



Fiksna kombinacija felodipina i metoprolola u liječenju arterijske hipertenzije

Fixed combination of felodipine and metoprolol in treatment of hypertension

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SAŽETAK: Terapija fiksnom kombinacijom felodipina i metoprolola u liječenju arterijske hipertenzije postiže se zadovoljavajući učinak kod hipertenzivnih pacijenata na sniženje vrijednosti sistoličkog i dijastoličkog arterijskog tlaka (AT). Taj učinak je postojan tijekom vremena duljem od dvije godine, a sa sniženjem sistoličkog i dijastoličkog AT postiže se smanjenje ukupnih kardiovaskularnih komplikacija: smanjenje incidencije moždanog udara za trećinu, a infarkta miokarda za šestinu. Ova fiksna kombinacija primjenjiva je kod osoba koje nisu uspjele regulirati AT primjenom drugih pojedinačnih antihipertenziva, ostvarujući postojano sniženje AT u 24-satnom razdoblju. Terapija je uz to s manje nuspojava nego većina dosadašnjih fiksnih kombinacija antihipertenziva, jer nema metabolički nepovoljnih učinaka i stoga se može primijeniti i u visokorizičnih bolesnika s metaboličkim sindromom i dijabetesom. Primjena fiksne kombinacije felodipina i metoprolola može ostvariti zadane ciljeve snižavanja AT i smanjenja kardiovaskularnog rizika učinkovito kod 70-89% pacijenata. I felodipin i metoprolol pojedinačno primjenjuje se i u liječenju koronarne bolesti srca čime se u ovoj kombinaciji ostvaruje i koronarna protekcija.

KLJUČNE RIJEČI: felodipin, metoprolol, arterijska hipertenzija.

SUMMARY: The therapy with combination of felodipine and metoprolol in treatment of hypertension results in satisfactory effect with hypertensive patients on lowering the values of systolic and diastolic blood pressure (BP). This effect is sustained during the period over two years, while lowering of systolic and diastolic BP results in reduction of total cardiovascular complications: reduction of incidence of stroke for one third of patients and myocardial infarction for one sixth of patients. This fixed combination is applicable with patients that did not manage to regulate BP by using some other specific antihypertensive drugs, achieving sustained lowering of BP in a 24-hour period. There are fewer side-effects associated with this therapy than with the fixed combinations of antihypertensive drugs used so far, since there are no negative metabolic effects and therefore it may be applied in high risk patients with metabolic syndrome and diabetes. The application of the fixed combination of felodipine and metoprolol may achieve the set targets related with lowering of BP and reducing cardiovascular risk efficiently in 70-89% patients. Both felodipine and metoprolol are individually applied in treatment of coronary heart disease whereas this combination may lead to coronary protection.

KEYWORDS: felodipine, metoprolol, hypertension.

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Arterijska hipertenzija (AH) predstavlja najčešću bolest kardiovaskularnog sustava, a procjenjuje se da od nje boluje oko trećina odrasle muške i četvrtina odrasle ženske populacije. Prema definiciji Europskog društva za hipertenziju i Europskog kardiološkog društva povišen arterijski tlak (AT) smatra se izmjerena vrijednost sistoličkog tlaka iznad 140 i/ili dijastoličkog tlaka iznad 90 mmHg¹. Primarni cilj u hipertenzivnog pacijenta jest dugoročno smanjenje sveukupnog kardiovaskularnog rizika. Shodno tome mora se liječiti ne samo povišen AT već i svi pridruženi rizični čimbenici. Cilj terapije je smanjenje AT ispod vrijednosti 140/90 mmHg odnosno 130/80 mmHg kod osoba s dijabetesom te onih s visokim ili vrlo visokim rizikom (osobe s preboljelim moždanim udarom, infarktomiokarda, bubrežnim zatajenjem i proteinurijom). Već je klinička studija Hypertension Optimal Treatment (HOT) 1998. godine pokazala da je najniža incidencija kardiovaskularnih komplikacija postignuta smanjenjem dijastoličkog AT na vrijednost od 82,6 mmHg, dok je kod dijabetičkih bolesnika smanjenje dijastoličkog AT ispod 80 mmHg rezultiralo u daljem smanjenju kardiovaskularnih komplikacija za 51%². Pri odabiru antihipertenzivne terapije smjernice za liječenje hipertenzije preporučuju individualni pristup koji se temelji na ravnomjernoj važnosti

Arterial hypertension is one of the most frequent diseases of cardiovascular systems and one third of adult male and one fourth of adult female population are considered to suffer from this disease. According to the definition of the European Society of Hypertension and the European Society of Cardiology, a high blood pressure (BP) is considered to be a measured value of systolic BP over 140 and/or diastolic BP over 90 mmHg¹. The primary goal in a hypertensive patient is a long-term reduction of total cardiovascular risk. Accordingly, it is not only a higher BP to be treated, but all associated risk factors. The goal of the therapy is reducing BP below the value 140/90 mmHg or 130/80 mmHg with persons with diabetes and those with a high or very high risk (persons who suffered from stroke, myocardial infarction, renal failure and proteinuria). The clinical study Hypertension Optimal Treatment (HOT) in 1998 showed that the lowest incidence of cardiovascular complications is achieved by reducing diastolic BP to the value of 82.6 mmHg, while in diabetic patients the reduction of diastolic BP below 80 mmHg resulted in further reduction of cardiovascular complications by 51%². Whilst selecting antihypertensive therapy the guidelines for hypertension treatment recommend individual approach that is based on equal importance of all drugs from any group of



svih lijekova iz bilo koje skupine antihipertenziva. Kod određenih kliničkih stanja prednost imaju pojedine skupinama antihipertenziva¹.

No, za postizanje ciljnih vrijednosti AT kod većine pacijenata potrebna je primjena dva ili više lijekova. U HOT studiji broj pacijenata koji je uzimao dva ili više lijekova za regulaciju AT rastao je sukladno postavljenim ciljnim vrijednostima dijastoličkog AT: za <90 mmHg 60% pacijenata, za <85 mmHg 69% pacijenata, a za <80 mmHg 76% pacijenata². Prema metaanalizama nekih dostupnih studija, postotak pacijenata koji su trebali dva i više lijekova za učinkovito snižavanje AT bio je od 33 do 100%³. S druge strane, uzimanje dva medikamenta u obliku dvije tablete smanjuje ustrajnost uzimanja lijekova tijekom godinu dana za 20% u usporedbi s pripravkom oba lijeka u jednoj tableti (fiksnoj kombinaciji)⁴.

Fiksna kombinacija felodipina u dozi od 5 mg i metoprolola ZOK u dozi od 50 mg ima za cilj učinkovito liječiti AH uz povećanje ustrajnosti uzimanja terapije. Svaka od komponenti pojedinačno dokazana je u indikaciji liječenja AH.

Felodipin je vazoselektivni blokator kalcijevih kanala koji se primjenjuje u liječenju AH i stabilne angine pectoris. Felodipin je derivat dihidropiridina koji smanjuje periferni vaskularni otpor, naročito arterija. Električna i kontraktilna aktivnost stanica glatkih mišića krvnih žila inhibira se učinkom na kalcijeve kanale u staničnoj membrani. Zbog selektivnog učinka na glatke mišiće u arterijama (smanjuje perifernu arterijsku rezistenciju), felodipin u terapijskim dozama nema negativnih inotropnih učinaka na srce, niti bilo kakvog klinički značajnog elektrofiziološkog srčanog učinka za razliku od nekih blokatora kalcijevih kanala ranijih generacija ili kemijskog sastava. Stoga, nije neobično što je felodipin bio uključen u velike kliničke studije u kojima se liječila AH, među kojima valja istaknuti STOP-Hypertension 2 te HOT studiju. Budući da je tijekom dugotrajnog liječenja felodipinom uočeno kako je lijek metabolički neutralan (nije primijećen značajan učinak niti na lipide niti na HbA1c) može se koristiti kod bolesnika sa šećernom bolesti, dislipidemijama, uričkom dijatezom što je neobično važno budući da danas dobro znamo kako je AH sindrom u kojem su isprepleteni brojni drugi čimbenici ubrzanog starenja, tj. ateroskleroze. S obzirom kako relaksira i glatko mišićje dišnih putova može se propisati i bolesnicima s bronhalnom astmom. Felodipin se u načelu može davati bolesnicima s narušenom funkcijom lijeve klijetke istodobno s konvencionalnom terapijom. No, kod ovih bolesnika, kao i ostali dihidropiridinski blokatori kalcijevih kanala, nije lijek izbora za početak liječenja. No, u slučaju nemogućnosti postizanja kontrole AT ostalim lijekovima može se uvrstiti u kombinaciju. Felodipin snižava AT smanjujući periferni vaskularni otpor. Liječenje felodipinom snižava AT u hipertoničara u sjedećem i u uspravnom položaju, u mirovanju te tijekom napora. Felodipin ne izaziva ortostatsku hipotenziju, jer pripravak ne djeluje na glatke mišiće u venama ili na adrenergične kontrolne mehanizme. Sniženi AT može u početku izazvati privremeno refleksno povećanje srčane frekvencije i minutnog volumena što je uobičajena pojava kod dihidropiridinskih blokatora kalcijevih kanala. U stanju dinamičke ravnoteže taj se učinak održava u cijelom rasponu doza i daje 24-satno sniženje AT. Liječenje felodipinom dovodi

antihypertensives. In case of certain clinical conditions, the advantage is given to specific groups of antihypertensives¹.

However, in order to achieve BP target values, most patients should take two or more drugs. In HOT study, the number of patients that took two or more drugs for regulation of BP grew according to set target values of diastolic BP: for <90 mmHg 60% of patients, for <85 mmHg 69% of patients, while for <80 mmHg 76% of patients². According to meta-analyses of some available studies, the percentage of patients who needed two or more drugs for efficient lowering of BP was from 33 to 100%³. On the other hand, taking two medicines in the form of two pills reduces persistence in taking drugs during the period of one year by 20% compared to the preparation of the both drugs in one pill (fixed combination)⁴.

The fixed combination of felodipine in 5 mg dose and metoprolol ZOK in 50 mg dose is aimed at efficient treatment of hypertension with higher persistence in taking the therapy. Each of the components is proved in the indication of hypertension treatment.

Felodipine is a vasoselective calcium channel blocker that is applied in treatment of hypertension and stable angina pectoris. Felodipine is a dihydropyridine derivative that reduces the peripheral vascular resistance, especially of arteries. Electrical and contractile activity of cells of blood vessel smooth muscles is inhibited by an effect on calcium channels in cell membrane. Due to selective effect on arterial smooth muscles (it reduces peripheral arterial resistance), felodipine in therapeutic doses has no negative inotropic effects on heart, and no clinically significant electrophysiological heart effects unlike some calcium-channel blockers of previous generations or chemical composition. Therefore, it is not unusual that felodipine was included in large clinical studies where hypertension was treated, whereas STOP-Hypertension 2 and HOT study are to be emphasized. Since during the long-term treatment with felodipine it was observed that the drug was metabolically neutral (no significant effect on lipids and HbA1c was perceived) and it may be used by diabetic patients, patients suffering from dyslipidemia, uric diathesis which is very important since we have learnt so far that hypertension is the syndrome that includes many other accelerated ageing factors, that is, atherosclerosis factors. Since it relaxes respiratory pathway smooth muscles, it may be prescribed to patients suffering from bronchial asthma. Felodipine may principally be given to patients with decreased left ventricular function together with conventional therapy. However, in such patients, just like the other dihydropyridine calcium channel blockers it is not a drug of choice at the beginning of the treatment. However, if it is not possible to achieve BP control with some other drugs, it may be included in the combination. Felodipine reduces BP by reducing peripheral vascular resistance. The treatment with felodipine lowers BP in hypertensive patients in sitting or upright position, while resting or under load. Felodipine causes no orthostatic hypotension since the preparation has no effect on venous smooth muscles or on adrenergic control mechanisms. The lowered BP may cause temporary reflex increase in heart rate and minute volume at the beginning which is a normal phenomenon for dihydropyridine calcium channel blockers. In the condition of dynamic balance, this effect is maintained in whole range of doses and results in 24-hour lowering of BP. The treatment with felodipine



do regresije hipertrofije lijeve klijetke. Kao i ostali dihidropiridinski blokatori kalcijevih kanala, felodipin ima natriuretsko i diuretsko djelovanje, ali nema kaliuretski učinak. Osim antihipertenzivnog učinka koji se ostvaruje djelovanjem na relaksaciju glatkih mišića krvnih žila, felodipin djeluje i tako da dilatira koronarne žile čime se poboljšava perfuzija i opskrbu srca kisikom. Srčano opterećenje se smanjuje sa smanjenjem perifernog otpora (smanjeni "afterload") i to dovodi do smanjene potrebe miokarda za kisikom. Felodipin suzbija koronarni vazospazam. Felodipin poboljšava toleranciju na napor i smanjuje napade angine u bolesnika sa stabilnom, naporom izazvanom anginom pectoris. Djelovanje felodipina započinje u roku od dva sata, a traje 24 sata. U liječenju bolesnika s anginom pectoris felodipin se može uzimati u kombinaciji s blokatorima beta-adrenergičkih receptora ili kao monoterapija.

Dokazana učinkovitost beta-blokatora na smanjenje kardiovaskularnih komplikacija u meta analizi primjena beta-blokatora baca pozitivno svjetlo na njihovu terapijsku primjenu u indikaciji liječenja AH⁵. Učinkovitost metoprolola analizirana je, pak, u brojnim ispitivanjima u bolesnika s AH 1. i 2. stupnja⁶. Pri tome su učinci metoprolola bili uspoređivani s placebom⁷, a uspoređivan je i obični kratkodjelujući pripravak metoprolola s onim s produljenim otpuštanjem i djelovanjem⁷⁻⁹. Uspoređen je i učinak metoprolola na AH u usporedbi sa standardnim beta-blokatorom, atenololom⁸⁻¹².

Metoprolol ZOK ispitivan je u studijama do 12 tjedana, a ispitane su brojne doze lijeka, kako fiksne tako i prilagođene prema postignutom antihipertenzivnom učinku^{8,9,12}. Metoprolol ZOK prema svim ispitivanjima uzrokuje značajno sniženje AT, u odnosu na bazalne vrijednosti⁵. Broj bolesnika s ostvarenim ciljnim dijastoličkim tlakom <90 mmHg u različitim studijama kretao se od 51% do 89%⁸⁻¹⁰. Usporedbom s atenololom¹² i standardnim oblikom metoprolola⁸ ostvaren je bolji učinak metoprolola ZOK na sniženje AT.

Kombinacija felodipina i metoprolola ZOK predstavlja primjer povoljne, sinergističke kombinacije dva antihipertenziva, s povoljnim konačnim učinkom, a bez potenciranja neželjenih posljedica. Prilikom primjene dihidropiridinskih blokatora kalcijevih kanala, zbog ostvarene periferne vazodilatacije dolazi do refleksne tahikardije u manjoj ili većoj mjeri, ovisno o primijenjenom preparatu. Beta-blokatori, pak, svojim učinkom blokade beta-adrenergičkih receptora smanjuju refleksnu tahikardiju, uz istodobno aditivno djelovanje u smislu smanjenja AT.

Podaci iz kliničkih studija koje su ispitivale učinak kombinacije felodipina i metoprolola s uključenih 1.350 ispitanika kod kojih AT nije bio adekvatno reguliran dotadašnjom terapijom, ili kod 193 ispitanika koji su imali nuspojave na ranije primijenjenu terapiju, upućuju na ostvarenu kontrolu AT kod 84,4% osoba¹³. I u ostalim ispitivanjima je kombinacija felodipina i metoprolola ostvarila kontrolu AT prema ciljnim vrijednostima u 63 do 76% osoba¹⁴⁻¹⁶. Usporedbom s kombinacijskim liječenjem nifedipinom i atenololom, kombinacija felodipina i metoprolola polučila je signifikantno bolju regulaciju AT¹⁷. Kada se ispitivala ostvarena kontrola AT u 24-satnom razdoblju, kombinacija felodipina i metoprolola je ostvarila veći stupanj kontrole u cijelom razdoblju od adekvatno liječenih am-

results in regression of hypertrophy of the left ventricle. As all other dihydropyridine calcium channel blockers, felodipine has natriuretic and diuretic effect, but it has no kaliuretic effect. Besides the antihypertensive effect that is achieved by exerting effect on relaxation of blood vessel smooth muscles, felodipine is effective and so dilates coronary vessels thereby improving perfusion and supply of the heart with oxygen. Heart load is reduced by reducing peripheral arterial resistance (reduced "afterload") and leads to reduced need of the myocardium for oxygen. Felodipine prevents coronary vasospasm. Felodipine improves the load tolerance and reduces the angina attacks in patients with stable angina pectoris caused by load. Felodipine starts being effective within a period of two hours and lasts for 24 hours. In treating the patients with angina pectoris, felodipine may be taken in combination with beta-adrenergic receptor blockers or as a monotherapy.

The proved efficacy of beta-blockers on reducing cardiovascular complications in meta-analysis of application of beta-blockers casts a positive light to their therapeutic application in indication of hypertension treatment⁵. The efficacy of metoprolol has been analyzed in a number of tests in patients with first and second degree of hypertension⁶. On that occasion the effects of metoprolol were compared to the effects of placebo⁷, while the usual short-term preparation of metoprolol was compared to the one with sustained release and effect⁷⁻⁹. The effect of metoprolol on hypertension was compared to standard beta-blocker, atenolol⁸⁻¹².

Metoprolol ZOK was tested in studies up to 12 weeks, while a great number of doses of the drug was tested, not only fixed ones, but also adapted to a specific achieved antihypertensive effect^{8,9,12}. According to all tests metoprolol ZOK causes a significant lowering of BP compared to basal values⁵. A number of patients with achieved target diastolic pressure <90 mmHg in different studies ranged from 51% to 89%⁸⁻¹⁰. The comparison with atenolol¹² and standard form of metoprolol⁸ has resulted in a better effect of metoprolol ZOK on lowering BP.

The combination of felodipine and metoprolol ZOK is an example of positive, synergic combination of two antihypertensive drugs with positive final effect without any adverse consequences. While applying dihydropyridine calcium channel blockers, peripheral vasodilatation causes reflex tachycardia to a greater or smaller extent, depending on applied preparation. Due to their effect of blocking beta-adrenergic receptors, beta-blockers reduce reflex tachycardia thereby additionally influencing lowering BP.

The data from clinical studies that tested the effect of the combination of felodipine and metoprolol with involved 1350 respondents who did not have BP adequately regulated by previous therapy, or in 193 respondents who had side effects from previously applied therapy, indicates the accomplished control of BP in 84.4% of persons¹³. In all other studies, the combination of felodipine and metoprolol resulted in a control of BP according to target values in 63 to 76% of persons¹⁴⁻¹⁶. Having compared the combination treatment with nifedipine and atenolol, the combination with felodipine and metoprolol has shown significantly better regulation of BP¹⁷. When the achieved control of BP in 24-hour period was tested, the combination of felodipine and metoprolol had achieved a higher level of control during the entire period than the amlodipine used



lodipinom (smanjenje AT nakon šest tjedana terapije 14,4/9,5 mmHg felodipin i metoprolol skupina te 8,9/5,5 mmHg amlodipinska skupina)¹⁸.

Tijekom praćenja učinka kombinacije felodipina i metoprolola u razdoblju do dvije godine, antihipertenzivni učinak ostvaren u prvih mjesec dana manjim dijelom se pojačava u sljedećem mjesecu te se zadržava do kraja praćenja od dvije godine¹⁹⁻²¹. Praktički u svim praćenjima postignut je povoljan odgovor AT u oko 90% ispitanika²¹.

Primjena ova dva lijeka u fiksnoj kombinaciji posebno je zanimljiva kod koronarnih bolesnika s hipertenzijom. Oba lijeka jesu lijekovi izbora u liječenju koronarne bolesti srca, a objedinjenje u jednoj tableti olakšava terapijsku primjenu i povećava ustrajnost bolesnika. Posebno jer koronarni bolesnici inače uzimaju i antagregacijsku i statinsku terapiju, a nerijetko i ACE inhibitore.

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Literature

1. Jelaković B. Smjernice za dijagnosticiranje i liječenje arterijske hipertenzija 2007. Radne skupine Europskog društva za hipertenziju i Europskog kardiološkog društva. *Kardio list*. 2007;2(12):79-81.
2. Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens*. 2006;24:2131-41.
3. Elliott WJ. What factors contribute to the inadequate control of elevated blood pressure? *J Clin Hypertens (Greenwich)*. 2008;10(1 Suppl 1):20-6.
4. Dezii CM. Medication noncompliance: what is the problem? *Manag Care*. 2000;9(9 suppl):2-6.
5. Sandberg A, Abrahamsson B, Regårdh C-G, et al. Pharmacokinetic and biopharmaceutical aspects of once daily treatment with metoprolol CR/ZOK: A review article. *J Clin Pharmacol*. 1990;30(Suppl):S2-16.
6. Lückner P, Moore G, Wiselgren I, et al. Pharmacokinetic and pharmacodynamic comparison of metoprolol CR/ZOK once daily with conventional tablets once daily and in divided doses. *J Clin Pharmacol*. 1990; 30(Suppl):S17-27.
7. Wiselgren I, Lundborg P Sandberg A, et al. Pharmacokinetic and pharmacodynamic evaluation of metoprolol controlled-release (CR/ZOK) 50 mg in young subjects. *J Clin Pharmacol*. 1990;30(Suppl):S28-32.
8. Jäätelä A, Baandrup S, Houtzagers J, et al. The efficacy of low dose metoprolol CR/ZOK in mild hypertension and in elderly patients with mild to moderate hypertension. *J Clin Pharmacol*. 1990;30(Suppl):S66-71.
9. Carruthers G, Shearer R, Taylor W, et al. A comparison of a controlled release (CR/ZOK) formulation of metoprolol, once daily, with conventional metoprolol tablets, twice daily, in mild to moderate hypertension. *J Clin Pharmacol*. 1990;30(Suppl):S61-5.
10. Klein G, Berger J, Olsson G, et al. A double-blind comparison of metoprolol CR/ZOK 50mg and atenolol 50mg once daily for uncomplicated hypertension. *J Clin Pharmacol*. 1990;30(Suppl):S72-77.
11. Dimenäs E, Östergren J, Lindvall K, et al. Comparison of CNS-related subjective symptoms in hypertensive patients treated with either a new controlled-release (CR/ZOK) formulation of metoprolol or atenolol. *J Clin Pharmacol*. 1990;30(Suppl):S82-90.
12. Kendall M, Akhlaghi S, Hughes B, et al. Is metoprolol CR/ZOK more selective than conventional metoprolol and atenolol. *J Clin Pharmacol*. 1990;30(Suppl):S98-102.
13. Missault LH, Friart A, Van BP. Efficacy, tolerability and quality of life in the Hypertension Optimal Reduction by Treatment Adjustments - trial. *Cardiovasc Drugs Ther*. 1999;13:68.
14. Dahlöf B, Jonsson L, Borgholst O, et al. Improved antihypertensive efficacy of the felodipine-metoprolol extended-release tablet compared with each drug alone. *Blood Press*. 1993;2 Suppl 1:37-45.
15. Dahlöf B, Hosié J. Antihypertensive efficacy and tolerability of a fixed combination of metoprolol and felodipine in comparison with the individual substances in monotherapy. *J Cardiovasc Pharmacol*. 1990;16:910-6.
16. Foffmann J. Comparison of a felodipine-metoprolol combination tablet vs each component alone as antihypertensive therapy. *Blood Press* 1993;2 Suppl 1:30-6.
17. Lohmann FW, Simon A, The French-German Multicentre Study Group. More effective blood pressure reduction with a felodipine-metoprolol combination tablet than with a capsule containing nifedipine and atenolol. *Eur J Clin Res*. 1997;9:199-208.
18. Zannad F, Boivin J-M, Lorraine General Physician Investigators Group. Ambulatory 24-h blood pressure assessment of the felodipine-metoprolol combination versus amlodipine in mild to moderate hypertension. *J Hypertens*. 1999;17:1023-32.
19. Berger A, Chima P, Dawes M et al. A fixed combination of felodipine 5 mg and metoprolol 50 mg compared with double doses of the individual components as antihypertensive therapy. *J Drg Dev*. 1992;4:199-206.
20. Hosié J, Dahlöf B, Klein G. The long-term antihypertensive efficacy and safety of a new felodipine-metoprolol combination tablet. *Blood Press*. 1993;2 Suppl 1:46-50.
21. Klein G. German Felodipine Study Group. Long-term evaluation of the fixed combination of felodipine and metoprolol in the treatment of hypertension. *Curr Ther Res*. 1992;52:238-42.