dose of 200 mg Betaloc ZOK once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 200 mg Betaloc ZOK once daily (or the highest tolerated dose).* *At each dose level the patient should be carefully evaluated with regard to tolerability. In case of hypotension, decrease in concomitant medication may be necessary. Initial hypotension does not necessarily mean that the dose cannot be tolerated in chronic treatment, but the patient should be kept at the lower dose until stabilized* *Maintenance treatment after myocardial infarction* *...*

INTRODUCTION

Betaloc Zok contains the active substance metoprolol and is a selective betablocker that targets β receptors. This drug has been accepted in Indonesia for indications: *Hypertension, Angina pectoris, Maintenance treatment after myocardial infraction*

The application is currently in order of addition indications, with indications submitted as follows:

Symptomatic mild to severe chronic heart failure as an adjunct to the other heart failure therapy; to increase survival, reduce hospitalization, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life

QUALITY ASPECTS
NA
There is no change in the quality of the drug product.

EFFICACY AND SAFETY ASPECTS

Non Clinical Studies
NA
There was no non-clinical studies submitted to support this application

Clinical Studies
Evaluation was conducted in 4 clinical studies to support the efficacy and safety of metoprolol Prolonged release tablets for the indication of symptoms of mild to severe chronic heart failure in addition to other heart failure treatments by randomised, double-blind, placebo controlled, parallel group design *(study SH-MET-0024, n=3991; study S-996,*n=83; study S-996 extension, n=83; and study SH-AHS-001RESOLVD, n=262)

Efficacy

Study SH-MET-0024
The study assessed the clinical efficacy of metoprolol Prolonged release tablets of 25 mg, 50 mg, 100 mg and 200 mg, once daily, according to the patient's individual dose vs. *placebo* in congestive heart failure patients (NYHA Class II-IV) who had received combination treatment of diuretics and ACE inhibitors. The results of the study showed:

- *Risk Reduction* (RR) of total deaths was 34%, 145 vs. 217, p=0.00009
- RR of death and hospital care due to heart failure by 31%, 30 vs. 58, p < 0.00001
- *Hospital* care (hospitalisations) due to worsening of heart failure was 317 vs. 451, p=0.0013

Study 996 and S 996 *extension*
This study assessed the tolerability/effect of metoprolol Prolonged release tablets 12.5 mg, 25 mg, 50 mg, 100 mg and 150 mg, once daily vs. *placebo* in patients with congestive heart failure (NYHA Class III-IV), *left ventricular ejection fraction* (LVEF) < 0.4 who were stable in the previous 30 days and had received diuretic/digoxin/vasodilator/ACE inhibitor/combination digoxin +vasodilator/ACE inhibitor. The results of the study showed:

- The frequency of hospital visits was 4.8% vs. 10.5% (26th week) and 9.1% vs. 30.0% (18 months)
- LVEF improvement at week 26 was 0.09 vs. 0.02, p=0.015

Studies 996 and S 996 extension showed that Metoprolol had a lower frequency of hospital visits compared to placebo. Improvement of LVEF was better in metoprolol group

SH- AHS-001 RESOLVD Study
The study assessed the clinical efficacy of Metoprolol added to Candesartan therapy. Studies were conducted with the administration of metoprolol 200 mg Prolonged release tablets, once daily for 24 weeks vs. *placebo* in patients with congestive heart failure (NYHA Class II-IV), LVEF < 0.4 as an adjunct to previously administered therapy of candesartan 4 mg, 8 mg or 16 mg; enalapril 20 mg; or a combination of candesartan 4 or 8 mg with enalapril 20 mg for 17 weeks. The results of the study showed:

- 6-minute walk*test distance* (meters) is comparable, 397+84 vs. 400+85 (baseline) and 396+94 vs. 397+103 (*week*46), p=0.909
- Improved improvements in pro-ANP and BNP values in the metoprolol group, namely: pro-ANP values (pmol/l) of 208+696 vs. -17+657, p < of 0.001 and BNP (pmol/l) of 11.3+41.5 vs. 2.0+31.2 p=0.002
- improvements in NYHA (%) and LVEF (%) scores at week 24 were comparable i.e. 12% vs. 10.2% and 0.025+0.06 vs. -0.005+0.06, p < 0.05

Safety
There were no reports of new types of side effects in any of the submitted studies

Mortality

- The number of deaths in the SH-MET-0024 study was 145 patients, which was lower than placebo by 217 patients
- The number of deaths in the SH-AHS-001 RESOLVD study was 8 patients (4%), which was lower than placebo by 17 patients (8%)

Other side effects

- The number of patients who reported non-fatal serious adverse events in the SH-MET-0024 study showed lower scores in the Metoprolol group compared to *placebo* (664 vs. 751). The most commonly reported adverse events are *cardiac failure/ aggravated cardiac failure* and *angina pectoris/ aggravated angina pectoris*
- The number of patients who reported serious non-fatal adverse events in study SH-AHS-0002 (RESOLVD) showed similar values between Metoprolol and placebo groups. The most commonly reported side effect is *cardiac failure/aggravated heart failure*

DECISION

Considering the above efficacy and safety data, the addition of new indications and posology Betaloc Zok Prolonged release tablets are accepted according to the proposed posology and with improvements in indications:
Heart failure, to reduce the risk of cardiovascular mortality and heart failure hospitalizations in patients with heart failure