Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Ribofan 12.5mg/50ml Concentrate Solution for Infusion.

2. Qualitative and quantitative composition

Vial contains 12.5 mg of Tirofeban as active substance.

3. Pharmaceutical form

Solution for intravenous infusion.

4. Clinical particulars

4.1 Therapeutic indications

Ribofan is indicated for the prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 12 hours and with ECG changes and/ or elevated cardiac enzymes.

Patients most likely to benefit from Ribofan treatment are those at high risk of developing myocardial infarction within the first 3-4 days after Onset of acute angina symptoms including for instance, those that are likely to undergo an early percutaneous coronary intervention (PCI). Ribofan is also indicated for the reduction of major cardiovascular events in patients with acute myocardial infarction (STEMI) intended for primary PCI.

Ribofan is indicated for use with acetylsalicylic acid and unfractionated heparin

4.2 Posology and method of administration

This product is for hospital use only, by specialist physicians experienced in the management of acute coronary syndromes. Ribofan Concentrate must be diluted before use.

Ribofan should be administered with unfractionated heparin and oral antiplatelet therapy, including ASA.

Posology:

In patients who are managed with an early invasive strategy NSTE-ACS and not planned to undergo angiography for at least 4 hours and up to 48 hours after diagnosis, Ribofan is given intravenously at an initial infusion rate of 0.4 microgram/kg/min for 30 minutes. At the end of the initial infusion, Ribofan should be continued at a maintenance infusion rate of 0.1 microgram/kg/min. Ribofan should be given with Unfractionated heparin (usually an intravenous bolus of (5-6 unit/kg) simultaneously with the start of Ribofan therapy, then approximately 1000 U per hour, titrated on the basis of the activated thromboplastin time (APTT), which should be about twice the normal value), and oral antiplatelet therapy, including but not limited to acetylsalicylic acid , (ASA)unless contraindicated.

In NSTE-ACS patients planned to undergo PCI within the first 4 hours of diagnosis or in patients with acute myocardial infarction intended for primary PCI, Ribofan should be administered utilizing an initial bolus of 25 microgram/kg given over a 3-minute period, followed by a continuous infusion at a rate of 0.15 microgram/kg/min for 12-24, and up to 48 hours. Ribofan should be administered

with unfractionated heparin (dosage as above) and oral antiplatelet therapy, including but not limited to ASA, unless contra-indicated

Elderly:
No dosage adjustment is necessary for the elderly
Patients with severe kidney failure:
In seven kidney failure (creatinine clearance <30 ml/min) the dosage of Ribofan should be reduced by 50%
Pediatric population
The safety and efficacy of Ribofan in children have not been established. No data are available.
The following table is provided as a guide to dosage adjustment by weight
Ribofan Concentrate must first be diluted to make up a concentration of 50 microgram/ml as noted under instructions for Use.

Patient Weight (Kg)	0.4 microgram/kg/min Loading Dose Regimen Most Patients		0.4 microgram/kg/min Loading Dose Regimen Severe Renal Insufficiency		25 microgram/kg Dose Bolus Regimen Most Patients		25 microgram kg Dose Bolus Regimen Severe Renal insufficiency	
	30 Min Loading Infusion Rate (ml/hr)	Maintenance Infusion rate (ml/hr)	30 Min Loading Infusion rate (ml/hr)	Maintenance Infusion rate (ml/hr)	Bolus (ml)	Maintenance Infusion Rate (ml/hr)	Bolus (ml)	Maintenance Infusion Rate (ml/hr)
30-37	16	4	8	2	17	6	8	3
38-45	20	5	10	3	21	7	10	4
46-54	24	6	12	3	25	9	13	5
55-62	28	7	14	4	29	II	15	5
63-70	32	8	16	4	33	12	17	6
71-79	36	9	18	5	38	14	19	7
80-87	40	10	20	5	42	15	21	8
88-95	44	11	22	6	46	16	23	8
96-104	48	12	24	6	50	18	25	9
105-112	52	13	26	7	54	20	27	10
113-120	56	14	28	7	58	21	29	10
121-128	60	15	30	8	62	22	31	11
129-137	64	16	32	8	67	24	33	12
138-145	68	17	34	9	71	25	35	13
146-153	72	18	36	9	75	27	37	13

Start and duration of therapy with Ribofan

In patients who are managed with an early invasive strategy for NSTE-ACS but not planned to undergo angiography for at least 4 hours and up to 48 hours after diagnosis, Ribofan 0.4

microgram/kg/min loading dose regimen should be initiated upon diagnosis. The recommended duration should be at least 48 hours. Infusion of Ribofan and unfractionated heparin may be continued during coronary angiography and should be maintained for at least 12 hours and not more than 24 hours after angioplasty/atherectomy. Once a patient is clinically stable and no coronary intervention procedure is planned by the treating physician, the infusion should be discontinued. The entire duration of treatment should not exceed 108 hours.
If the patient diagnosed with NSTE-ACS and managed with an invasive strategy undergoes angiography within 4 hours after the diagnosis, the Ribofan 25 microgram/kg dose bolus regimen should be initiated at the start of PCI with the infusion continued for 18-24 hours and up to 48 hours. Concurrent therapy (unfractionated heparin, oral antiplatelet therapy).
Treatment with unfractionated heparin is initiated with an i.v. bolus of 5000 U and then continued with a maintenance infusion of 1,000 U per hour. The heparin dosage is titrated to maintain an APTT of approximately twice the normal value.
Unless contraindicated, all patients should receive oral antiplatelet agents, including but not limited to ASA, before the start of Ribofan. This medication should be continued at least for the duration of the infusion of Ribofan.
If angioplasty (PTCA) is required, heparin should be stopped after PTCA, and the sheaths should be withdrawn once coagulation has returned to normal, e.g. when the activated clotting time (ACT) is less than 180 seconds (usually 2-6 hours after discontinuation of heparin).

Method of administration
Instructions for use
Ribofan Concentrate must be diluted before use:
Draw 50 ml from a 250 ml container of sterile 0.9% saline or 5% glucose in water and replace with 50 ml Ribofan (from one 50 ml puncture vial) to make up a concentration of 50 microgram/ml. Mix well before use.
Use according to the dosage table above.
Where the solution and container permit, parenteral drugs should be inspected for visible particles or discoloration before use.
Ribofan should only be given intravenously and may be administered with unfractionated heparin through the same infusion tube.
It is recommended that Ribofan be administered with a calibrated infusion set using sterile equipment.
Care should be taken to ensure that no prolongation of the infusion of the initial dose occurs and that miscalculation of the infusion rates for the maintenance dose on the basis of the patient's weight is avoided.

4.3 Contraindications

Ribofan is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients of the preparation or who developed thrombocytopenia during earlier use of a GP IIb/IIIa receptor antagonist.

Since inhibition of platelet aggregation increases the bleeding risk, Ribofan is contraindicated in patients with:
History of stroke within 30 days or any history of hemorrhagic stroke.
Known history of intracranial disease (e.g. neoplasm, arteriovenous malformation, aneurysm).
Active or recent (within the previous 30 days of treatment) clinically relevant bleeding (e.g. gastro-intestinal bleeding).
Malignant hypertension.
Relevant trauma or major surgical intervention within the past six weeks.
Thrombocytopenia (platelet count <100,000/mm3), disorders of platelet function; Clotting disturbances (e.g. prothrombin time >1.3 times normal or INR [International Normalized Ratio] >1.5).
Severe liver failure.

4.4 Special warnings and precautions for use
The administration of Ribofan alone without unfractionated heparin is not recommended. There is limited experience with concomitant administration of Ribofan with enoxaparin. The concomitant administration of Ribofan with enoxaparin is associated with a higher frequency of cutaneous and oral bleeding events, but not in TIMI bleeds, when compared with the concomitant administration of Ribofan and unfractionated heparin. An increased risk of serious bleeding events associated with the concomitant administration of Ribofan and enoxaparin cannot be excluded, particularly in patients given additional unfractionated heparin in conjunction with angiography and/or PCI. The efficacy of Ribofan in combination with enoxaparin has not been established. The safety and efficacy of Ribofan with other low molecular weight heparins has not been investigated.
There is insufficient experience with the use of tirofiban hydrochloride in the following diseases and conditions, however, an increased risk of bleeding is suspected. Therefore, tirofiban hydrochloride is not recommended in:
Traumatic or protracted cardiopulmonary resuscitation, organ biopsy or lithotripsy within the past 2 weeks
Severe trauma or major surgery >6 weeks but <3 months previously
Active peptic ulcer within the past three months
Uncontrolled hypertension (>180/110 mm Hg)
Acute pericarditis
Active or a known history of vasculitis
Suspected aortic dissection
Hemorrhagic retinopathy
Occult blood in the stool or hematuria
Thrombolytic therapy
Concurrent use of drugs that increase the risk of bleeding to a relevant degree.
There is no therapeutic experience with Tirofiban hydrochloride in patients for whom thrombolytic therapy is indicated (e.g. acute transmural myocardial infarction with new physiological Q-waves or elevated ST-segments or left bundle branch block in ECG). Consequently, the use of tirofiban hydrochloride is not recommended in these circumstances.

Ribofan infusion should be stopped immediately if circumstances arise that necessitate thrombolytic therapy (including acute occlusion during PTCA) or if the patient must undergo an emergency coronary artery bypass graft (CABG) operation or requires an intra-aortic balloon pump.
Pediatrics population
There is no therapeutic experience with Tirofiban in children, thus, the use of Ribofan is not recommended in these patients.
Other precautionary notes and measures
There are insufficient data regarding the re-administration of Ribofan.
Patients should be carefully monitored for bleeding during treatment with Ribofan. If treatment of hemorrhage is necessary, discontinuation of Ribofan should be considered. In cases of major or uncontrollable bleeding, Tirofiban hydrochloride should be discontinued immediately.
Ribofan should be used with special caution in the following conditions and patient groups:
Recent clinically relevant bleeding (less than one year)
Puncture of a non-compressible vessel within 24 hours before administration of Ribofan
Recent epidural procedure (including lumbar puncture and spinal anesthesia)
Severe acute or chronic heart failure
Cardiogenic shock
•Mild to moderate liver insufficiency
Platelet count <150,000/mm3, known history of coagulopathy or platelet function disturbance or thrombocytopenia
Hemoglobin concentration less than 11 g/dl or hematocrits <34%.
Special caution should be used during concurrent administration of ticlopidine, clopidogrel, adenosine, dipyridamole, sulfinpyrazone, and prostacyclin.
Efficacy with regard to dose
The administration of a 10 microgram/kg bolus regimen of Tirofiban failed to show noninferiority in clinically relevant endpoints at 30 days compared to abciximab
Elderly patients, female patients, and patients with low body weight
Elderly and/or female patients had a higher incidence of bleeding complications than younger or male patients, respectively. Patients with a low body weight had a higher incidence of bleeding than patients with a higher body weight. For these reasons Ribofan should be used with caution in these patients and the heparin effect should be carefully monitored.
Impaired renal function
There is evidence from clinical studies that the risk of bleeding increases with decreasing creatinine clearance and hence also reduced plasma clearance of Tirofiban. Patients with decreased renal function (creatinine clearance <60ml/min) should therefore be carefully monitored for bleeding during treatment with Ribofan and the heparin effect should be carefully monitored. In severe kidney failure the Ribofan dosage should be reduced
Femoral artery line
During treatment with Ribofan there is a significant increase in bleeding rates, especially in the femoral artery area, where the catheter sheath is introduced. Care should be taken to ensure that

only the anterior wall of the femoral artery is punctured. Arterial sheaths may be removed when coagulation has returned to normal, e.g. when activated clotting time (ACT) is less than 180 seconds, (usually 2–6 hours after discontinuation of heparin).
After removal of the introducer sheath, careful homeostasis should be ensured under close observation.
General nursing care
The number of vascular punctures, and intramuscular injections should be minimized during the treatment with Ribofan. I.V. access should only be obtained at compressible sites of the body. All vascular puncture sites should be documented and closely monitored. The use of urinary catheters, nasotracheal intubation and nasogastric tubes should be critically considered.
Monitoring of laboratory values
Platelet count, hemoglobin and hematocrit levels should be determined before treatment with Ribofan as well as within 2-6 hours after start of therapy with Ribofan and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). In patients who have previously received GPIIb/IIIa receptor antagonists (cross reactivity can occur), the platelet count should be monitored immediately e.g. within the first hour of administration after re-exposure
If the platelet count falls below 90,000/mm^3, further platelet counts should be carried out in order to rule out pseudo thrombocytopenia. If thrombocytopenia is confirmed, Ribofan and heparin should be discontinued. Patients should be monitored for bleeding and treated if necessary.
In addition, activated thromboplastin time (APTT) should be determined before treatment and the anticoagulant effects of heparin should be carefully monitored by repeated determinations of APTT and the dose should be adjusted accordingly. Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting homeostasis, such as GPIIb/IIIa receptor antagonists.
Sodium content
Ribofan concentrate for solution for infusion contains approximately 189 mg of sodium per 50 ml vial which should be taken into consideration by patients on a controlled sodium diet.
4.5 Interaction with other medicinal products and other forms of interaction
The use of several platelet aggregation inhibitors increases the risk of bleeding, likewise their combination with heparin, warfarin and thrombolytic. Clinical and biological parameters of homeostasis should be regularly monitored.
The concomitant administration of Ribofan and ASA increases the inhibition of platelet aggregation to a greater extent than ASA alone, as measured by ex vivo APD-induced platelet aggregation test.
The concomitant administration of Ribofan and unfractionated heparin increases the prolongation of the bleeding time to a greater extent as compared to unfractionated heparin alone.
With the concurrent use of Ribofan, unfractionated heparin, ASA, and clopidogrel there was a comparable incidence of bleeding than when only unfractionated heparin, ASA, and clopidogrel were used together Ribofan prolonged bleeding time; however, the combined administration of Ribofan and ticlopidine did not additionally affect bleeding time.

Concomitant use of warfarin with Ribofan plus heparin was associated with an increased risk of bleeding.
Ribofan is not recommended in thrombolytic therapy –concurrent or less than 48 hours before administration of Tirofiban hydrochloride or concurrent use of drugs that increase the risk of bleeding to a relevant degree (e.g. oral anticoagulants, other parenteral GP IIb/IIIa inhibitors, dextran solutions). There is insufficient experience with the use of Tirofiban hydrochloride in these conditions; However, an increased risk of bleeding is suspected.

4.6 Pregnancy and Lactation
For Thydrochloride, no clinical data on exposed pregnancies are available. Animal studies provide limited information with respect to effects on pregnancy, embryonal fetal development, parturition, and postnatal development Ribofan should not be used during pregnancy unless clearly necessary.
Breastfeeding
It is not known whether Ribofan is execrated in human milk but it is known to be execrated in rat milk.
Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Fertility
Fertility and reproductive performance were not affected in studies with male and female rats treated with different doses of Tirofiban hydrochloride.
However, animal studies are insufficient to draw conclusions with respect to reproductive toxicity in humans.
4.7 Effects on ability to drive and use machines
Not Applicable.

4.8 Undesirable effects
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders				Acute and/or severe (<20,000/mm^3) decreases in platelet counts

Immune System Disorders				Severe allergic reactions including

				anaphylactic reactions.
Nervous system disorders	Headache			Intracranial bleeding, spinal epidural hematoma
Cardiac disorders				Hemopericardium
Vascular disorders	Hematoma			
Respiratory, thoracic and mediastinal disorders		Hemoptysis, epistaxis		Pulmonary (alveolar) hemorrhage
Gastrointestinal disorders	Nausea	Oral hemorrhage gingival hemorrhage	GI hemorrhage, hematemesis	Retroperitoneal bleeding
Skin and subcutaneous tissue disorders	Ecchymosis			
Renal and urinary disorders		Hematuria		
General disorders and administration site conditions		Fever		
Injury, poisoning and procedural complications	Post-operative hemorrhage*	Vessel puncture site hemorrhage		
Investigations	Occult blood in stool or urine	Decreases in hematocrits and hemoglobin, platelet counts <90,000/mm3	Platelet counts <50,000/mm3	

*Primarily related to catheterization sites.

Reporting of suspected adverse reactionsReporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the Pharmacy and Poisons Board (PPB) through the Pharmacovigilance Electronic Reporting

System (PvERS) at https://pv.pharmacyboardkenya.org/ or by using the approved PPB ADR reporting forms

4.9 Overdose

Inadvertent overdose with Tirofiban hydrochloride occurred in the clinical studies, up to 50 micrograms/kg as a three-minute bolus or 1.2 microgram/kg/min as an initial infusion. Overdose with up to 1.47 microgram/kg/min as a maintenance infusion rate has also occurred.

Symptoms of overdose

The symptom of overdose most commonly reported was bleeding, usually mucosal bleeding and localized bleeding at the arterial puncture site for cardiac catheterization but also single cases of intracranial hemorrhages and retroperitoneal bleedings

Measures

Overdose with tirofiban hydrochloride should be treated in accordance with the patient's condition and the attending physician's assessment. If treatment of hemorrhage is necessary, the Ribofan infusion should be discontinued. Transfusions of blood and/or thrombocytes should also be considered. Ribofan can be removed by hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

ANTITHROMBOTIC AGENTS
Platelet aggregation inhibitors excl.

heparin
ATC code: B01AC17

A reversible antagonist of fibrinogen binding to the glycoprotein (GP) IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, it inhibits ex vivo platelet aggregation in a dose- and concentration-dependent manner. When given according to the recommended regimen, >90% inhibition is attained within 10 minutes after initiation. Platelet aggregation inhibition is reversible following cessation of the infusion
5.2 Pharmacokinetic properties
Distribution
Vdss: 22 to 42 L
Metabolism
Negligible
Excretion
Urine (65%) and feces (25%) primarily as unchanged drug
Onset of Action
>90% inhibition of platelet aggregation (reversible after discontinuation) seen within 10 minutes
Half-Life Elimination
2 hours; Note: In ~90% of patients, ex vivo platelet aggregation returns to near baseline in 4 to 8 hours after discontinuation.
Protein Binding
65% (concentration dependent)

5.3 Preclinical safety data
Not Applicable.

6. Pharmaceutical Particulars
6.1 List of Excipients
Citric acid anhydrous, Sodium citrate dehydrate, Sodium chloride, Sodium hydroxide and water for injection.

6.2 Incompatibilities
Not Applicable.

6.3 Shelf-Life
2 years
6.4 Special Precautions for storage

Do not store above 30°C, protect from light, do not freeze and after dilution the product should be used immediately. If not used immediately, in use storage conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.5 Nature and Content of container

Clear Mould Glass Vial 50 ml USP Type I and Rubber Stopper 20mm

6.6 Special precautions for disposal and other handling

Not Applicable.

7. Marketing Authorization Holder

MS Pharma Jordan
Amman/ Jordan /Sahab- street no.6, building no.356 Tel: 06-4020680
Fax: 06-4020681
06-4162905
MS Pharma Jordan is responsible for the manufacture, packaging and QC Testing of this product& batch releasing to the market.

8. Marketing Authorization Number

H2024/CTD7024/13441
9. Date of first authorization/renewal of the authorization
2024 March 24
10. Date of revision of the text
2024 March 24