X-PLENDED® EZ (Rosuvastatin+Ezetimibe)

ایکس۔پلینڈڈ ایزی

COMPOSITION
X-Plended EZ 5/10mg
Each film-coated tablet contains:
Rosuvastatin.....5mg (as Rosuvastatin calcium USP)
Ezetimibe USP ……. 10mg

X-Plended EZ 10/10mg
Each film-coated tablet contains:
Rosuvastatin.....10mg (as Rosuvastatin calcium USP)
Ezetimibe USP ……. 10mg

X-Plended EZ 20/10mg
Each film-coated tablet contains:
Rosuvastatin.....20mg (as Rosuvastatin calcium USP)
Ezetimibe USP ……. 10mg

(As per innovator's specs.)

DESCRIPTION
X-Plended EZ tablets contain rosuvastatin calcium and ezetimibe. Rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor. Ezetimibe is a dietary cholesterol absorption inhibitor.

The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl2[methyl(methyl sulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt to [S-[R*,S*-(E)]]-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1). The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14 g.mol^{-1}. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

The chemical name of ezetimibe is (3R,4S)-1-(p-Fluorophenyl)-3-[(3S)-3-(p-fluorophenyl)-3-hydroxypropyl]-4-(p-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.43 g.mol^{-1}.

CLINICAL PHARMACOLOGY

Mechanism of Action
Rosuvastatin
Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In in vivo and in vitro studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Ezetimibe
The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Pharmacodynamics
The maximum therapeutic response of rosuvastatin is usually achieved by 4 weeks and is maintained after that. The maximum therapeutic response of ezetimibe is generally achieved within 2 weeks and is maintained during chronic therapy.

Pharmacokinetics

Absorption
Rosuvastatin
In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%. The AUC of rosuvastatin does not differ following evening or morning drug administration.

Administration of rosuvastatin with food did not affect the AUC of rosuvastatin.

Ezetimibe
After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (Cmax) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (Tmax). Ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours (Tmax). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ezetimibe 10-mg tablets. The Cmax value of ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution
Rosuvastatin
Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Ezetimibe
Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Elimination
Rosuvastatin
Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t1/2) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Ezetimibe
Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Pharmacokinetics in special populations

Geriatric Patients
Rosuvastatin
There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

Ezetimibe
In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Hepatic Impairment
Rosuvastatin
In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, Cmax and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Ezetimibe
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3-to 4-fold and 5-to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold on both Day 1 and Day 14 when compared to healthy subjects.

Renal Impairment
Rosuvastatin
Mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CLcr>80 mL/min/1.73 m^2). Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Ezetimibe
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CLcr≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Asian Population
Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Adjust the X-Plended EZ dosage in Asian patients.

INDICATIONS
X-Plended EZ is indicated in adults:
• As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).
• Alone or as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

DOSAGE AND ADMINISTRATION
• Swallow X-Plended EZ tablets whole at any time of day, with or without food. Do not crush, dissolve, or chew tablets.
• The dosage range is 5 mg/10 mg to 40 mg/10 mg once daily.
• The recommended dose of X-Plended EZ depends on a patient's indication for usage, LDLC, and individual risk for cardiovascular events.
• The starting dosage for patients switching to X-Plended EZ from co-administration of a statin and ezetimibe is based on an equivalent dose of rosuvastatin and 10 mg of ezetimibe.
• Assess LDL-C when clinically appropriate, as early as 2 weeks after initiating X-Plended EZ, and adjust the dosage if necessary.

Recommended Dosage in Asian Patients
Initiate X-Plended EZ at 5 mg/10 mg daily due to increased rosuvastatin plasma concentrations. Consider the risk/benefit when treating Asian patients not adequately controlled at doses up to 20 mg/10 mg once daily.

Pediatric Use
The safety and effectiveness of X-Plended EZ have not been established in pediatric patients.

Dosage adjustment
Patients with Renal Impairment
In patients with severe renal impairment (CLcr less than 30 mL/min/1.73 m^2) not on hemodialysis, the recommended starting dosage is 5 mg/10 mg once daily and should not exceed 10 mg/10 mg once daily.

There are no dosage adjustment recommendations for patients with mild and moderate renal impairment.

Patients with Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment. Treatment with X-Plended EZ is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction. X-Plended EZ is contraindicated in patients with acute liver failure or decompensated cirrhosis.

CONTRAINDICATIONS
X-Plended EZ is contraindicated in patients with:
• Acute liver failure or decompensated cirrhosis.
• Hypersensitivity to rosuvastatin, ezetimibe, or any excipients in X-Plended EZ.

WARNING AND PRECAUTIONS

Myopathy and Rhabdomyolysis
X-Plended EZ may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase [CK] above ten times the upper limit of normal) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including rosuvastatin.

Risk Factors for Myopathy
Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs including other lipid-lowering therapies, and higher X-Plended EZ dosage; Asian patients on X-Plended EZ may be at higher risk for myopathy. The myopathy risk is greater in patients taking X-Plended EZ 40 mg/10 mg daily compared with lower X-Plended EZ dosages.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis
The concomitant use of X-Plended EZ with cyclosporine or gemfibrozil is not recommended. X-Plended EZ dosage modifications are recommended for patients taking certain antiviral medications, darolutamide, and regorafenib. Niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis.

Discontinue X-Plended EZ if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if X-Plended EZ is discontinued. Temporarily discontinue X-Plended EZ in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the X-Plended EZ dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Immune-Mediated Necrotizing Myopathy
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

Hepatic Dysfunction
Increases in serum transaminases have occurred with rosuvastatin. In most cases, the elevations appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to more than three times the ULN occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo. Marked persistent increases of hepatic transaminases have also occurred with rosuvastatin. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before X-Plended EZ initiation and thereafter, when clinically indicated. X-Plended EZ is contraindicated in patients with acute liver failure or decompensated cirrhosis. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue X-Plended EZ.

Proteinuria and Hematuria
In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients. These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, consider a dose reduction for patients on X-Plended EZ therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Increases in HbA1c and Fasting Serum Glucose Levels
Increases in HbA1c and fasting serum glucose levels have been reported with statins, including rosuvastatin. Based on clinical trial data with rosuvastatin, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the label:
• Myopathy and Rhabdomyolysis [see Warnings and Precautions]
• Hepatic Dysfunction [see Warnings and Precautions]

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of rosuvastatin and ezetimibe. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rosuvastatin
Arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares), peripheral neuropathy, interstitial lung disease and gynecomastia. There have been rare reports of immune-mediated necrotizing myopathy associated with statin use. There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Ezetimibe
Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; erythema multiforme; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis; elevations in liver transaminases; hepatitis; abdominal pain; thrombocytopenia; pancreatitis; nausea; dizziness; paresthesia; depression; headache; cholelithiasis; cholecystitis.

DRUG INTERACTIONS
Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with X-Plended EZ
Rosuvastatin is a substrate of CYP2C9 and transporters (such as OATP1B1, BCRP). Rosuvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP2C9 and transporters. Table 1 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with X-Plended EZ and instructions for preventing or managing them.

Table 1: Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with X-Plended EZ

Cyclosporine or Gemfibrozil	
Clinical Impact:	Cyclosporine increased rosuvastatin exposure 7-fold. In addition, ezetimibe and cyclosporine used concomitantly can increase exposure to both ezetimibe and cyclosporine. Gemfibrozil significantly increased rosuvastatin exposure and gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with X-Plended EZ.
Intervention:	Avoid concomitant use of cyclosporine or gemfibrozil with X-Plended EZ.
Anti-Viral Medications	
Clinical Impact:	Rosuvastatin plasma levels were significantly increased with concomitant administration of many anti-viral drugs, which increases the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid concomitant use of sofosbuvir/velpatasvir/voxilaprevir and ledipasvir/sofosbuvir with X-Plended EZ. In patients taking simeprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, atazanavir/ritonavir, and lopinavir/ritonavir initiate with a dose of X-Plended EZ 5 mg/10mg once daily, and do not exceed a dose of X-Plended EZ 10 mg/10 mg once daily. No dose adjustment is needed for concomitant use with fosamprenavir/ritonavir or tipranavir/ritonavir. Monitor all patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward titration of either drug.
Darolutamide	
Clinical Impact:	Darolutamide increased rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking darolutamide, do not exceed a dose of X-Plended EZ 5 mg/10 mg once daily.
Regorafenib	
Clinical Impact:	Regorafenib increased rosuvastatin exposure and may increase the risk of myopathy.
Intervention:	In patients taking regorafenib, do not exceed a dose of X-Plended EZ 10 mg/10 mg once daily.
Fenofibrates (e.g., fenofibrate and fenofibric acid)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with X-Plended EZ.
Intervention:	Consider if the benefit of using fibrates concomitantly with X-Plended EZ outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have occurred with concomitant use of niacin with rosuvastatin.
Intervention:	Consider if the benefit of using niacin concomitantly with X-Plended EZ outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with X-Plended EZ
Intervention:	Consider if the benefit of using colchicine concomitantly with X-Plended EZ outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.

USE IN SPECIAL POPULATIONS

Pregnancy
Rosuvastatin
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of Rosuvastatin/ ezetimibe, treatment should be discontinued immediately.

Ezetimibe
No clinical data are available on the use of ezetimibe during pregnancy.
Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.

X-Plended EZ (Rosuvastatin/ Ezetimibe) is contraindicated in pregnancy.

Breast-feeding
Rosuvastatin
Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion of rosuvastatin in milk in humans.

Ezetimibe
Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

X-Plended EZ (Rosuvastatin/ Ezetimibe) is contraindicated in breast-feeding.

Pediatric
The safety and effectiveness of X-Plended EZ have not been established in pediatric patients.

Geriatric
Advanced age (≥65 years) is a risk factor for X-Plended EZ associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease or other drug therapy; and the higher risk of myopathy. Monitor geriatric patients receiving X-Plended EZ for the increased risk of myopathy.

Renal Impairment
Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor patients with renal impairment for development of myopathy. In patients with severe renal impairment not on hemodialysis, the recommended starting dosage is 5 mg/10 mg daily and should not exceed 10 mg/10 mg daily.

Hepatic Impairment
X-Plended EZ is contraindicated in patients with acute liver failure or decompensated cirrhosis.

OVER DOSAGE
No specific treatments of over dosage with X-Plended EZ are known. Hemodialysis does not significantly enhance clearance of rosuvastatin.

PRESENTATION
X-Plended EZ 5/10mg: Pack of 10 tablets
X-Plended EZ 10/10mg: Pack of 10 tablets
X-Plended EZ 20/10mg: Pack of 10 tablets

INSTRUCTIONS:
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

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1200002656

Rev: DI XPZ 00 06/2022

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