NEBIVOLOL HYDROCHLORIDE

3.1 Identifiers

Generic name: Nebivolol Hydrochloride

Synonym(s): Nebivolol, hidrocloruro de; R-067555; R-67555 R-65824.

Brand name: Bystolic (Forest Pharmaceuticals Incorporated), Nebilet (A. Menarini Pharmaceuticals UK Ltd) Nebilet. Nebivolol is manufactured by Forest Laboratories, Inc. In India, Nebivolol is available as Nebilong 5 mg (Micro Labs) Nebicard-5 (Torrent), Nubeta (Abbott Healthcare Pvt Ltd -India) and Nodon (Cadila Pharmaceuticals). In Greece and Italy, Nebivolol is marketed under the name Lobivon from Menarini pharmaceutical. In the middle east and in Australia it is marketed under the name Nebilet. In the US, it is marketed under the brand name Bystolic from Mylan Laboratories and Forest Laboratories.

CAS number: 99200-09-6; 118457-14-0

Therapeutic classification: Martindale – Cardiovascular drugs
BNF – Beta-adrenoceptor blocking drugs

Drug Type: Approved Drug

State: Solid

Chemistry

![Figure 12. Structure of Nebivolol Hydrochloride](image)

Chemical name: (1 RS, 1 'RS)-III '[-{(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1 -benzopyran-2-yl)}-2,2'-iminodiethanol

IUPAC Name: 1-(6-fluorochroman-2-yl)-{(2-(6-fluorochroman-2-yl)-2-hydroxy-ethyl] amino} ethanol

OR

2,2'-azanediylbis(1-(6-fluorochroman-2-yl)ethanol)
OR

1-(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)-2-\{2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl\}amino\}ethan-1-ol

**Structural formula:** Nebivolol is a racemate of d-nebivolol and l-nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol

![Structural formula of d-nebivolol hydrochloride and l-nebivolol hydrochloride](image)

**Figure 13. Structure of d and l- Nebivolol hydrochloride**

**Molecular weight:** 441.9 g/mol

**Molecular formula:** C\textsubscript{22}H\textsubscript{25}F\textsubscript{2}NO\textsubscript{4} · HCl (www.medicinescomplete.com)

### 3.2 Description

**Solubility:** Nebivolol is soluble in N,N-dimethylformamide, dimethylsulfoxide, methanol; sparingly soluble in polyethylene glycol, polypropylene glycol and ethanol; and very slightly soluble in hexane, methylbenzene and dichloromethane.

**Crystals. M.p.** 220-222 °C.  Boiling point: 600.5 °C at 760 mmHg

**Appearance:** White to almost-white powder

**Log P(octanol/water):** 3.23; 4.03 (pH 11.8, 23°C). (www.accessdata.fda.gov)

**Ultraviolet Spectrum**

Quantification of nebivolol hydrochloride (NEB-H) was determined by simultaneous equation method and absorbance ratio method. In simultaneous equation method absorbance measurements at 282.5 nm (λ\textsubscript{max} NEB-H) & in absorbance ratio method absorbance measurements at 282.5 nm in methanol (Dhandapani et al., 2010). Nebivolol exhibited λ\textsubscript{max} at 282 nm in methanol (Giri et al., 2010). The wavelength
fixed for spectrophotometric measurement of nebivolol HCl at 280.2 nm for the simultaneous equation in methanol (Birajdar et al., 2011). The partial simultaneous equation method, using methanol as solvent Nebivolol hydrochloride has absorbance maxima at 281 nm (Mishra et al., 2009). In the Niacinamide solution, Nebivolol hydrochloride show maximum absorbance at a wavelength of about 286.5 nm (Sharma et al., 2010).

**FT-IR Spectrum**

FT-IR study revealed that, in pure Nebivolol, gave peaks at respective wave numbers i.e aliphatic sec amine (1493, 1435 cm\(^{-1}\)), carbonyl (1214, 1192 cm\(^{-1}\)) and sulphur-oxy group (1074, 1030 cm\(^{-1}\)) (Kumar et al., 2011).

**Reverse Phase High Performance Liquid Chromatography**

In RPHPLC method, the drugs were resolved using a mobile phase of 30 mM phosphate buffer (K\(_2\)HPO\(_4\)), acetonitrile and triethylamine (50:50:0.1% v/v) with pH 5.5 using orthophosphoric acid on a C18-ODS- Phenomenex (5 µm, 250 mm x 4.6 mm) column in isocratic mode, Atorvastatin (ATR) used as a internal standard. The retention time of NEB-H 4.30 min (Dhandapani et al., 2010). For the HPLC method, Lichrospher 100 C-18, 5 µm column consisting of 200×4.6 mm i.d. in isocratic mode, with mobile phase containing 50 mM KH\(_2\)PO\(_4\) buffer (pH 3.0 ± 0.1) : acetonitrile : (45:55 v/v) was used. The flow rate was 1.0 ml/min and effluent was monitored at 282 nm. The retention time was found to be 3.76 ± 0.02 min (Patel et al., 2007).

**Quantifications of drug from various methods**

**High Performance Thin Layer Chromatography**

In the HPTLC method, the chromatograms were developed using a mobile phase of ethyl acetate: methanol: ammonia (8.5:1:0.5 v/v) Rf value: 0.41 (Dhandapani et al., 2010). The solvent system consisted of Ethyl acetate: Methanol: Dilute ammonia (8.5:1:1, v/v/v) Rf 0.60 ± 0.02 (Dangi et al., 2010). The mobile phase of 1,4-dioxane: toluene: triethylamine (5:3:0.1 v/v) Rf values were found to be 0.75 (Kumbhar et al., 2011). The ethyl acetate: methanol: ammonia in the ratio 8.5:1: 0.5 v/v as mobile phase. The R\(_f\) value of Nebivolol hydrochloride was found to be 0.52 ± 0.02 (Dhandapani et al.,
Drug profile

2006). The ethyl acetate: toluene: methanol: ammonium hydroxide (1:6:2:0.1 v/v/v/v) mobile phase were used. The Rf value was found to be 0.33±0.02 (Patel et al., 2007).

**Liquid Chromatography Using Fluorescence Detection**

The method of choice for measurement of Nebivolol in biological fluids is Liquid Chromatography Using Fluorescence Detection after simple acetonitrile extraction. The calibration curve was linear over the concentration range 0.2-20 ng/mL (Abdel-Fattah et al., 2010).

**Liquid Chromatographic-Tandem Mass Spectrometry Method**

The method of choice for measurement of Nebivolol in biological fluids is liquid chromatographic-tandem mass spectrometry method after simple acetonitrile extraction. The mobile phase consisting of a mixture of acetonitrile and 0.05 mM formic acid (50:50 v/v, pH 3.5) was delivered at a flow rate of 0.25 ml/min. The linearity was obtained over the concentration range of 0.01-50.0 ng/ml (Selvan et al., 2007).

### 3.3 Pharmacology

Nebivolol hydrochloride is the racemate (dl-nebivolol hydrochloride) of the enantiomers l-nebivolol hydrochloride and d-nebivolol hydrochloride. It is a competitive and highly selective β₁ receptor antagonist with mild vasodilating properties, possibly due to an interaction with the L-arginine/nitric oxide pathway. In animal models nebivolol hydrochloride has been shown to induce endothelium-dependent arterial relaxation in a dose dependent manner, by stimulation of the release of endothelial nitric oxide (Robertson, 1999). Nitric oxide is produced in artery walls and acts to relax vascular smooth muscle cells. It also inhibits platelet aggregation and adhesion and may protect against vascular damage as it inhibits leukocyte activation and vascular smooth muscle cell proliferation (Moncada, 1994). Human studies in small numbers of healthy volunteers where nebivolol hydrochloride was infused into phenylephrine preconstricted superficial hand veins of eleven volunteers (Bowman et al., 1994) or into the brachial artery in five groups of eight volunteers (Cockcroft et al. 1995) have confirmed that nebivolol hydrochloride has nitric oxide mediated venodilator effects. These studies were
extended in a series of eight patients with essential hypertension, and similar results were obtained.

3.3.1 Pharmacodynamics

Clinically, nebivolol hydrochloride is administered as a racemic mixture of equal proportions of “d” and “l” isomers. Nebivolol hydrochloride has 4 asymmetric centres, d-isomer refers to (S,R,R,R)-nebivolol hydrochloride and lisomer to (R,S,S,S)-nebivolol hydrochloride. The enantiomers have unequal potency with regard to β-receptor blocking activity and nitric oxide mediated vasodilation (Leysen et al., 1991). The combination has greater antihypertensive activity than either enantiomer alone (Van Peer et al., 1991). Nebivolol hydrochloride binds to the β receptor on cell membrane leading to 1 activation of adenyl cyclase resulting in accumulation secondary messenger cAMP. This cAMP dependent protein kinase Coupling of nitric oxide synthase (NOS) increases NO production via L- arginine / NO pathway phosphorylates specific proteins causing modification of actions (Hoffman, 2004). Nebivolol induces nitric oxide production via activation of β 3 adrenergic receptors (Maffei & Lembo, 2009). This activates phospholipase C, which breaks down the membrane phospholipid PIP (Phosphotidyl 2 inositol bisphosphate) to IP (Inositol triphosphate) and DAG 3 (Diacyl-glycerol) releases calcium from endoplasmic reticulum producing an increase in free cytoplasmic calcium which binds to calmodulin, this calcium-calmodulin complex is responsible for stimulating nitric oxide synthase (NOS),which acts as a catalyst.

L-arginine + O + NADPH → L-citrulline + NO +NADP

The enzyme consists of two domains the oxygenase domain and the reductase domain. It requires flow of electrons for its function. NADPH→ Flavin adenine dinucleotide→ Flavin mononucleotide (FMN) →heme → O 2

Binding of calmodulin to NOS has been shown to regulate the catalytic activity by triggering electron flow from FMN to heme, thereby coupling the oxygenase and reductase domains, thus nebivolol prevents NOS uncoupling. Metabolites of the drug cause a significant increase in free calcium content of endothelial cells. This results in a subsequent rise in endothelial NO synthase dependent NO production. This mechanism leads to effective control of blood pressure by vasodilatation of blood vessels.
Other actions produced by nebivolol are

- It has a protective effect on left ventricular function. It reduces preload, afterload and increases stroke volume. It decreases pre-ejection period and lengthens left ventricular ejection time. Reduces cardiac output and total peripheral resistance when given at the dose of 5mg once daily (Van Bortel et al., 1993; Marceau et al., 1998).
- Decreases resting heart rate (Breed et al., 1993) and reduces exercise induced tachycardia (Derman et al., 1993).
- Reduces total cholesterol and low density lipoprotein levels (Chan et al., 1992; Fogari et al., 1997).
- Reduces plasma renin and aldosterone levels (Chan et al., 1992).

3.3.2 Pharmacokinetics

The absorption of nebivolol hydrochloride is rapid and not affected by food. It is extensively metabolised, partly to active hydroxy-metabolites (Robertson, 1999). The mean peak plasma drug concentration ($C_{\text{max}}$) is 1.42μg/L. The time to reach $T_{\text{max}}$ for racemic mixture is 0.5-2hrs. For most individuals, steady state plasma concentration is achieved within 1 day for nebivolol and in a few days for active metabolites (Janssen's & Snoeck, 1997). The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. The oral bioavailability of nebivolol averages 12% in fast metabolizing patients and is virtually complete in slow metabolisers. (McNeely & Goa, 1999, Mangrella et al., 1998).

The plasma protein binding is 98%, with limited distribution in adipose tissue due to its lipophilicity and hence no need for dosage adjustment in obese patients. The volume of distribution being 695-2755 litres (Mangrella et al., 1998).

It undergoes extensive first pass metabolism and produces active β-blocking hydroxylated metabolites. The metabolism of nebivolol shows genetic polymorphism in gene encoding the CYP2D6 isoenzyme where individuals may be phenotypically divided as “poor” or “extensive” metabolizers (Janssen's & Snoeck, 1997). The poor metabolisers are unable to adequately hydroxylate aromatic moiety of the drug thus retaining t of high
concentration of unchanged drug. In extensive metabolisers there is formation of the active hydroxyl metabolites, with low concentration of unchanged drug. Stereoselective Radioimmunoassay measures active fractions of the isomers and hydroxylated metabolites (Kamali et al., 1997).

Urinary excretion of unchanged nebivolol is less than 0.5% of the dose (Robertson, 1999) but increased plasma concentrations of the drug and the hydroxy metabolites have been found in hypertensive patients with moderate to severe renal disease (McNeely & Goa, 1999). Elimination half life of nebivolol is about 10hrs, increased by 5 times in poor metabolisers and for its metabolites it is about 24hrs. 38% of dose is excreted in urine and 48% in faeces (Janssen's & Snoeck, 1997). In renal insufficiency therefore, the recommended starting dose is 2.5mg daily which may be increased to 5mg, if necessary.

3.3.3 Clinical efficacy

The FDA’s approval of nebivolol was based on its antihypertensive effectiveness in the two pivotal randomized, double-blind, multicenter, placebo-controlled trials conducted in the U.S. Both studies concluded that nebivolol was safe, well tolerated, and effective for patients with mild-to-moderate hypertension. The nebivolol groups, with doses ranging from 1.25 to 20 mg once daily, also had significantly greater LS mean reductions in trough diastolic and systolic BP, compared with placebo patients, from baseline to day 84. Placebo-subtracted LS mean reductions in trough diastolic and systolic BP ranged from 5.1 to 8.3 mm Hg and 6.6 to 11.7 mm Hg, respectively. Little difference was noted in diastolic BP with 2.5 to 20 mg, compared with placebo. No significant differences were observed in the incidence of adverse drug events between treated and placebo groups (Weiss et al., 2007). Placebo-subtracted LS mean reductions in trough diastolic BP from baseline were statistically significant for nebivolol doses of 5 to 40 mg (4.9–5.5 mm Hg), as well as in trough systolic BP for doses of 10 to 40 mg (6–6.8 mm Hg), compared with patients receiving placebo. All nebivolol groups showed reductions in trough heart rate, with doses of 10 mg or more being statistically significant compared with placebo. No significant differences were observed in the incidence of ADEs between treated and placebo groups (Saunders et al., 2007). The addition of
nebivolol (at any dose) to ongoing antihypertensive therapy produced significant additional reductions in trough diastolic and systolic BP (LS mean reductions from baseline of 6.6 to 7.9 mm Hg and 5.7 to 6.3 mm Hg, respectively) compared with placebo. There were also significant reductions in peak diastolic BP (up to 13.6 mm Hg) and systolic BP (13.3 mm Hg) from baseline with all doses of nebivolol. No significant differences were seen in the incidence of ADEs between treatment and placebo groups (Gradman et al., 2007).

3.3.4 Comparisons with placebo

In a multicentre, double-blind, randomised, parallel group dose-finding study in 509 pts with primary essential hypertension, nebivolol 2.5, 5 and 10mg, but not 0.5 or 1mg, for 4 weeks significantly reduced mean supine diastolic BP (by 7.1 to 10.2 mmHg; p<0.05) at trough drug levels (23-25 h post-dosing), compared with placebo. There was no significant difference between the nebivolol 5mg and 10mg groups. The trough-to-peak ratio for supine diastolic BP with nebivolol 5mg once daily was 0.894 (Van Nueten et al., 1997). In a noncomparative study nebivolol 5mg was given once daily to 37 pts with mild to moderate essential hypertension (diastolic BP between 95 and 114 mmHg). Significant (p<0.0001 vs baseline) reductions were maintained during therapy over 12 months (DeCree et al. 1992). Other comparative studies found a similar reduction in 24-hour ambulatory BP with nebivolol 2.5mg to 10mg daily compared with lisinopril 10 to 40mg daily, enalapril 10mg daily, atenolol 100mg daily and nifedipine 20mg bd for up to 12 weeks (p<0.01 for systolic and diastolic BP for all drugs vs baseline or placebo) (McNeely & Goa, 1999).

3.3.5 Dosage and Administration:

The recommended starting dose of nebivolol hydrochloride is 5 mg once daily. The drug may be taken without regard to food. The dosage must be adjusted for each individual, according to the patient’s BP. If additional reductions in BP are necessary, the dose may be increased slowly at two week intervals up to a maximum dose of 40 mg daily. In patients with renal insufficiency or moderate hepatic insufficiency, the recommended starting dose is reduced to 2.5 mg once daily. Nebivolol hydrochloride is
not recommended for patients with severe hepatic impairment (Forest Laboratories, Inc.; December 2007).

3.3.6 Adverse Effects

Nebivolol hydrochloride has been studied in over 3000 patients with hypertension, who have received the drug for at least one month, and some for 3 years (Robertson, 1999). Nebivolol 5mg once daily is well tolerated (McNeely & Goa, 1999). The adverse events are transient and mild to moderate (Van Nueten et al., 1997) and not dose related (Lacourciere et al., 1994). The adverse effects with a frequency of 1-10% incidence included headache, dizziness, paraesthesias, dyspnoea, constipation, nausea, diarrhea, tiredness and oedema. The less frequently reported are impaired vision, bradycardia, heart failure, hypotension, bronchospasm, pruritus and impotence.

3.3.7 Contraindications

Nebivolol hydrochloride, same as other beta-blockers is contraindicated in patients with asthma, uncontrolled heart failure, marked bradycardiac and hypotension, prinzmetal’s angina, sick sinus syndrome, 2nd and 3rd degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease and phaeochromocytoma. It is also contraindicated in patients with hepatic impairment as well as lactating and pregnant women.

3.3.8 Drug-Drug Interactions (Janssen's et al., 1997; Mangrella et al., 1998, British Medical Association, 2007)

- **Acei** – enhanced hypotensive effect
- **Adrenergic neurone blocker** – enhanced hypotensive effect
- **Alcohol** – enhanced hypotensive effect
- **Aldesleukin** – enhanced hypotensive effect
- **Alpha blocker** – enhanced hypotensive effect; also increase risk of first dose hypotension with post–synaptic alpha blocker such as prazosin.
- **General anaesthetic** – enhanced hypotensive effect
- **Analgesic** – hypotensive effect antagonized by nsaid
- **Angiotensin-II receptor antagonist** – enhanced hypotensive effect
- **Anti-arrhythmics** – increase myocardial depression; increase risk of bradycardia, AV block and myocardial depression with amiodarone; increase risk of bradycardia and myocardial depression with flecainide
- **Antidiabetics** – may mask warning sign of hypoglycaemia (such as tremor); enhance hypoglycaemic effect of insulin
- **Antimalarials** – increase risk of bradycardia with mefloquine
- **Antipsychotic** – enhance hypotensive effect with phenothiazines
- **Anxiolytics and hypnotic** – enhance hypotensive effect
- **Calcium channel blocker** – enhance hypotensive effect; possible severe hypotension and heart failure with nifedipine or nisoldipine; increase risk of AV block and bradycardia with diliazem; asystole, severe hypotension and heart failure with verapamil
- **Cardiac glycoside** – increase risk of AV block and bradycardia
- **Clonidine** – increase risk of withdrawal hypertension with clonidine, to reduce the risk, withdraw Nebivolol several days before slowly withdraw clonidine
- **Corticosteroids** – hypotensive effect antagonized by corticosteroid
- **Diazoxide** – enhance hypotensive effect
- **Diuretics** – enhance hypotensive effect
- **Dopaminergics** – enhance hypotensive effect with levodopa
- **Ergot alkaloids** – increase peripheral vasoconstriction with ergotamine and methysergide
- **5HT1 antagonist** – increase risk of ventricular arrhythmias with tropiseton
- **Methyldopa** – enhance hypotensive effect
- **Moxisylyte** – possible severe postural hypotension
- **Moxonidine** – enhance hypotensive effect
- **Muscle relaxant** – enhance hypotensive effect with baclofen; possible enhanced hypotensive effect and bradycardia with tizanidine
- **Nitrates** – enhance hypotensive effect
- **Oestrogen** – hypotensive effect antagonized by oestrogen
• *Pilocarpine* – increase risk of arrhythmia
• *Alprostadil* – enhance hypotensive effect
• *Sympathomimetics* – severe hypertensive effect with adrenaline, noradrenaline or dobutamine vasodilator antihypertensive: enhance hypotensive effect with hydralazine, minoxidil or sodium nitroprusside

### 3.3.8.1 Drug-Food Interactions

Food does not alter the pharmacokinetics of nebivolol hydrochloride but under fed conditions, Nebivolol glucuronides are slightly reduced. Bystolic may be administered without regarding to meals.

### 3.3.9 Therapeutic Indication and Uses

- Nebivolol is a cardioselective beta blocker approved for the treatment of hypertension. It produces unique nitric oxide–mediated vasodilatory effects, lacks intrinsic sympathomimetic activity and possesses a tolerability profile similar to that of other beta blockers (Hilas & Danielle Ezzo, 2009).
- Nebivolol therapy reduced the effects of VR in rats after MI. These beneficial effects were not related to its heart rate and blood pressure reducing effects. Nitric oxide regulatory action of this compound may contribute these beneficial effects on VR developed after MI (Mercanoğlu et al., 2010).
- The effect of Nebivolol on renal complication in diabetic rats. Ischemia/reperfusion injury, which is commonly seen in the field of renal surgery or transplantation in diabetic condition, is a major cause of acute renal failure (Kakadiya et al., 2010).
- Nebivolol has protective effects against neuronal damage induced by spinal cord ischemia/reperfusion (I/R) (Ilhan et al., 2004).
- Nebivolol improves penile endothelial function as a surrogate of erectile function in apolipoprotein E mice. These effects may be related to a reduction of reactive oxygen species production, which is independent of heart rate reduction, because metoprolol did not increase endothelial function (Baumhäkel et al., 2008).
Nebivolol, a $\beta_1$-selective blocker with respect to nitric oxide (NO) and peroxynitrite (ONOO$^2$) generation in the endothelium of normotensive Wistar Kyoto (WKY rats) and spontaneously hypertensive rats (SHR). The endothelial effects of nebivolol and its 2 optical enantiomers were correlated with its antioxidant activity (Mason et al., 2006).

Nebivolol is mediated through the release of NO via a $\beta_2$ adrenoceptor–dependent mechanism. Thus, nebivolol may be of benefit in conditions of increased large artery stiffness, such as isolated systolic hypertension (McEniery et al., 2004).

Coadministration of either carvedilol or nebivolol with doxorubicin was able to ameliorate up to almost contradict doxorubicin-induced myocardial injury, glomerular filtration disturbance and renal tubular damage with upper hand for nebivolol. So, they can be considered a feasible candidate to protect against nephrotoxicity & cardiotoxicity commonly encountered with doxorubicin treatment (Shafik et al., 2011).

Nebivolol is a new selective beta 1-adrenoceptor antagonist with nitric oxide (NO)–releasing properties (Fortepiani et al., 2002).

Nebivolol is a $\beta_1$-blocker that is highly selective for $\beta_1$-adrenergic receptors with vasodilating properties. Nebivolol may have beneficial effects via nitric oxide and antioxidant action in osteoporosis Treatment (Toker et al., 2009).

Nebivolol may be a helpful agent in preventing the development of early restenosis following vascular interventions (Akar et al., 2011).

Nebivolol treatment may be beneficial to improve oxidative stress parameters in patients with SCF (Ahmet et al., 2010).

Nebivolol, a highly selective $\beta$-1-blocker, endowed with additional vasodilating activity mediated by NO endothelial release, differs from other $\beta$-blocking agents, and that the combination of $\beta$-1 blockade and NO-mediated vasodilation leads to a broader favorable metabolic profile, and to beneficial effects on arterial stiffness (Rosei et al., 2009).

Nebivolol showed antiepileptic effects in addition to its reported antihypertensive effect, which could be attributed to action of the two drugs through different
mechanisms or due to drug interaction that may be pharmacodynamic or pharmacokinetic needing elucidation (Goel et al., 2009).

3.4 Patient Monitoring Guidelines

To ensure the efficacy of Nebivolol in antihypertensive management, blood pressure should be monitored regularly. Additional antihypertensive agents may be required provided if the blood pressure is not well controlled.

The adverse reactions of Nebivolol are generally tolerable, but patients should consult the physicians if significant adverse effects, for instance hypotension, difficulty in breathing due to bronchospasm, bradycardia, increasing shortness of breath and weight as the symptoms of deteriorating heart failure, are experienced (www.bystolic.com). Beta-blocker is not contraindicated for diabetic patients, but it can affect glucose tolerance and mask the symptoms of hypoglycaemia. Thus, the effect of Nebivolol in diabetic patients should be monitored and appropriate dosage adjustment should be considered if necessary. The effects of Nebivolol in patients with renal and hepatic impairment should be closely monitored as these may affect the drug metabolisms or excretions. Dosage adjustment is also required (www.medicinescomplete.com).

3.5 Special Precautions

Dosage adjustment is needed for the elderly (>65 years old) and renal compromised patients. The initial dose of Nebivolol should be reduced to 2.5 mg once daily for the management of hypertension. As of all other beta-blockers, Nebivolol should be used with cautions in patients with 1st degree AV block, portal hypertension, history of obstructive airway disease, myasthenia gravis, and history of hypersensitivity response. It may also mask the symptoms of hypoglycemia and thyrotoxicosis. Abrupt withdrawal should be avoided especially in patients with ischemic heart disease (British Medical Association, 2007). Users should also be aware that the use of Nebivolol (along with other beta-blockers) is prohibited in certain sports, either in-competition and/or off-competition (http://www.wada-ama.org).