SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Beacrestin 10 mg film-coated tablets.
Beacrestin 20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).
Each tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).

Excipients with known effect:
Contains lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

10 mg tablets:
Pink, round, biconvex, coated tablet, embossed 'ROS' over '10' on one side and nothing on the other, with diameter 7 mm.

20 mg tablets:
Pink, round, biconvex, coated tablet, embossed 'ROS' over '20' on one side and nothing on the other, with diameter 9 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BEACRESTIN is indicated for patients with primary hypercholesterolaemia and mixed dyslipidaemia (including Fredrickson Type IIa, IIb; and heterozygous familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.

BEACRESTIN is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyper lipoproteinaemia) as an adjunct to diet when response to diet and exercise is inadequate.

BEACRESTIN reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol, thereby enabling most patients to achieve relevant treatment guidelines. BEACRESTIN also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I.

BEACRESTIN is also indicated in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

Primary prevention of cardiovascular disease: BEACRESTIN is indicated in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, BEACRESTIN is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

BEACRESTIN is indicated in children and adolescents 10 to 17 years of age as an adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present: LDL-C > 190 mg/dL or > 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors. Paediatric studies were conducted mainly in the non-Asian population and data on Asian children/adolescents is limited.

4.2 Posology and method of administration

The dosage of BEACRESTIN should be individualised according to the goal of therapy and patient response. The recommended start dose is 5 or 10 mg once daily in both statin naive patients or patients switched from another HMG CoA reductase inhibitor. The choice of starting dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4-6 weeks, if necessary (see Pharmacodynamic properties). Increasing the dose to 40 mg should be reserved for patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg and should only be initiated under close specialist supervision (see Special warnings and precautions for use of the 40 mg dose). The physician who elects to use BEACRESTIN at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of BEACRESTIN for the individual patient. BEACRESTIN should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis (see Special warnings and precautions for use; skeletal muscle).

BEACRESTIN may be given at any time of day, with or without food.

Use in Asian population

Increased plasma concentration of rosuvastatin has been observed in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry (see Special warnings and precautions for use & Pharmacokinetic properties). Increased systemic exposure, which is considered a pre- disposing factor for myopathy, should be taken into consideration when making dose decisions for Asian patients. Initiation of BEACRESTIN therapy with 5 mg once daily should be considered for Asian patients. This should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. Doses exceeding 20 mg are not generally

recommended and should only be considered for patients with high cardiovascular risk whose hypercholesterolaemia is not controlled with doses up to 20 mg. In rare cases where BEACRESTIN at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision. The physician who elects to use BEACRESTIN at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of BEACRESTIN for the individual patient.

Use in children

In paediatric patients with heterozygous familial hypercholesterolemia the recommended starting dose of BEACRESTIN is 5 mg taken orally once daily. The BEACRESTIN dose should be individualized according to baseline LDL-C levels and the recommended goal of therapy. The maximum daily dose in this patient population is 10 mg. Adjustments should be made at intervals of 4 weeks or more.

The safety and efficacy of BEACRESTIN doses greater than 20 mg have not been studied in this population. Treatment experience in paediatric patients with heterozygous familial hypercholesterolaemia is limited to 52 weeks.

Use in the elderly

No dose adjustment is necessary.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment.

For patients with severe renal impairment the use of BEACRESTIN is contraindicated (see Pharmacokinetic properties).

Dosage in patients with hepatic insufficiency

The usual dose range applies in patients with mild hepatic impairment [Child-Pugh scores of ≤ 7].

Increased systemic exposure to rosuvastatin has been observed in patients with moderate hepatic impairment [Child-Pugh scores of 8 or 9]. There is no experience in patients with severe hepatic impairment. BEACRESTIN is contraindicated in patients with active liver disease. (see Pharmacokinetic properties).

Genetic polymorphisms

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of BEACRESTIN is recommended (see Special warnings and precautions for use, Interactions and Pharmacokinetic properties).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when BEACRESTIN is administered concomitantly with certain medicinal products that may increase the plasma concentration of

rosuvastatin due to interactions with these transporter proteins (e.g. cyclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see Special warnings and precautions for use and Interactions). It is recommended that prescribers consult the relevant product information when considering administration of such products together with BEACRESTIN. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing BEACRESTIN therapy. In situations where co-administration of these medicinal products with BEACRESTIN is unavoidable, the benefit and the risk of concurrent treatment and BEACRESTIN dosing adjustments should be carefully considered (see Interactions).

4.3 Contraindications

BEACRESTIN is contraindicated in patients with hypersensitivity to any component of this product.

BEACRESTIN is contraindicated in patients with active liver disease or unexplained, persistent elevations of serum transaminases.

BEACRESTIN is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

BEACRESTIN is contraindicated in patients receiving concomitant cyclosporin.

BEACRESTIN is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

4.4 Special warnings and precautions for use

In rare cases where BEACRESTIN at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision. The physician who elects to use BEACRESTIN at doses higher than 20 mg should periodically re-evaluate the long-term risk/benefit of BEACRESTIN for the individual patient.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry compared with Caucasians (see Posology and method of administration and Pharmacokinetic properties.) A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian, Hispanic, Black and Afro-Caribbean groups.

Children and adolescents 10 to 17 years of age

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a one year period. (see Pharmacodynamic properties).

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of BEACRESTIN, in particular 40 mg. The effects were generally transient

and not associated with worsening of renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered in patients with unexplained persistent proteinuria during routine urinalysis testing. An assessment of renal function is recommended during routine follow-up of patients treated with a dose of 40 mg.

Skeletal muscle

Effects on skeletal muscle e.g. myalgia and myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin, as with other HMG-CoA reductase inhibitors. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post- marketing use is higher at the highest marketed dose. Rare cases of rhabdomyolysis, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin and with other marketed statins.

There have been very rare reports of an immune-mediated necrotising myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

Creatinine Kinase Measurement

Creatinine kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase, which may confound interpretation of the result.

Before treatment
If CK levels are significantly elevated at baseline (> 10xULN), treatment should not be started.

BEACRESTIN, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- renal impairment
- Hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor, fibrate or niacin
- alcohol abuse
- age ≥ 65 years
- situations where an increase in plasma levels may occur
- concomitant use of fibrates or niacin

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with BEACRESTIN.

Whilst on treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (> 10xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels ≤ 10xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing BEACRESTIN

or an alternative HMG-CoA reductase inhibitor at lowest dose with close monitoring.

Routine monitoring of CK levels in asymptomatic patients is not warranted.

The risk of myopathy during treatment with BEACRESTIN may be increased in circumstances which increase rosuvastatin drug levels (see Pharmacokinetic properties, special populations).

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with BEACRESTIN and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivates including gemfibrozil, cyclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. The benefit of further alterations in lipid levels by the combined use of BEACRESTIN with fibrates or niacin should be carefully weighed against the potential risks of such combinations. When used in combination with fibrates or lipid lowering doses of niacin (≥ 1 g/day), the dose of BEACRESTIN should not exceed 10 mg/day.

BEACRESTIN should be temporarily withheld in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Diabetes Mellitus

As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin, and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus (see Undesirable effects and Pharmacodynamic properties).

Liver

As with other HMG-CoA reductase inhibitors, BEACRESTIN should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests are performed before and at 3 months following both the initiation of treatment and any increase of dose, and periodically (semi-annually) thereafter. Patients with increased transaminases levels should be monitored until abnormalities resolve.

BEACRESTIN should be discontinued or the dose reduced if the level of serum transaminases is > 3 ULN.

Protease inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of BEACRESTIN in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating BEACRESTIN doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of BEACRESTIN is adjusted. (see Table 1, Posology and method of administration and Interactions).

Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin (see Undesirable Effects).

4.5 Interactions with other medical products and other forms of interaction

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors
Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of BEACRESTIN with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see Table 1, Posology and method of administration and Special warnings and precautions for use).

Cyclosporin
Co-administration of BEACRESTIN with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state AUC (0-t) increased up to 7-fold over that seen in healthy volunteers administered the same dose. Concomitant use of BEACRESTIN and cyclosporin is contraindicated (see Table 1 and Contraindications).

Protease inhibitors
Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately 3- fold increase in rosuvastatin AUC. The concomitant use of BEACRESTIN and some protease inhibitor combinations may be considered after careful consideration of BEACRESTIN dose adjustments based on the expected increase in rosuvastatin exposure (Table 1, Posology and method of administration and Special warnings and precautions for use).

Gemfibrozil and other lipid-lowering products
Concomitant use of BEACRESTIN and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (0-t). Based on data from specific interaction studies, no pharmacokinetic relevant interaction with fenofibrate is expected, however pharmacodynamic interaction may occur.

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (≥ 1g/day) of niacin (nicotinic acid) increase the risks of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, the dose of BEACRESTIN should not exceed 10 mg/day when given in combination with fibrates or niacin. (see Posology and method of administration and Special warnings and precautions for use).

Antacid
The simultaneous dosing of BEACRESTIN with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after BEACRESTIN. The clinical relevance of this interaction has not been studied.

Erythromycin
Concomitant use of BEACRESTIN and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes
Results from in vitro and in vivo studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Interactions requiring rosuvastatin dose adjustments (see also Table 1)
When it is necessary to co-administer BEACRESTIN with other medicinal products known to increase exposure to rosuvastatin, doses of BEACRESTIN should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with BEACRESTIN.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of BEACRESTIN should not exceed 5 mg once daily.

The maximum daily dose of BEACRESTIN should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of the recommended maximum daily dose of BEACRESTIN taken without interacting medicinal products.

For example, where the recommended dose of BEACRESTIN is 20mg; the dose of BEACRESTIN taken with a ritonavir/atazanavir combination (3.1-fold increase) should not exceed 5 mg, and the dose of BEACRESTIN taken with gemfibrozil (1.9-fold increase) should not exceed 10 mg.

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the BEACRESTIN dose above 20mg.

Table 1. Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg single dose	7.39 -fold ↑
Cyclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5mg, single dose	5.2-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8 -fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑

Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2.69-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID	5mg single dose	2.59-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10mg single dose	2.26-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5mg once daily	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Teriflunomide	Not available	2.51-fold ↑
Capmatinib 400mg BID	10mg, single dose	2.08-fold ↑
Fostamatinib 100mg twice daily	20mg, single dose	1.96-fold ↑
Febuxostat 120mg OD	10mg, single dose	1.9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg or 80 mg, single dose	1.4-fold ↑**
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑**
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone.
Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑",decrease as "↓".
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily
** Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio

The following medicinal product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:

Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

4.5.2 Effect of rosuvastatin on co-administered medicinal products

Warfarin

As with other HMG-CoA reductase inhibitors, co-administration of BEACRESTIN and warfarin may result in a rise in INR compared to warfarin alone. In patients taking vitamin K antagonists monitoring of INR is recommended both at initiation or cessation of therapy with BEACRESTIN or following dose adjustment.

Oral contraceptive/hormone replacement therapy (HRT)

Concomitant use of BEACRESTIN and an oral contraceptive resulted in an increase in ethinyl oestradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant BEACRESTIN and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products

Based on data from specific interaction studies, no clinically relevant interaction with digoxin is expected.

Endocrine function

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol levels or impairs adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other lipid-lowering agent is administered concomitantly with drugs that may decrease levels or activity of endogenous steroid hormones (ketoconazole, spironolactone, cimetidine).

Fusidic Acid

Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Therefore, the combination rosuvastatin and fusidic acid is not recommended. If possible, temporary suspension of rosuvastatin treatment is recommended. If unavoidable, patients should be closely monitored.

4.6 Fertility, pregnancy and lactation

The safety of BEACRESTIN during pregnancy and whilst breast feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures (see Contraindications).

4.7 Effects on ability to drive and use machines

Studies to determine the effect of BEACRESTIN on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, BEACRESTIN is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

The adverse events seen with rosuvastatin are generally mild and transient. In controlled clinical trials less than 4% of rosuvastatin treated patients were withdrawn due to adverse events.

Common (≥ 1/100, < 1/10)	Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus[1].
Uncommon (≥ 1/1000, < 1/100)	Pruritus, rash and urticaria
Rare (≥ 1/10,000, < 1/1000)	Myopathy (including myositis), hypersensitivity reactions (including angioedema), rhabdomyolysis, pancreatitis.

[1]Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) mostly in patients with fasting glucose 5.6 to 6.9 mmol/L (see Special warnings and precautions for use and Pharmacodynamic properties).

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Laboratory Effects

Renal Effects
Proteinuria detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in < 1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and has not been shown to be predictive of acute or progressive renal disease.

Skeletal muscle effects
Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses. A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (> 10xULN), treatment should be discontinued. (see Special warnings and precautions for use).

Liver effects
As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin (see Special warnings and precautions for use and Pharmacodynamic properties); the majority of cases were mild, asymptomatic and transient.

Other effects
In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens.

Post Marketing Experience
In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin.

Nervous system disorders
Very rare: polyneuropathy, memory loss;
Frequency unknown: peripheral neuropathy

Respiratory, thoracic and mediastinal disorders
Not known: cough, dyspnoea

Gastrointestinal disorders
Not known: diarrhoea

Haematological disorders
Frequency unknown: thrombocytopenia

Hepatobiliary disorders
Very rare: Jaundice, hepatitis;
Rare: increased hepatic transaminases

Skin and subcutaneous tissue disorders
Not known: Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Musculoskeletal disorders
Not known: immune-mediated necrotising myopathy;
Very Rare: arthralgia
As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose

Renal disorders
Very rare: haematuria

General disorders and administration site conditions
Not known: oedema

Reproductive system and breast disorders
Not known: gynaecomastia

The following adverse events have been reported with some statins
- Depression
- Sleep disturbances, including insomnia and nightmares

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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Children and adolescents 10 to 17 years of age
The safety profile of rosuvastatin is similar in children or adolescent patients and adults although CK elevations > 10xULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in a clinical trial of children and adolescents. However, the same special warnings and special precautions for use in adults also apply to children and adolescents (see Special warnings and precautions for use).

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic Classification
ATC code: C10A A07

Mechanism of action

Rosuvastatin is a selective, potent and competitive inhibitor of HMG-CoA reductase, the rate- limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Clinical efficacy

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 2).

Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio’s.

A therapeutic response to rosuvastatin is obtained within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Table 2 Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

The data in Table 2 are confirmed by the broader clinical programme of over 3,500 patients given rosuvastatin.

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses of rosuvastatin showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to 40 mg (12 weeks of treatment) LDL-C was reduced by 53%.

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20-40 mg titrated at a 6 week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C of less than 15%, 3 had no response or an increase in LDL-C.

In the METEOR study, the effect of rosuvastatin 40 mg on the progression of atherosclerosis was assessed by B-mode ultrasound of the carotid arteries. In this multi-center, double blind, placebo-controlled clinical trial, 984 subjects at low risk for coronary heart disease (defined as Framingham risk < 10% over ten years) and with a mean LDL-C of 154.5 mg/dL but with subclinical atherosclerosis as detected by CIMT (Carotid Intima Media Thickness) were randomized in a 5:2 ratio to treatment with either rosuvastatin 40 mg or placebo for 2 years. Rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the rate of change in the maximum CIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI -0.0196, -0.0093; p<0.0001). The change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI -0.0041, 0.0014), but was not significantly different from zero (p=0.3224). The beneficial effects of rosuvastatin were consistent across all 4 secondary CIMT endpoints. There was significant progression in the placebo group (+0.0131 mm/year; 95% CI 0.0087, 0.0174; p<0.0001). In the rosuvastatin group, 52.1% of patients demonstrated an absence of disease progression (i.e. regressed) compared to 37.7% of patients in the placebo group (p=0.0002). Rosuvastatin 40 mg was well-tolerated and the data were consistent to the established safety profile for rosuvastatin.

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with ε2/ ε2 genotype and 4 with apo E mutation [Arg145Cys]) with dysbetalipoproteinaemia (Fredrickson type III) received rosuvastatin 10 or 20 mg daily for 6 weeks. Rosuvastatin reduced non-HDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

Table 3 Lipid-modifying effects of Rosuvastatin 10mg and 20mg in Dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia) after six weeks by median percent change (95% CI) from baseline (N=32)

Dose	Total-C	TG	NonHDL-C	VLDL-C + IDL-C	LDL-C	HDL-C	RLP-C	Apo-E
10	-43.3 (-46.9, -37.5)	-40.1 (-44.9, -33.6)	-48.2 (-56.7, -45.6)	-46.8 (-53.7, -39.4)	-54.4 (-59.1, -47.3)	10.2 (1.9, 12.3)	-56.4 (-67.1, -49.0)	-42.9 (-46.3, -33.3)
20	-47.6 (-51.6, -42.8)	-43.0 (-52.5, -33.1)	-56.4 (-61.4, -48.5)	-56.2 (-67.7, -43.7)	-57.3 (-59.4, -52.1)	11.2 (8.3, 20.5)	-64.9 (-74.0, -56.6)	-42.5 (-47.1, -35.6)

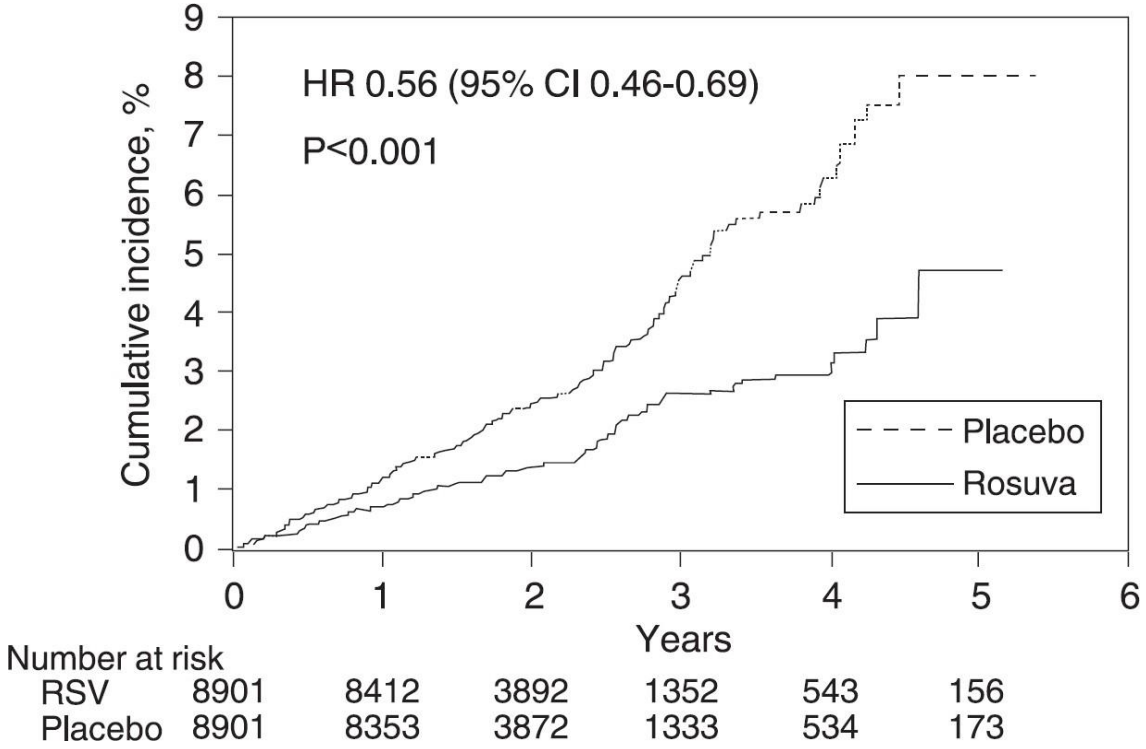
Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥ 50 years) and women (≥ 60 years) who had no clinically evident cardiovascular disease, LDL-C levels < 130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥ 2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary endpoint was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant ($p<0.001$) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 1). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C or hsCRP levels.

Figure 1 Time to occurrence of major cardiovascular events in JUPITER



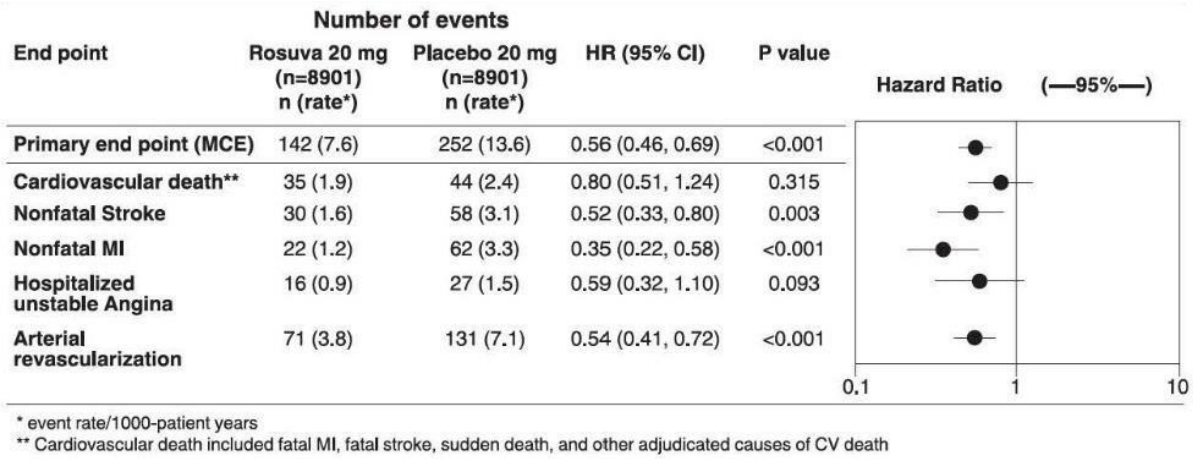
The individual components of the primary end point are presented in Figure 2. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58 nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

In JUPITER, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2.8% of patients in the rosuvastatin group and 2.3% of patients in the placebo group (HR: 1.27, 95% CI: 1.05-1.53, p=0.015). The difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c change from baseline was approximately 0.1%. The cardiovascular and mortality benefits of rosuvastatin therapy exceeded the diabetes hazard in the trial population as a whole (see Special warnings and precautions for use and Undesirable effects).

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin=725, placebo=680) with a hsCRP ≥ 2 mg/L and no other traditional risk factors (smoking, BP ≥ 140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

Figure 2 Major CV events by treatment group in JUPITER



* event rate/1000-patient years
** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

Children and Adolescents with Hypercholesterolaemia

In a double blind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open label, rosuvastatin dose titration phase, 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10-13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V respectively.

Rosuvastatin reduced LDL-C (primary end point), total cholesterol and ApoB levels. Results are shown in Table 4 below.

Table 4 Lipid-modifying effects of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia (least-square mean percent change from baseline to week 12)

Dose (mg)	N	LDL-C	HDL-C	Total-C	TG	Non-HDL-C	ApoB	ApoA-1
Placebo	46	-0.7	6.9	-0.0	5.1	-0.9	-1.7	2.8
5	42	-38.3	4.2	-29.9	0.3	-36.1	-31.7	1.8
10	44	-44.6	11.2	-34.2	-13.6	-43.0	-38.1	5.4
20	44	-50.0	8.9	-38.7	-8.1	-47.5	-40.7	4.0

At the end of the 40 week, open label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 110 mg/dL (2.8 mmol/L).

After 52 weeks' of study treatment, no effect on growth or sexual maturation was detected (see Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Rosuvastatin is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Exposure increases linearly over the dose range. The half life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance.

Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound, accounts for greater than 90% of the circulating active HMG CoA reductase inhibitor activity.

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Special populations

Age and sex
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Renal insufficiency
In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency
In a study in 12 subjects with mild to moderate hepatic impairment there was evidence of increased exposure to rosuvastatin in the 2 subjects with the higher Child-Pugh scores (8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Race
Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects including subjects of Japanese, Chinese, Malay and Indian ancestry compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Genetic polymorphisms
Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

Preclinical safety data
Preclinical data reveal no special hazards for humans based on conventional studies of safety

pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose PH-101
Microcrystalline cellulose PH-102
Colloidal anhydrous silica
Crospovidone type A
Lactose monohydrate
Magnesium stearate

Tablet coat
Hypromellose
Titanium dioxide
Lactose monohydrate
Triacetin
Iron Oxide Red

6.2 Shelf life

2 years

6.3 Special precautions for storage

Store below 30°C in cool, dry place and away from light.

6.4 Pack Size

OPA-Alu-PVC/Alu blisters in cartons of 30 tablets

6.5 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Beacons Pharmaceuticals Pte. Ltd.
2 Second Chin Bee Road,
Singapore 618769.

8. DATE OF REVISION OF THE TEXT
April 2023