SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ivarin 20 mg F.C. Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains: Rosuvastatin Calcium equivalent to Rosuvastatin 20 mg.

3. PHARMACEUTICAL FORM

Ivarin 20 mg F.C. Tablets: Light pink colored round shaped film-coated tablets engraved with "ZM" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ivarin is indicated for the:

Treatment of hypercholesterolaemia

Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of Cardiovascular Events

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; Ivarin is indicated to:

- Reduce the risk of stroke.
- Reduce the risk of myocardial infarction.
- Reduce the risk of arterial revascularization procedures.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet

that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.
Ivarin may be given at any time of day, with or without food.

Treatment of hypercholesterolaemia

The recommended start dose is 5 mg or 10 mg orally once daily in both statins naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start 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 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in 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 in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated.
Prevention of cardiovascular events
In the cardiovascular events risk reduction study, the dose used was 20 mg daily.

Pediatric population

Pediatric use should only be carried out by specialists.
Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1-year post-menarche)
In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the pediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.
The 40 mg tablet is not suitable for use in paediatric patients. Children younger than 10 years
Ivarin is not recommended for use in children younger than 10 years.

Use in the elderly

A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment.
The use of Ivarin in patients with severe renal impairment is contraindicated for all doses.

Dosage in patients with hepatic impairment

Ivarin is contraindicated in patients with active liver disease. Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg in patients with predisposing factors to myopathy. The 40 mg dose is contraindicated in some of these patients.

If you forget to take a dose

Don't worry, just take your next scheduled dose at the correct time. Do not take a double dose to make up for the one you have missed.

4.3 Contraindications

Ivarin is contraindicated:

- In patients with hypersensitivity to Ivarin or to any of the excipients.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- In patients with severe renal impairment (creatinine clearance <30 ml/min).
- In patients with myopathy.
- In patients receiving concomitant ciclosporin.
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Moderate renal impairment (creatinine clearance < 60 ml/min).
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Situations where an increase in plasma levels may occur.
- Concomitant use of fibrates.

4.4 Special warnings and precautions for use

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in **Ivarin**-treated patients with all doses and in particular with doses >20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with **Ivarin** in post-marketing use is higher at the 40 mg dose.

Creatine Kinase Measurement

Creatine 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. If CK levels are significantly elevated at baseline (> 5 x ULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment should not be started.

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 (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing **Ivarin** or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring.

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

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with **Ivarin** 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 derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of **Ivarin** and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of **Ivarin** with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate.

Ivarin should not be used 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).

Liver Effects: As with other HMG-CoA reductase inhibitors, **Ivarin** 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 be carried out prior to, and 3 months following, the initiation of treatment. **Ivarin** should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post- marketing use is higher at the 40 mg dose.

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

Protease inhibitors: The concomitant use with protease inhibitors is not recommended. **Lactose intolerance:** Patients with rare hereditary problems of galactose intolerance, the Lapp lactase

deficiency or glucose-galactose malabsorption should not take this medicine.

Interstitial lung disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus: In patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Ciclosporin: During concomitant treatment with **Ivarin** and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers.
Concomitant administration did not affect plasma concentrations of ciclosporin.

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of **Ivarin** in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of **Ivarin** may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Ezetimibe: Concomitant use of **Ivarin** and ezetimibe resulted in no change to AUC or C_{max} for either drug. However, a pharmacodynamic interaction, in terms of adverse effects, between **Ivarin** and ezetimibe cannot be ruled out.

Gemfibrozil and other lipid-lowering products: Concomitant use of **Ivarin** and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC.
Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. In a pharmacokinetic study, co-administration of 20 mg rosuvastatin and a combination product of two protease inhibitors (400 mg lopinavir/100 mg ritonavir) in healthy volunteers was associated with an approximately two-fold and five-fold increase in rosuvastatin steady-state $AUC_{(0-24)}$ and C_{max} respectively. Therefore, concomitant use of rosuvastatin in HIV patients receiving protease inhibitors is not recommended.

Antacid: The simultaneous dosing of **Ivarin** 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 **Ivarin**. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of **Ivarin** and erythromycin resulted in a 20% decrease in $AUC_{(0-t)}$ and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of **Ivarin** and an oral contraceptive resulted in an increase in ethinyl estradiol 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 **Ivarin** 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.

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. 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). Concomitant administration of itraconazole (an inhibitor of CYP3A4) and rosuvastatin resulted in a 28%

increase in AUC of rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

4.6 Pregnancy and lactation

Ivarin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

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

4.7 Effects on ability to drive and use machines

Studies to determine the effect of **Ivarin** on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, **Ivarin** 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

Like all medicines, **Ivarin** can cause side effects, although not everybody gets them.

It is important that you are aware of what these side effects may be. They are usually mild and disappear after a short time.

In controlled clinical trials, less than 4% of **Ivarin**-treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders

Rare: Hypersensitivity reactions including angioedema.

Endocrine disorders

Common: Diabetes mellitus.

Nervous system disorders

Common: Headache, dizziness.

Gastrointestinal disorders

Common: Constipation, nausea, abdominal pain.

Rare: Pancreatitis.

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, rash and urticaria.

Musculoskeletal, connective tissue and bone disorders

Common: Myalgia.

Rare: Myopathy (including myositis) and rhabdomyolysis.

General disorders

Common: Asthenia, feeling sick, feeling weak.

Urinary Tract Disorders

An increase in the amount of protein in the urine-this usually returns to normal on its own without having to stop taking your **Ivarin** tablets (only **Ivarin** 40 mg).

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin.

Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-treated patients with all doses and in particular with doses >20 mg.

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 (> 5 x ULN), treatment should be discontinued.

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; the majority of cases were mild, asymptomatic and transient.

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.

Respiratory, thoracic and mediastinal disorders: Not known: Cough, dyspnoea.

Gastrointestinal disorders: Not known: Diarrhoea.

Hepatobiliary disorders: Very rare: Jaundice, hepatitis; rare: Increased transaminases.

Skin and subcutaneous tissue disorders: Not known: Stevens-Johnson syndrome.
Musculoskeletal disorders: Very rare: Arthralgia.
Renal disorders: Very rare: Haematuria.
General disorders and administration site conditions: Not known: Oedema.
The following adverse events have been reported with some statins: Depression.
Sleep disturbances, including insomnia and nightmares.
Sexual dysfunction.
Exceptional cases of interstitial lung disease, especially with long term therapy.
The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.
Consult your Pharmacist or Physician if any side effect is observed.

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. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

The mechanism of action of Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.
Rosuvastatin 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.

5.2 Pharmacokinetic properties

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%).

Excretion: Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium phosphate.
Microcrystalline cellulose
Lactose monohydrate
Crospovidone
Magnesium Stearate
Opadry
Ferric oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

Do not use beyond the expiry date or if the product shows any sign of deterioration.

6.5 Nature and contents of container

Three Aluminum- Aluminum blisters of 10 tablets each, packed in a printed carton with folded leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorization Numbers in Ethiopia: 06891/08156/REN/2021

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

- Date of first authorization in Ethiopia: 16 August 2017
- Date of latest renewal in Ethiopia: 28 November 2021

10. DATE OF REVISION OF THE TEXT

August 2023