For PPB use only	
1.17	**Product Information**
1.17.1	**Summary Product Characteristics (SPC)**

1. Name of the medicinal product

Rosuvastatin 20mg and Clopidogrel 75mg Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains
Rosuvastatin Calcium USP Eqv. to Rosuvastatin 20mg
(As Granules)
Clopidogrel Bisulfate USP Eqv. to Clopidogrel 75mg
(As Tablet)

Materials required and standard quantities – For Rosuvastatin Granules Part					
S. No.	**Wt. / capsule (mg)**	**Ingredient**	**Specification**	**Overages**	**Std. Qty for 100,000 capsules (in kg)**
1.	21.40	Rosuvastatin Calcium	USP	Nil	2.140
2.	89.30	Maize Starch	BP	Nil	8.930
3.	10.00	Croscarmellose Sodium	BP	Nil	1.000
4.	30.00	Microcrystalline Cellulose	BP	Nil	3.000
5.	49.30	Lactose	BP	Nil	4.930
6.	10.00	Povidone K30	BP	Nil	1.000
7.	---	*Isopropyl Alcohol	BP	Nil	3.000
Materials required and standard quantities – For Clopidogrel Tablets Part					
S. No.	**Wt. / 2 tablets (mg)**	**Ingredient**	**Specification**	**Overages**	**Std. Qty for 200,000 Tablets for 100,000 Capsules (in kg)**
1.	97.50	Clopidogrel Bisulfate	USP	Nil	9.750
2.	7.40	Croscarmellose Sodium	BP	Nil	0.740
3.	15.00	Maize Starch	BP	Nil	1.500
4.	7.50	Lactose	BP	Nil	0.750
5.	7.00	Crospovidone	BP	Nil	0.700
6.	2.80	Povidone K30	BP	Nil	0.280
7.	---	*Isopropyl Alcohol	BP	Nil	2.000
	Lubrication				
8.	1.40	Colloidal Anhydrous Silica	BP	Nil	0.140
9.	1.40	Magnesium Stearate	BP	Nil	0.140
	Filling				
10.	1 (nos)	Empty hard gelatin capsules Size – '1' Colour: Black/Orange	IHS	3 %	103000 (nos)

*Represents solvents will not be present in finished product.
USP-United States Pharmacopoeia, BP – British Pharmacopoeia & IHS-In-House Specification.

3. Pharmaceutical form

Capsule: A black/ orange color hard gelatin capsule containing off white color granules and two tablets of white coloured circular shaped uncoated plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications

Rosuvastatin and Clopidogrel, which prevents heart attack and stroke. Rosuvastatin is a lipid lowering medication that blocks the body's ability to produce “bad” cholesterol (LDL) and improves the level of "good" cholesterol (HDL). Clopidogrel is an antiplatelet medication. It prevents the platelets from sticking together and decreases the formation of harmful blood clots.

4.2 Posology and method of administration

A single dose is recommended or as directed by physician.
Method of administration: Oral.
Not recommended for children below 18 years.
Paediatric population: Rosuvastatin and Clopidogrel should not be used in children.

4.3 Contraindications

Rosuvastatin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed. Contraindication of Clopidogrel is severe hepatic impairment. Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.4 Special warnings and precautions for use

Rosuvastatin: Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. 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. Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment.
Clopidogrel: Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician. Caution is required in patients

treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin.

Concomitant administration did not affect plasma concentrations of ciclosporin. Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC. Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by Clopidogrel.

4.6 Fertility, Pregnancy and lactation

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures. As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure. It is unknown whether clopidogrel is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

Caution is recommended, during driving or operating dangerous or poor precision machines as well as performing other activities requiring concentration.

4.8 Undesirable effects

Thrombocytopenia, Hypersensitivity reactions including angioedema, Diabetes mellitus, Depression, Headache, Dizziness, Cough, Dyspnoea, Nausea, Serum sickness, anaphylactoid reactions, Hallucinations, confusion, Taste disturbances, ageusia and Serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension

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. Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Rosuvastatin Calcium:

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A07

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.

Clopigrel Bisulfate:

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04. Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

5.2 Pharmacokinetic properties

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%. After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing.

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 l.

Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin. Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively). The binding is non-saturable in vitro over a wide concentration range.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%). In vitro metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450.

Elimination: 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. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch
Croscarmellose Sodium
Microcrystalline Cellulose
Lactose
Povidone K30
Crosopovidone
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's

3 x 10's (10 capsules are packed in one Alu-Alu blister and 3 such Alu-Alu blisters are kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder and Manufacturing Site Address

Marketing authorisation holder:

Company name: INNOCIA LIFESCIENCES PVT. LTD.,

Address: Block A, No.12, Balaji Nagar, Ambattur, Chennai-600 053

Country: INDIA.

Manufacturing Site:

ATOZ Pharmaceutials Pvt.Ltd.,

No.12, Balaji Nagar, Ambattur, Chennai-600053,

India.

8. Marketing authorisation number(s)

Telephone: 044 26585811, 26585855

Telefax: -

E-Mail: ah@innocialife.com

9. Date of first registration / Renewal of the registration

Date of first Authorization: 18.01.2021

Date of Latest Renewal: Not Applicable

10. Date of revision of the text: Not Applicable

11. Dosimetry (If Applicable): Not Applicable

12. Instructions for preparation of radiopharmaceuticals (If Applicable): Not Applicable