PACKAGE INSERT TEMPLATE FOR CARVEDILOL TABLET

Brand or Product Name

[Product name] Tablet 6.25mg
[Product name] Tablet 12.5mg
[Product name] Tablet 25mg

Name and Strength of Active Substance(s)

Carvedilol 6.25mg
Carvedilol 12.5mg
Carvedilol 25mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '100' on one side]

Pharmacodynamics

Carvedilol is a multiple action adrenergic receptor blocker with α_1, β_1 and β_2 adrenergic receptor blockade properties. Carvedilol has been shown to have organ-protective effects. Carvedilol is a potent antioxidant and a scavenger of reactive oxygen radicals. Carvedilol is racemic, and both R(+) and S(-) enantiomers have the same α-adrenergic receptor blocking properties and antioxidant properties. Carvedilol has antiproliferative effects on human vascular smooth muscle cells. A decrease in oxidative stress has been shown in clinical studies by measuring various markers during chronic treatment of patients with carvedilol.

Carvedilol's β-adrenergic receptor blocking properties are non-selective for the β_1 and β_2-adrenoceptors and are associated with the levorotatory S(-) enantiomer. Carvedilol has no intrinsic sympathomimetic activity and (like propranolol) it has membrane stabilising properties. Carvedilol suppresses the renin-angiotensin-aldosterone system through β-blockade, which reduces the release of renin, thus making fluid retention rare. Carvedilol reduces the peripheral vascular resistance via selective blockade of α1-adrenoceptors. Carvedilol attenuates the increase in blood pressure induced by phenylephrine, an α1-adrenoceptor agonist, but not that induced by angiotensin II. Carvedilol has no adverse effect on the lipid profile. A normal ratio of high-density lipoproteins to low density lipoproteins (HDL/LDL) is maintained.

Pharmacokinetics

Absorption

Following oral administration, carvedilol is rapidly absorbed. Carvedilol is a substrate of the intestinal efflux transporter P-glycoprotein which plays a major role in the bioavailability of certain drugs. In healthy volunteers the maximum serum concentration is reached after approximately one hour. The absolute bioavailability of carvedilol in humans is approximately 25%.

Distribution

Carvedilol is a highly lipophilic compound, approximately 98% to 99% bound to plasma proteins. The distribution volume is approximately 2 l/kg.

Metabolism

In humans, carvedilol is extensively metabolized in the liver via oxidation and conjugation into a variety of metabolites that are eliminated mainly in the bile. The first-pass effect after oral administration amounts to about 60-75%. Enterohepatic circulation of the parent substance has been shown in animals.

The oxidatiove metabolism of carvedilol is stereoselective. The R-enantiomer is predominantly metabolized by CYP2D6 and CYP1A2, while the S-enantiomer is mainly metabolised by CYP2C9 and to a lesser extend by CYP2D6. Other CYP450 isoenzymes involved in the metabolism of carvedilol include CYP3A4, CYP2E1 and CYP2C19. The maximal plasma concentration of R-carvedilol are approximately 2 fold higher than that S-carvedilol. The R-enantiomer is predominantly metabolised through hydroxylation

In slow metabolisers of CYP2D6 an increase of the plasma concentration of carvedilol mainly the R-enantiomer may occur, leading to an increase in the α-blocking activity. Demethylation and hydroxylation at the phenol ring produce 3 metabolites with β-adrenergic receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenol metabolite is approximately 13 times more potent than carvedilol for β-blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. In humans, the concentrations of the three active metabolites are about 10 times lower than that of the parent substance. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, demonstrating a 30 to 80 fold greater potency than carvedilol.

Elimination

*The average elimination half-life of carvedilol is approximately 6 hours. Plasma clearance is approximately 500-*700 ml/min. The primary route of excretion is via the feces. Elimination is mainly biliary. A minor part is eliminated via the kidneys in the form of various metabolites.

Pharmacokinetics in Special Populations

Patients with renal impairment

The autoregulatory blood supply is preserved and the glomerular filtration is unchanged during chronic treatment with carvedilol. In patients with hypertension and renal insufficiency, the area under plasma level-time curve, elimination half-life and maximum plasma concentration does not change significantly. Renal excretion of the unchanged drug decreases in the patients with renal insufficiency; however, changes in pharmacokinetic parameters are modest.

Several open studies have shown that carvedilol is an effective agent in patients with renal hypertension. The same is true in patients with chronic renal failure, or those on hemodialysis or after renal transplantation. Carvedilol causes a gradual reduction in blood pressure both on dialysis and non-dialysis days, and the blood pressure-lowering effects are comparable with those seen in patients with normal renal function. Carvedilol is not eliminated during dialysis because it does not cross the dialysis membrane, probably due to its high plasma protein binding. On the basis of results obtained in comparative trials on hemodialysed patients, it was concluded that carvedilol was more effective than calcium channel blockers and was better tolerated.

Patients with hepatic impairment

In patients with cirrhosis of the liver, the systemic availability of the drug is increased by up to 80% because of a reduction in the first-pass effect. Therefore, carvedilol is contraindicated in patients with clinically manifest liver dysfunction.

Patient with hepatic failure

The clearance of R- and S-carvedilol was significantly lower than previously estimated in healthy volunteers. These results suggested that the pharmacokinetics of R-and S-carvedilol is significantly altered by heart failure.

Geriatric use

Age has no statistically significant effect on the pharmacokinetics of carvedilol in hypertensive patients. A study in elderly hypertensive patients showed that there was no difference in the

adverse event profile compared to younger patients. Another study which included elderly patients with coronary heart disease showed no difference in the adverse events reported vs those reported by younger patients.

Pediatric use

There is limited data available on pharmacokinetics in people younger than 18 years of age.

Diabetic patients

In hypertensive patients with non-insulin-dependent diabetes no influence of carvedilol on fasting or post-prandial blood glucose concentration, glycolated hemoglobin A_1 or need for change of the dose of antidiabetic agents was found. In patients with non-insulin dependent diabetes, carvedilol had no statistically significant influence on the glucose tolerance test. In hypertensive non-diabetic patients with impaired insulin sensitivity (syndrome X) carvedilol improved the insulin sensitivity. The same results were found in hypertensive patients with non–insulin dependent diabetes.

Indication

Hypertension

Carvedilol is indicated primarily for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents (e.g. calcium channel blockers, diuretics).

Treatment of angina pectoris

Chronic Heart Failure

Unless a contraindication exists, carvedilol is indicated for the treatment of all patients with stable and symptomatic, mild, moderate and severe chronic heart failure of ischemic or non-ischemic etiology in combination with standard therapy (including ACE inhibitors and diuretics with or without digitalis).

Recommended Dosage

Duration of treatment

Treatment with carvedilol is a long-term therapy. Treatment should not be stopped abruptly but rather gradually reduced at weekly intervals. This is particularly important in the case of patients with concomitant coronary heart disease.

Essential hypertension

The recommended dose for initiation of therapy is 12.5 mg once a day for the first two days. Thereafter, the recommended dosage is 25 mg once a day. If necessary, the dosage may subsequently be increased at intervals of at least two weeks to the recommended maximum daily dose of 50 mg given once daily or in divided doses (twice daily).

Coronary Heart Disease

The recommended dose for initiation of therapy is 12.5 mg twice a day for the first two days. Thereafter the recommended dosage is 25 mg twice a day. If necessary, the dosage may thereafter be increased at intervals of at least two weeks, up to the recommended maximum daily dose of 100 mg given in divided doses (twice daily)

Symptomatic, stable, Chronic Heart Failure

Dosage must be tailored to suit the individual and closely monitored by a physician during up-titration. For those patients receiving digitalis, diuretics and ACE inhibitors, dosing of these drugs should be stabilized before initiation of carvedilol treatment.

The recommended dose for initiation of therapy is 3.125 mg twice daily for two weeks. If this dose is tolerated, the dose may thereafter be increased, at intervals of not less than two weeks, to 6.25 mg, 12.5 mg and 25 mg twice daily. Doses should be increased to the highest level tolerated by the patient.

The maximum recommended dose is 25 mg twice daily for all patients with severe CHF and for patients with mild to moderate CHF weighing less than 85 kg (187 lbs). In patients with mild or moderate CHF weighing more than 85 kg, the maximum recommended dose is 50 mg twice daily.

Before each dose increase, the patient should be evaluated by the physician for symptoms of vasodilation or worsening heart failure. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics. Occasionally, it may be necessary to lower the dose of carvedilol and, in rare cases, temporarily discontinue carvedilol treatment.

If carvedilol treatment is discontinued for more than one week, therapy should be recommenced at a lower dose level (twice daily) and up-titrated in line with the above dosing recommendation. If carvedilol is discontinued for more than two weeks, therapy should be recommenced at 3.125 mg in line with the above dosing recommendation.

Symptoms of vasodilation may be managed initially by a reduction in the dose of diuretics. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of carvedilol if necessary. Under these circumstances, the dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

Special Dosage Instructions

Renal impairment

Available pharmacokinetic data in patients with varying degrees of renal impairment (including renal failure) suggest no changes in carvedilol dosing recommendations are warranted in patients with moderate to severe renal insufficiency.

Hepatic impairment

Carvedilol is contraindicated in patients with clinical manifestations of liver dysfunction.

Elderly

There is no evidence to support dose adjustment.

Mode of Administration
Oral. The tablets are to be swallowed with sufficient fluid.

Contraindications

Carvedilol must not be used in patients with:
- Hypersensitivity to carvedilol or any component of the product
- Unstable/decompensated heart failure
- Clinically manifest liver dysfunction

As with other β-blockers, carvedilol must not be used in patients with:
- 2^{nd} and 3^{rd} degree AV block (unless a permanent pacemaker is in place)
- severe bradycardia (< 50 bpm)
- sick sinus syndrome (including sino-atrial block)
- severe hypotension (systolic blood pressure < 85 mmHg)

- cardiogenic shock
- history of bronchospasm or asthma

Warnings and Precautions

Chronic Congestive Heart Failure

In congestive heart failure patients, worsening cardiac failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes. Occasionally, it may be necessary to lower the carvedilol dose or, in rare cases, temporarily discontinue it. Such episodes do not preclude subsequent successful titration of carvedilol. Carvedilol should be used with caution in combination with digitalis glycosides, as both drugs slow AV conduction.

Renal function in Congestive Heart Failure

Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low blood pressure (systolic BP <100 mmHg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency.

Chronic obstructive pulmonary disease

Carvedilol should be used with caution, in patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic component who are not receiving oral or inhaled medication, and only if the potential benefit outweighs the potential risk. In patients with a tendency to bronchospasm, respiratory distress can occur as a result of a possible increase in airway resistance. Patients should be closely monitored during initiation and up-titration of carvedilol and the dose of carvedilol should be reduced if any evidence of bronchospasm is observed during treatment.

Diabetes

Care should be taken in the administration of carvedilol to patients with diabetes mellitus, as the early signs and symptoms of acute hypoglycemia may be masked or attenuated. In chronic heart failure patients with diabetes, the use of carvedilol may be associated with worsening control of blood glucose.

Peripheral vascular disease

Carvedilol should be used with caution in patients with peripheral vascular disease as β-blockers can precipitate or aggravate symptoms of arterial insufficiency.

Raynaud's phenomenon

Carvedilol should be used with caution in patients suffering from peripheral circulatory disorders (e.g. Raynaud's phenomenon) as there may be exacerbation of symptoms.

Thyrotoxicosis

Carvedilol, like other agents with β-blocking properties, may obscure the symptoms of thyrotoxicosis.

Anesthesia and major surgery

Caution should be exercised in patients undergoing general surgery, because of the synergistic negative inotropic effects of carvedilol and anesthetic drugs.

Bradycardia

Carvedilol may induce bradycardia. If the patient's pulse rate decreases to less than 55 beats per minute, the dosage of carvedilol should be reduced.

Hypersensitivity

Care should be taken in administering carvedilol to patients with a history of serious hypersensitivity reactions, and in those undergoing desensitisation therapy, as β-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Psoriasis

Patients with a history of psoriasis associated with β-blocker therapy should take carvedilol only after consideration of the risk-benefit ratio.

Concomitant use of calcium channel blockers

Careful monitoring of ECG and blood pressure is necessary in patients receiving concomitant therapy with calcium channel blockers of the verapamil or diltiazem type or other antiarrhythmic drugs.

Pheochromocytoma

In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although carvedilol has both α- and β-blocking pharmacological

activities, there is no experience with its use in this condition. Caution should therefore be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Prinzmetal's variant angina

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There is no clinical experience with carvedilol in these patients although the α-blocking activity of carvedilol may prevent such symptoms. Caution should, however, be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

Contact lenses

Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

Withdrawal syndrome

Carvedilol treatment should not be discontinued abruptly, particularly in patients suffering from ischemic heart disease. The withdrawal of carvedilol should be gradual (over a period of two weeks).

Ability to Drive and Use Machines

No studies have been performed on the effects of carvedilol on patients' fitness to drive or to operate machinery. Because of individually variable reactions (eg. dizziness, tiredness), the ability to drive, operate machinery, or work without firm support may be impaired. This applies particularly at the start of treatment, after dose increases, on changing products, and in combination with alcohol.

Interactions with Other Medicaments

Pharmacokinetic interactions

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore the bioavailability of drugs transported by P-glycoprotein may be increased with concomitant administration of carvedilol. In addition, the bioavailability of carvedilol can be modified by inducers or inhibitors of P-glycoprotein.

Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or presystemic metabolism of carvedilol stereoselectively, leading to increased or decreased plasma concentrations of R and S-carvedilol. Some examples observed in patients or in healthy subjects are listed below but the list is not exhaustive.

Digoxin

Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing carvedilol.

Cyclosporin

Studies in renal and cardiac transplant patients receiving oral cyclosporin have shown an increase in cyclosporin plasma concentration following the initiation of carvedilol. It appears that carvedilol increases the absorption of cyclosporin po through inhibition of P-glycoprotein activity in the intestine. In an attempt to maintain therapeutic cyclosporin levels, an average 10-20% reduction of the cyclosporin dose was necessary. Therefore, due to wide interindividual variability of cyclosporin levels, it is recommended that cyclosporin concentrations are monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate. In case of IV administration of cyclosporin, no interaction with carvedilol is expected.

Rifampicin

Rifampicin administration decreased the carvedilol plasma levels most likely by induction of P-glycoprotein leading to a decrease of the intestinal absorption of carvedilol and a decrease of the antihypertensive effect.

Amiodarone

In patients with heart failure, amiodarone decreased the clearance of S-carvedilol likely by inhibition of CYP2C9. The mean R-carvedilol plasma concentration was not altered. Consequently, there is a potential risk of increased β-blockade caused by a raised of the plasma S-carvedilol concentration.

Fluoxetine

Co-administration of fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no difference in adverse events, blood pressure or heart rate were noted between treatment groups.

<u>Pharmacodynamic interactions</u>

Insulin or oral hypoglycemic

Agents with β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. The signs of hypoglycemia may be masked or attenuated (especially tachycardia). In patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is therefore recommended.

Catecholamine-depleting agents

Patients taking both agents with β-blocking properties and a drug that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Digoxin
The combined use of beta-blockers and digoxin may result in additive prolongation of atrioventricular (AV) conduction time.

Verapamil, diltiazem, amiodarone or other antiarrhythmics

In combination with carvedilol can increase the risk of AV conduction disturbances

Clonidine

Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Calcium channel blockers

Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co-administered with diltiazem. As with other agents with β-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Antihypertensives

As with other agents with β-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that are anti-hypertensive in action (e.g. α_1-receptor antagonists) or have hypotension as part of their adverse effect profile.

Anesthetic agents

Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic negative inotropic and hypotensive effects of carvedilol and anaesthetic drugs.

NSAIDs

The concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic blockers may result in an increase in blood pressure and lower blood pressure control.

Beta-agonist bronchodilators

Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators**.** Careful monitoring of patients is recommended

Statement on Usage During Pregnancy and Lactation

Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, and immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in the fetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. There is no evidence from animal studies that carvedilol has any teratogenic effects. There is no adequate clinical experience with carvedilol in pregnant women. Carvedilol should not be used during pregnancy unless the potential benefit outweighs the potential risk.

Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human milk. Breast-feeding is therefore not recommended during administration of carvedilol.

Adverse Effects / Undesirable Effects

<u>Undesirable effects in chronic heart failure</u>

Adverse experiences most frequently observed in the carvedilol group in clinical trials in congestive heart failure patients and not seen at an equivalent incidence among placebo treated patients are described below.

Central nervous system

Very common: dizziness, headaches are usually mild and occur particularly at the start of treatment. Asthenia (including fatigue) also occurs very commonly.

Cardiovascular system

Common: bradycardia, postural hypotension, hypotension, edema (including generalized, peripheral, dependent and genital edema, edema of the legs, hypervolemia and fluid overload).

Uncommon: syncope (including presyncope), AV-block and cardiac failure during up-titration.

Gastro-intestinal system

Commonly, nausea, diarrhea and vomiting

Hematology

Rare: thrombocytopenia. Leucopenia has been reported in isolated cases.

Metabolic

Commonly: weight increase and hypercholesterolemia. Hyperglycemia, hypoglycemia and worsening control of blood glucose are also common in patients with pre-existing diabetes mellitus.

Others

Commonly: vision abnormalities. Rarely: renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function.

<u>Undesirable effects in hypertension and the long term management of coronary heart disease</u>

The profile of adverse events associated with the use of carvedilol in the treatment of hypertension and the long-term management of coronary heart disease is consistent with that observed in chronic heart failure. The incidence of adverse events in these patient populations is lower, however. Adverse experiences reported in patients with hypertension and coronary heart disease are:

Central nervous system

Common: dizziness, headaches and fatigue, which are usually mild and occur particularly at the beginning of treatment.
Uncommon: depressed mood, sleep disturbance, paresthesia.

Cardiovascular system

Common: bradycardia, postural hypotension and uncommonly syncope, especially at the beginning of treatment.

Uncommon: disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynauds phenomenon), AV-block, angina pectoris (including chest pain), symptoms of heart failure and peripheral edema.

Respiratory system

Common: asthma and dyspnea in predisposed patients.
Rare: stuffy nose.

Gastro-intestinal system

Common: gastro-intestinal upset (with symptoms such as nausea, abdominal pain, diarrhea).
Uncommon: constipation and vomiting.

Skin and appendages

Uncommon: skin reactions (eg. allergic exanthema, dermatitis, urticaria and pruritus).

Blood chemistry and hematology

Isolated cases of increases in ALAT, ASAT and gamma GT, thrombocytopenia and leucopenia have been reported.

Others

Common: pain in the extremities, reduced lacrimation and eye irritation.
Uncommon: cases of sexual impotence and disturbed vision.
Rare: dryness of the mouth and disturbances of micturition.
Isolated cases of allergic reactions have been reported.

Post Marketing Undesirable Effects

Metabolism and nutrition disorders

Due to the β-blocking properties, it is also possible for latent diabetes mellitus to become manifest, manifest diabetes to be aggravated, and blood glucose counter-regulation to be inhibited.

Skin and subcutaneous tissue disorders

Alopecia

Renal and urinary disorders

Isolated cases of urinary incontinence in women, which resolved upon discontinuation of the medication, have been reported.

Overdose and Treatment

Symptoms and signs of intoxication

In the event of overdosage, there may be severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness and generalized seizures.

Treatment of intoxication

In addition to general procedures, the vital parameters must be monitored and corrected, if necessary, under intensive care conditions. The following supportive therapies can be used:
Patients should be placed in the supine position.
Atropine: 0.5 to 2 mg i.v. (for excessive bradycardia).
Glucagon: initially 1 to 10 mg i.v. then 2 to 5 mg/h as a long-term infusion (to support cardiovascular function).
Sympathomimetics according to body-weight and effect: dobutamine, isoprenaline, orciprenaline or adrenaline. If positive inotropic effect is required, phosphodiesterase inhibitors (PDE) e.g. milrinone should be considered.
If peripheral vasodilation dominates the intoxication profile then norfenephrine or noradrenaline should be administered with continuous monitoring of the circulatory conditions.
In the case of drug-resistant bradycardia, pacemaker therapy should be initiated.

Treatment of bronchospasm

For bronchospasm, β-sympathomimetics (as aerosol or i.v.) or aminophylline i.v. should be given.

Treatment of seizures

In the event of seizures, slow i.v. injection of diazepam or clonazepam is recommended.

Important note
In cases of severe intoxication with shock, supportive treatment must be continued for a sufficiently long period, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected. The duration of the supportive/antidote therapy

depends on the severity of the overdosage. The supportive treatment should therefore be continued until the patient's condition has stabilized.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size eg Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box etc]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]