PIONEERING THE CHANGE IN HYPERTENSION THERAPY IN NIGERIA WITH

BICEDOLOL®

*Bisoprolol Fumarate 5mg & Hydrochlorothiazide 6.25mg

HIGH EFFICACY - LOW DOSAGE

*With low-dose combination therapy BICEDOLOL® provides classic antihypertensive benefits of beta-blockers and diuretics without their dose-related side effects.
TABLE OF CONTENT

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG EVALUATION &amp; RESEARCH RECOMMENDATION</td>
<td>3</td>
</tr>
<tr>
<td>FIRST LINE TREATMENT IN HYPERTENSION</td>
<td>4</td>
</tr>
<tr>
<td>CLINICAL TRIALS</td>
<td>5</td>
</tr>
<tr>
<td>RESPONSE RATE UP TO 73%</td>
<td>6</td>
</tr>
<tr>
<td>ADVERSE EVENTS COMPARABLE TO PLACEBO</td>
<td>7</td>
</tr>
<tr>
<td>REDUCTION IN DIASTOLIC BLOOD PRESSUR</td>
<td>8</td>
</tr>
<tr>
<td>REDUCTION IN SYSTOLIC BLOOD PRESSUR</td>
<td>9</td>
</tr>
<tr>
<td>RESPONSE &amp; SAFETY PROFILE VS. ACE INHIBITORS &amp; CA-ANTAGONISTS</td>
<td>10</td>
</tr>
<tr>
<td>LOWEST DISCONTINUATION RATES</td>
<td>11</td>
</tr>
<tr>
<td>EFFICACY REGARDLESS OF AGE, RACE OR GENDER</td>
<td>12</td>
</tr>
<tr>
<td>NOTIFICATION DELIVERED BY NAFDAC</td>
<td>13</td>
</tr>
<tr>
<td>ABSTRACTS</td>
<td>14</td>
</tr>
<tr>
<td>ABSTRACTS</td>
<td>15</td>
</tr>
<tr>
<td>ABSTRACTS</td>
<td>16</td>
</tr>
<tr>
<td>ABSTRACTS</td>
<td>17</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>18</td>
</tr>
<tr>
<td>CONTACTS</td>
<td>19</td>
</tr>
</tbody>
</table>
DRUG EVALUATION & RESEARCH RECOMMENDATION

NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL

NAFDAC CORPORATE HQ:
Plot 2023 Ologun Olassijo Way,
Wuse Zone 7, Abuja
Tel: +234-9-8713008
Email: nafdac@nafdac.gov.ng
website: www.nafdac.gov.ng

LABS LICENCE OFFICE:
Central Laboratory
No.375, Freedom Way, Apapa Expressway
Lagos State
Tel: +234-1-4738643

Your Ref: Our Ref: Date: October 17, 2014

The Managing Director
Blackcedar Pharmaceuticals Limited
18, Osode Street, Abule Egba,
Lagos.

Attn: Superintendent Pharmacist

RE: EVALUATION OF DATA ON CLINICAL TRIALS OF ANTI-HYPTERTENSIVE FORMULATION: Bisoprolol + Hydrochlorothiazide.

Your above submission in support of application for registration of Bicedol Tablets (Bisoprolol 5mg + Hydrochlorothiazide 6.25mg) dated September 2, 2014 refers:

The review of clinical data submitted on the product was found satisfactory for the management of mild to moderate hypertension.

You may therefore wish to liaise with Registration and Regulatory Affairs Directorate for further processing of the application.

Regards.

Mrs. Titilope O. Owohali
Director, Drug Evaluation and Research

For: DG (NAFDAC)
FIRST LINE TREATMENT IN HYPERTENSION

**BICEDOLOL®** is recommended by Drug Evaluation and Research (DER) and approved by NAFDAC for the treatment of mild to moderate essential hypertension.

The combination & dosage in **BICEDOLOL®** is Recommended as a first line treatment in hypertension by the American Joint National Committee on Prevention, Detection, Evaluation & Treatment of High Blood Pressure.

It is recommended by NAFDAC’s Drug Evaluation & Research Unit for the treatment of mild to moderate essential hypertension.

BLACKCEDAR PHARMACEUTICALS LTD is pioneering this change in Hypertension therapy in Nigeria with **BICEDOLOL®**.

**BICEDOLOL®** was approved by NAFDAC in December 2014 for the treatment of hypertension.

### HIGH EFFICACY
- Control of hypertension in up to 84% of patients
- Effective in a broad range of patients regardless of age, race or gender
- Recommended by the JNC VI and other guidelines
- Approved by NAFDAC as treatment of mild to moderate essential hypertension
- Approved by the FDA as first-line treatment of hypertension

### LOW RATE OF ADVERSE EVENTS
- Low-dose drug
- Specifically developed to minimize dose-related side effects
- Side-effect profile comparable to placebo

### MULTI-ACTIVE MODE OF ACTION
- Additive antihypertensive efficacy
- Blood pressure reduction via different mechanisms
- Metabolically neutral

### IMPROVED COMPLIANCE
- Improvement in quality of life
- Once-daily dosage (consistent 24 hour-efficacy)
- Low discontinuation rates

**BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE**
The US National Hypertension Trial with 12'629 patients confirmed positive data of BICEDOLOL® (Bisoprolol Fumarate 5mg + HCTZ 6.25 mg) regarding efficacy, side-effects profile and quality of life in actual clinical practice under usual care conditions.
RESPONSE RATE UP TO 73%

Response rate for BICEDOLOL® is up to 73%. Other antihypertensive monosubstances will require much higher dosages to achieve similar results in terms of response rate. BICEDOLOL® and traditional dosage combinations are equivalent in terms of response rate BUT with additional advantage.

**LOW SIDE EFFECTS BECAUSE OF THE LOW DOSAGES OF THE TWO ACTIVE SUBSTANCES**

Response rate is defined as a sitting diastolic blood pressure of ≤ 90mm Hg and or decrease from baseline of ≥10mm Hg measured 24 hours after dosing.

BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE
ADVERSE EVENTS COMPARABLE TO PLACEBO

In all clinical trials including more than 14'000 patients BICEDOLOL® (Bisoprolol Fumarate 5mg + HCTZ 6.25mg) demonstrated a side-effect profile comparable to placebo on a minimum level.
Therapy with BICEDOL® produced significant reductions from baseline sitting diastolic blood pressure than placebo. The mean reduction in SiDBP was also greater for patients taking BICEDOL® versus HCTZ alone in a much higher dosage.

The low-dosed antihypertensive therapy with BICEDOL® results in a strong blood pressure reduction with a side-effect profile comparable to placebo.
REDUCTION IN SYSTOLIC BLOOD PRESSURE

Therapy with BICEDOLOL® produced significant reductions from baseline sitting systolic blood pressure than placebo.
The mean reduction in SISBP was also greater for patients taking BICEDOLOL® versus HCTZ alone in a comparable dosages.

The low-dosed antihypertensive therapy with BICEDOLOL® results in a strong blood pressure reduction with a side-effect profile comparable to placebo.

BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE
RESPONSE & SAFETY PROFILE VS. ACE INHIBITORS & CA-ANTAGONISTS

RESPONSE VS. ACE INHIBITORS & CA-ANTAGONISTS

EXCELLENT SAFETY PROFILE FOR BICEDOLOL

BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE
Discontinuation rates for BICEDOLOL® were lowest in comparative studies vs Amlodipine, Enalapril and placebo due to adverse events, lack of efficacy (Blood Pressure not controlled) as well as due to other reasons.

A total of only 16.6% of patients who were treated with BICEDOLOL® discontinued therapy, 26.6% of patients under Amlodipine and 26.1% patients under Enalapril.

Placebo treatment resulted in a discontinuation rate of 58.2%, including 41.8% due to lack of efficacy (Neutel et al., 1996)

Discontinuation rates for BICEDOLOL® were also lower compared to ACE inhibitors due to adverse events 7.1% for BICEDOLOL® vs. 9.5% for ACE inhibitors, due to lack of efficacy 2.7% vs. 5.6% and due to administrative and other reasons 16.7% vs. 17.9%, in total 26.5% vs. 33.0% (Frishman, 1996)
Efficacy Regardless of Age, Race or Gender

**Age:** **BICEDOLOL**® allows low-dose therapy in elderly patients, who are particularly sensitive to the effects of blood pressure manipulation and medication side effects as a result of the physiological changes due to aging. Thus all age-groups may benefit from the low incidence of side effects of **BICEDOLOL**®

**Race:** **BICEDOLOL**® addresses the physiological mechanism of hypertension (low renin and volume expansion) common among the black population, and therefore produces effects which are as high as those observed in non-black population.
ABSTRACTS


A new antihypertensive strategy for black patients: low-dose multi-mechanism therapy.

Abstract: Hypertension poses serious health risks for blacks because this population presents with earlier onset and more severe forms of the disease than do nonblack. Although diuretics are the cornerstone of antihypertensive therapy in the black population, investigators have expressed concern about adverse metabolic effects, such as hypokalaemia, produced by the high doses of diuretics traditionally prescribed for blacks.

Recent evidence suggests that black patients may respond equally well to the new generation of cardio selective beta-blockers and angiotensin-converting enzyme inhibitors, particularly when these agents are used together with a diuretic.

A new low-dose multi-mechanism agent that combines the cardio selective beta-blocker Bisoprolol Fumurate with hydrochlorothiazide, a benzothiazine diuretic, is now available for first-line therapy for hypertension.

Results of two US multicentre trials--including a subset analysis of black patients--indicate that the once-daily agent is highly effective in reducing diastolic and systolic blood pressure throughout a 24-hour period in both black and nonblack patients. The agent is well tolerated in blacks and non-blacks and has a side-effect profile comparable to placebo. Because of its efficacy and safety in black patients, Bisoprolol Fumarate-/hydrochlorothiazide is an appropriate therapeutic option for first-line therapy of hypertension in the black population.


Papadopoulos DP1, Papademetriou V.

Low-dose fixed combination of Bisoprolol/hydrochlorothiazide as first line for hypertension: a review of the rationale and clinical evidence.

Abstract: Essential hypertension is a heterogeneous multifactorial disease. Data from the National Health and Nutritional Examination Survey and from the World Health Organization have clearly demonstrated that, worldwide, less than 30% of hypertensive patients are adequately controlled by our currently accepted blood pressure goals. Although monotherapy is often unable to achieve blood pressure goals, the use of fixed low-dose combination drugs as alternative treatment seems to be related to a better antihypertensive efficacy and higher response rates in the low range of doses as the result of complementary mechanisms of antihypertensive effects. Indeed clinical trials have shown that initial low-dose combination therapy is superior as compared with treatment by the stepped-care and the sequential monotherapy approach, while recently, low-dose combination therapy for initial antihypertensive therapy instead of the stepped-care approach or of sequential monotherapy has been recommended. This review summarizes the beneficial effect of low-dose bisoprolol/hydrochlorothiazide combination in the treatment of patients with stage I and II hypertension.


A clinical trial evaluating the 24-hour effects of bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination in patients with mild to moderate hypertension.

Abstract: This study used 24-h ambulatory blood pressure (BP) monitoring to investigate the effectiveness of a novel low-dose combination of bisoprolol/hydrochlorothiazide in adult patients with mild to moderate essential hypertension. Thirty-six patients with stable mild to moderate hypertension (sitting diastolic BP 95-114 mmHg) after a placebo run-in phase received oral bisoprolol/hydrochlorothiazide 5 mg/6.25 mg once daily for 4 weeks in a single-blind regimen. At office visits, BP and pulse were measured with statistically significant reductions (p < 0.01) recorded after 2 and 4 weeks of treatment. Twenty-four-h ambulatory BP monitoring at the completion of therapy revealed significant reductions (p < 0.01) in both systolic and diastolic 24-h, daytime, and night-time BP, compared with the end of the placebo treatment phase. Systolic and diastolic load were also reduced (p < 0.01). The combination was well tolerated, and overall quality-of-life questionnaire scores indicated an improvement after bisoprolol/hydrochlorothiazide therapy (p = 0.02). No clinically significant changes from baseline in laboratory parameters were observed; in particular, serum potassium was unchanged. This is the first study to demonstrate the 24-h effectiveness of the bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination, using 24-h ambulatory BP monitoring. In addition, antihypertensive therapy with low doses of bisoprolol/hydrochlorothiazide in combination may improve tolerability.

BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE
ABSTRACTS


Efficacy and tolerance of the bisoprolol/hydrochlorothiazide combination in arterial hypertension

Luna RL1, Oigman W, Ramirez JA, Mion D, Batlouni M, da Rocha JC, Feitosa GS, Castro I, Chaves Júnior Hde C, God EM, Maia LN, Ortega KC, Raineri AM.

PURPOSE: Multicentre, open and non-controlled study to evaluate the efficacy and the tolerability of a low-dose combination of two anti-hypertensive agents: a cardio selective beta-blocker, Bisoprolol (2.5 and 5.0 mg) with 6.25 mg of hydrochlorothiazide.

METHODS: One hundred and six patients in the stage I and stage II of the systemic hypertension (mild to moderate) were given the Bisoprolol/hydrochlorothiazide combination once daily and the diastolic and systolic blood pressures were monitored during the 8-week trial.

RESULTS: The Bisoprolol/hydrochlorothiazide combination reduced the initial mean values of systolic and diastolic blood pressures, respectively, from the 157.4 mmHg and 98.8 mmHg to 137.3 mmHg and 87.4 mmHg. At the end of the treatment period, 61% of the patients normalized blood pressure values (< 90 mmHg) and 22.9% of them had responded to the treatment, resulting in a total response rate (normalized + responsive) of 83.9% of cases. Adverse events were described only in 18.9% of the patients and dizziness and headache were the most common.

There were no clinically significant changes on plasma levels of potassium, uric acid, glucose, or in the lipid profile.

CONCLUSION: The combination of low dosages of Bisoprolol and hydrochlorothiazide may be considered an effective, well tolerated and rational alternative for the initial treatment of the patients with mild to moderate hypertension


Zachariah PK1, Messerli FH, Mroczek W.

Abstract

Two recent, multicenter, double-blind, placebo-controlled studies established the efficacy and safety of low-dose bisoprolol/hydrochlorothiazide (HCTZ) in patients with mild to moderate essential hypertension. Bisoprolol, a cardio selective beta-blocker, was used in a dose of 2.5 mg, 5 mg, or 10 mg. HCTZ was used at a dose of 6.25 mg. This low-dose compound was developed to minimize dose-related adverse effects. The addition of HCTZ to each of the doses of bisoprolol was compared with monotherapy and placebo. Results of both studies demonstrated that this once-a-day, low-dose option effectively reduced sitting diastolic and systolic blood pressure measured at the end of the 24-hour dosing period. Drug-related adverse effects, including those generally associated with traditional beta-blocker therapy, were infrequent in individuals who received the low-dose bisoprolol/HCTZ regimen. Dose-related side effects were minimized because of the low doses of the two agents used together. There were no significant changes in mean total cholesterol, triglycerides, or serum glucose with bisoprolol/HCTZ 6.25 mg therapy versus placebo (analysis of variance statistical methods). The incidence of treatment-induced hypokalaemia with bisoprolol/HCTZ 6.25 mg was not significant; uric acid elevations were minimized, and the incidence of hyperuricemia was significantly (P < 0.01) less with bisoprolol/HCTZ 6.25 mg than with 25 mg of HCTZ. Once-a-day dosing with the low-dose agent controlled (defined as a sitting diastolic blood pressure < or = 90 mmHg and/or a decrease from baseline > or = 10 mmHg) blood pressure in up to 80% of patients for a full 24 hours after dosing.
ABSTRACTS


Progress report on the first sub-Saharan Africa trial of newer versus older antihypertensive drugs in native black patients.


Abstract

BACKGROUND: The epidemic surge in hypertension in sub-Saharan Africa is not matched by clinical trials of antihypertensive agents in Black patients recruited in this area of the world. We mounted the Newer versus Older Antihypertensive agents in African Hypertensive patients (NOAAH) trial to compare, in native African patients, a single-pill combination of newer drugs, not involving a diuretic, with a combination of older drugs including a diuretic.

METHODS: Patients aged 30 to 69 years with uncomplicated hypertension (140 to 179/90 to 109 mmHg) and ≥2 associated risk factors are eligible. After a four week run-in period off treatment, 180 patients have to be randomized to once daily Bisoprolol/hydrochlorothiazide 5/6.25 mg (R) or amlodipine/valsartan 5/160 mg (E).

To attain blood pressure <140/<90 mmHg during six months, the doses of Bisoprolol and amlodipine should be increased to 10 mg/day with the possible addition of up to 2 g/day α-methylidopa.

RESULTS: At the time of writing of this progress report, of 206 patients enrolled in the run-in period, 140 had been randomized. At randomization, the R and E groups were similar (P ≥ 0.11) with respect to mean age (50.7 years), body mass index (28.2 kg/m²), blood pressure (153.9/91.5 mmHg) and the proportions of women (53.6%) and treatment naïve patients (72.7%). After randomization, in the R and E groups combined, blood pressure dropped by 18.2/10.1 mmHg, 19.4/11.2 mmHg, 22.4/12.2 mmHg and 25.8/15.2 mmHg at weeks two (n = 122), four (n = 109), eight (n = 57), and 12 (n = 49), respectively. The control rate was >65% already at two weeks. At 12 weeks, 12 patients (24.5%) had progressed to the higher dose of R or E and/or had α-methylidopa added. Cohort analyses of 49 patients up to 12 weeks were confirmatory. Only two patients dropped out of the study.

CONCLUSIONS: NOAAH (NCT01030458) demonstrated that blood pressure control can be achieved fast in Black patients born and living in Africa with a simple regimen consisting of a single-pill combination of two antihypertensive agents. NOAAH proves that randomized clinical trials of cardiovascular drugs in the indigenous populations of sub-Saharan Africa are feasible.

-----------------------------------------------------------------


First-line therapy option with low-dose bisoprolol Fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension.

Frischman WH1, Burris JF, Mroczek WJ, Weir MB, Alemayahu D, Simon JS, Chen SY, Bryzinski BS.

1 Department of Medicine, Albert Einstein School of Medicine, Bronx, New York 10461, USA.

Abstract: This 30-center, randomized, double-blind, placebo-controlled, parallel-group study was designed to (1) establish that 6.25 mg of hydrochlorothiazide (HCTZ) given once daily with 5 mg of Bisoprolol Fumarate can contribute to antihypertensive effectiveness in patients with stage I and stage II (mild to moderate) systemic hypertension; and (2) assess whether this formulation was more effective or possessed a safety advantage over standard monotherapy with Bisoprolol or 25 mg of HCTZ. Results showed that HCTZ 6.25 mg contributed significantly to the antihypertensive effectiveness of Bisoprolol 5 mg. Bisoprolol 5 mg + HCTZ 6.25 mg (BS/H6.25) produced significantly greater mean reductions from baseline in sitting systolic and diastolic blood pressure (-15.8 mm Hg/-12.6 mm Hg) than Bisoprolol 5 mg alone (-10.0 mm Hg/-10.5 mm Hg) and HCTZ 25 mg alone (-10.2 mm Hg/-8.5 mm Hg). A 73% response rate was achieved with the low-dose formulation compared with 61% for the Bisoprolol 5 mg (BS) group and 47% for the HCTZ 25 mg (H25) group. BS/H6.25 was found to be significantly more effective than BS or H25 in all subgroups of patients, regardless of gender, race, age, or smoking history. Antihypertensive effects were maintained during the 24-hour dosing interval. The incremental effectiveness of BS/H6.25 was not accompanied by an increase in the frequency or severity of adverse experiences; the incidence of adverse experiences in the BS/H6.25 group was comparable to that in the placebo group. BS/H6.25 was shown to provide safety advantages over H25, as shown by less hypokalaemia (< 1% with BS/H6.25 versus 6.5% with H25).

BICEDOLOL® - MAXIMUM CLINICAL BENEFITS - MAXIMUM SAFETY PROFILE - COST EFFECTIVE
Clinical results with bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg combination in systolic hypertension in the elderly.

Benetos A1, Adamopoulos C, Argyriadis P, Bean K, Consoli S, Safar M.

1IPC Center, Paris, France. benetos@ipc.asso.fr

Abstract: Hypertension in the elderly, especially systolic hypertension, has been recognized as a major cardiovascular risk factor. Several international studies, using primarily diuretics and/or beta-blockers, have shown the benefits of antihypertensive treatment in elderly patients in terms of cardiovascular morbidity and mortality reduction. However, because the risk of side-effects is a major concern when treating the elderly, the use of low-dose combination treatments may be of particular interest. A randomized, multicentre, double-blind, parallel group study was conducted to compare the efficacy and safety of bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg (biso 2.5/HCTZ 6.25) (n = 84) versus amlodipine 5 mg (n = 80) in subjects over 60 years of age with isolated systolic hypertension. The effects of these two treatment strategies on patients’ quality of life were also assessed. After a two- to four-week placebo washout period, both drugs were administered once daily and taken for 12 weeks. Blood pressure was measured 24 h after treatment administration. Systolic blood pressure/diastolic blood pressure changes from baseline to week 12 were similar for both biso 2.5/HCTZ 6.25 and amlodipine (-20.0/-4.5 mmHg and -19.6/-2.4 mmHg, respectively). Overall adverse events for biso 2.5/HCTZ 6.25 and amlodipine were 39% and 40%, respectively. Both treatments improved quality of life scores in the same way. This study demonstrates comparable efficacy and tolerability of biso 2.5/HCTZ 6.25 and amlodipine. Low-dose combination of bisoprolol and hydrochlorothiazide may be an appropriate alternative for elderly patients with systolic hypertension.
REFERENCES


• FRISHMAN WH. ZIAC National Hypertension Trial Report. March 1996.


CONTACTS

Contact us for any inquiries:

Country Director: +234 809 574 1998
Head of Sales & Marketing – Lagos territory: +234 809 574 1913
Medical Sales Rep. – Lagos Island: +234 809 574 1967
Medical Sales Rep. – Oyo State: +234 809 574 1972
Account & Administrative Coordinator: +234 809 574 1925
Swiss Rep. Office: +41 79 603 9042

admin@theblackcedar.com
www.theblackcedar.com

Registered Office
Blackcedar Pharmaceuticals Ltd.
18 Owode Street, Abule-Egba
Lagos, Nigeria

Representative Office
The Blackcedar GmbH
Hôtel-de-Ville 46
2300 La Chaux-de-Fonds
Switzerland