ART WORK APPROVAL FORM

Product Name: TGSON-60	**Market:** Malaysia (Healol Pharma)	**Mfg. Location:** UNIT-3

Dummy Pharmacode

Dummy Pharmacode

520 mm

1. Name of the Medicinal Product

TGSON-60
Ticagrelor Film Coated Tablets 60 mg

2. Qualitative and Quantitative Composition
Each tablet contains 60 mg of Ticagrelor.

Ticagrelor Film Coated Tablets 60 mg contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium free'.

For the full list of excipients, see section "6.1 List of excipients".

3. Pharmaceutical Form
Tablet
Light pink to pink, round, biconvex film coated tablets debossed with "C12" on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications

History of Myocardial Infarction (at least one year ago)
Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with a history of myocardial infarction (MI) (MI occurred at least one year ago), and a high risk of developing an atherothrombotic event.

Coronary Artery Disease, Type 2 Diabetes Mellitus and History of Percutaneous Coronary Intervention
Ticagrelor, co-administered with low-dose acetylsalicylic acid (ASA: 75-150mg), is indicated to reduce the risk of a first myocardial infarction or stroke in patients with Coronary Artery Disease (CAD), Type 2 Diabetes Mellitus (DM) and a history of percutaneous coronary intervention (PCI), who are also at high risk of developing an atherothrombotic events.

4.2 Posology and method of administration

Posology

***History of Myocardial Infarction* (at least one year ago)**
Patients taking Ticagrelor should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.
Ticagrelor 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of Ticagrelor beyond 3 years of extended treatment.
If a switch is needed, the first dose of Ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

Patients with Coronary Artery Disease (CAD) and Type 2 Diabetes Mellitus (DM) with a history of percutaneous coronary intervention (PCI)
Ticagrelor 60 mg twice daily is recommended dose for patients with CAD and type 2 DM with a history of PCI with no prior MI. No loading dose of Ticagrelor is required.
Patient may start treatment with Ticagrelor 60 mg twice daily, regardless of their previous antiplatelet regimen.
Treatment with Ticagrelor should be continued in patients with CAD and type 2 DM for as long as the patient remains at high risk of an atherothrombotic events and low risk of bleeding, for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of Ticagrelor still outweigh the risks after three years of treatment.
If a switch is needed, the first dose of Ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

Missed dose
Lapses in therapy should also be avoided. A patient who misses a dose of Ticagrelor Film Coated Tablets should take only one tablet (their next dose) at its scheduled time.

Special populations
Elderly
No dose adjustment is required in elderly.
Renal impairment
No dose adjustment is necessary for patients with renal impairment.
Hepatic impairment
Ticagrelor has not been studied in patients with severe hepatic impairment and its use in these patients is therefore contraindicated. Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor should be used with caution. No dose adjustment is necessary for patients with mild hepatic impairment.
Paediatric population
The safety and efficacy of ticagrelor in children below the age of 18 years have not been established. There is no relevant use of ticagrelor in children with sickle cell disease.

Method of administration
For oral use.
Ticagrelor Film Coated Tablets can be administered with or without food.
For patients who are unable to swallow the tablet(s) whole, the tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients of this medicine.
- Active pathological bleeding.
- History of intracranial haemorrhage.
- Severe hepatic impairment
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor

4.4 Special warnings and precautions for use

Benefit- risk in patients with coronary artery disease (CAD) and type-2 diabetes mellitus (DM)
In the THEMIS trial, a positive benefit-risk profile was observed in the pre-specified subgroup of patiens who have a history of percutaneous intervention (PCI), representing 58% of the overall THEMIS trial population. In the full THEMIS population, the benefit-risk profile was not considered favourable to support use of ticagrelor. Before initiating treatment in patients with CAD, type-2 diabetes and a history of PCI, it should be confirmed that a patient is at high risk of atherothombotic events and low risk of bleeding.

Bleeding risk
The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. The treating physicia should regularly reassess whether treatment with ticagrelor remains appropriate, particularly if there is a change in the factors associated with an increased risk of bleeding.
If clinically indicated, ticagrelor should be used with caution in the following patient groups:
- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding) or who are at increased risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of ticagrelor dosing.

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ticagrelor with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.
Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.

Surgery
Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.
In PLATO patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery. If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.

Patients with prior ischaemic stroke
In PEGASUS, (history of MI ≥ one year) and THEMIS (CAD and type 2 DM) trials, patients with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients. Treatment in patients with CAD, type 2 DM and prior ischaemic stroke is also not recommended.

Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients.

Patients at risk for bradycardic events
Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) have been excluded from the main studies evaluating the safety and efficacy of ticagrelor as they may be at increased risk of developing bradyarrhythmias with ticagrelor. Therefore, due to the limited clinical experience, ticagrelor should be used with caution in these patients.
Bradyarrhythmic events, including 2nd and 3rd degree AV block, have however been reported in the post-marketing setting in patients with or without history of bradyarrhythmia, in most cases, shortly after initiation of treatment with ticagrelor. Therefore, ticagrelor should be used with caution and these patients should be closely monitored during the first few weeks on treatment.
In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia. However, no evidence of clinically significant adverse reactions was observed in the PLATO and the PEGASUS trials during concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil and 4% digoxin). In THEMIS, 73.8% of patients took beta blocker at study-entry.
During the Holter substudy in PLATO, more patients had ventricular pauses >3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population.

Dyspnoea
Dyspnoea was reported in patients treated with ticagrelor. Dyspnoea is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/chronic obstructive pulmonary disease (COPD) may have an increased absolute risk of experiencing dyspnoea with ticagrelor. Ticagrelor should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped.

Central sleep apnoea
Central sleep apnoea including Cheyne-Stokes respiration has been reported in the post-marketing setting in patients taking ticagrelor. If central sleep apnoea is suspected, further clinical assessment should be considered.

Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with ticagrelor, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase
Hyperuricaemia may occur during treatment with ticagrelor. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)
In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies in patient serum activate platelets of healthy donors in the presence of heparin. False negative results in a platelet function test (to include, but may not be limited to the HIPA test) for HIT have been reported in patients administered ticagrelor. This is related to inhibition of the $P2Y_{12}$-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma.
Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.
In patients who have developed HIT, the benefit-risk of continued treatment with ticagrelor should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.

Other
Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended.

Premature discontinuation
Premature discontinuation with any antiplatelet therapy, including ticagrelor, could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction
Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates. Ticagrelor is a breast cancer resistance protein (BCRP) inhibitor.

Effects of medicinal and other products on ticagrelor
CYP3A4 inhibitors
- *Strong CYP3A4 inhibitors* – Co-administration of ketoconazole with ticagrelor increased the ticagrelor Cmax and AUC equal to 2.4-fold and 7.3-fold, respectively. The Cmax and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and therefore concomitant use of strong CYP3A4 inhibitors with ticagrelor is contraindicated.
- *Moderate CYP3A4 inhibitors* – Co-administration of diltiazem with ticagrelor increased the ticagrelor Cmax by 69% and AUC to 2.7-fold and decreased the active metabolite Cmax by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin and fluconazole) would be expected to have a similar effect and can as well be co-administered with ticagrelor.
- A 2-fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

CYP3A inducers
Co-administration of rifampicin with ticagrelor decreased ticagrelor Cmax and AUC by 73% and 86%, respectively. The Cmax of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A inducers (e.g. phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well. Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor, therefore, their concomitant use with ticagrelor is discouraged.

Cyclosporine (P-gp and CYP3A inhibitor)
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor Cmax and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and Cmax was decreased by 15% in the presence of cyclosporine.
No data are available on concomitant use of ticagrelor with other active substances that also are potent P-gp inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution.

Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and ASA or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that alter haemostasis should be used with caution in combination with ticagrelor.
A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral $P2Y_{12}$ inhibitor may be considered.

Effects of ticagrelor on other medicinal products
Medicinal products metabolised by CYP3A4
- Simvastatin – Co-administration of ticagrelor with simvastatin increased simvastatin Cmax by 81% and AUC by 56% and increased simvastatin acid Cmax by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse effects of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Ticagrelor may have similar effect on lovastatin. The concomitant use of ticagrelor with doses of simvastatin or lovastatin greater than 40 mg is not recommended.
- Atorvastatin – Co-administration of atorvastatin and ticagrelor increased atorvastatin acid Cmax by 23% and AUC by 36%. Similar increases in AUC and Cmax were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of ticagrelor and CYP3A4 substrates with narrow therapeutic indices (i.e. cisapride or ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products.

P-gp substrates (including digoxin, cyclosporine)
Concomitant administration of ticagrelor increased the digoxin Cmax by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2-fold. In the presence of digoxin, the Cmax and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin concomitantly with ticagrelor.
There was no effect of ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not been studied.

Medicinal products metabolised by CYP2C9
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either medicinal product, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicinal products like warfarin and tolbutamide.

Rosuvastatin (BCRP substrate) Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

Oral contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with ticagrelor.

Medicinal products known to induce bradycardia
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia. However, no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil and 4% digoxin).

Other concomitant therapy
In clinical studies, ticagrelor was commonly administered with ASA, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers as needed for concomitant conditions for long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations. No evidence of clinically significant adverse interactions with these medicinal products was observed.
Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of ticagrelor with medicinal products known to alter haemostasis.
Due to reports of cutaneous bleeding abnormalities with SSRIs (e.g. paroxetine, sertraline and citalopram), caution is advised when administering SSRIs with ticagrelor as this may increase the risk of bleeding.

400 mm
Front

Font Type : Times New Roman
Font Size : 10 & 12 pt

DATE: 17/01/2026 VERSION: 11
DATE: 12/01/2026 VERSION: 10
DATE: 09/01/2026 VERSION: 09
DATE: 11/08/2025 VERSION: 08
DATE: 21/05/2025 VERSION: 07
DATE: 03/05/2025 VERSION: 06
DATE: 21/04/2025 VERSION: 05
DATE: 10/06/2024 VERSION: 04
DATE: 31/05/2024 VERSION: 03
DATE: 30/01/2024 VERSION: 02
DATE: 08/01/2024 VERSION: 01
DATE: 16/12/2023 VERSION: 00

Size: 520 x 400 mm
Colour: P P Black C

Pharmacode: XXXX

Note: Position of box is not fixed. it might be change as per machine suitability. Tape should be use for folding.

INSERT/PIL/OUTSERT SPECIFICATION

Artwork Code	XX XXX XXXX XX	**Open Size**	520 x 400 mm	**Close Size**	60 x 31 mm	**Folding Condition**	Folded	**Type of Paper**	Bible
GSM of Paper	40 gsm	**Colour of Paper**	White	**Colour of Matter**	P P Black C	**Pharmacode**	XXXX	**Any other special process**	Final fold by Tape
Old Artwork Code	N.A.	**Old Pharmacode**	N.A.	**Reference Change Control no.**	N.A.	**of Plant**	N.A.		

Review & Approved By Contract Giver/Customer/Authority/MA Holder (If Applicable) :

Sign & Date :	
Name :	
Designation :	
Department :	

ART WORK APPROVAL FORM

Product Name: TGSON-60	**Market:** Malaysia (Healol Pharma)	**Mfg. Location:** UNIT-3

520 mm

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor therapy.

Pregnancy

There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity. Ticagrelor is not recommended during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ticagrelor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Ticagrelor had no effect on male or female fertility in animals.

4.7 Effects on ability to drive and use machines

Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

Adverse reactions are listed by MedDRA System Organ Class (SOC). Within each SOC the adverse reactions are ranked by frequency category. Frequency categories are defined according to the following conventions: 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).

Table 1 – Adverse reactions by frequency and system organ class (SOC)

SOC	Very Common	Common	Uncommon	Not Known
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[a]	
Blood and lymphatic system disorders	Blood disorder bleedings[b]			Thrombotic Thrombocytopenic Purpura[c]
Immune system disorders			Hypersensitivity including angioedema[c]	
Metabolism and nutrition disorders	Hyperuricaemia[b]	Gout/Gouty arthritis		
Psychiatric disorders			Confusion	
Nervous system disorders		Dizziness Syncope, Headache	Intracranial haemorrhage[m]	
Eye disorders			Eye haemorrhage[e]	
Ear and labyrinth disorders		Vertigo	Ear haemorrhage	
Vascular disorders		Hypotension		
Cardiac disorders				Bradyarrhythmia[c] AV block (2nd and 3rd degree)[c]
Respiratory, thoracic and mediastinal disorders	*Dyspnoea*	Respiratory system bleedings[f]		
Gastrointestinal disorders		Gastrointestinal haemorrhage[g] Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage	
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[h], Rash, Pruritus		
Musculoskeletal and connective tissue disorders			Muscular bleeding[i]	
Renal and urinary disorders		Urinary tract bleedings[j]		
Reproductive system and breast disorders			Reproductive system bleedings[k]	
Investigations		Blood creatinine increased[d]		
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[l]		

AV = atrioventricular

[a] e.g. bleeding from bladder cancer, gastric cancer, colon cancer

[b] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

[c] Identified in post-marketing experience

[d] Frequencies derived from lab observations (Uric acid increases to >upper limit of normal from baseline below or within reference range. Creatinine increases of >50% from baseline.) and not crude adverse event report frequency.

[e] e.g. conjunctival, retinal, intraocular bleeding

[f] e.g. epistaxis, haemoptysis

[g] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

[h] e.g. ecchymosis, skin haemorrhage, petechiae

[i] e.g. haemarthrosis, muscle haemorrhage

[j] e.g. haematuria, cystitis haemorrhagic

[k] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage

[l] e.g. contusion, traumatic haematoma, traumatic haemorrhage

[m] i.e. spontaneous, procedure related or traumatic intracranial haemorrhage

4.9 Overdose

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses. In the event of an overdose, the above potential adverse reactions could occur and ECG monitoring should be considered.

There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not dialysable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged duration of bleeding risk associated with platelet inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding. If bleeding occurs other appropriate supportive measures should be taken.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC24

Mechanism of action

Ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI or stroke.

Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).

Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood in vitro) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated.

Pharmacodynamic effects

Onset of action

In patients with stable coronary artery disease (CAD) on ASA, ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean inhibition of platelet aggregation (IPA) for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 89% by 2-4 hours post dose, and maintained between 2-8 hours. 90% of patients had final extent IPA>70% by 2 hours post dose.

Offset of action

If a CABG procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

5.2 Pharmacokinetic properties

Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.

Absorption

Absorption of ticagrelor is rapid with a median tmax of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median tmax of approximately 2.5 hours. Following an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, Cmax is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for Cmax and 0.42 for AUC. The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor Cmax was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg Cmax was 627 ng/ml and AUC was 6255 ng*h/ml at steady state.

The mean absolute bioavailability of ticagrelor was estimated to be 36%. Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite Cmax but had no effect on ticagrelor Cmax or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. Ticagrelor as well as the active metabolite are P-gp substrates.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and Cmax for ticagrelor and the active metabolite. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.0%).

Biotransformation

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition.

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by in vitro binding to the platelet P2Y12 ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

Elimination

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose.

The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean t1/2 was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 25% for both Cmax and AUC) and the active metabolite were observed in elderly (≥75years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant.

Paediatric population

Limited data are available in children with sickle cell disease.

In the HESTIA 3 study, patients aged 2 to less than 18 years weighing ≥ 12 to ≤ 24 kg, > 24 to ≤ 48 kg and > 48 kg, were administered ticagrelor as paediatric dispersible 15 mg tablets at doses of respectively 15, 30 and 45 mg twice daily. Based on population pharmacokinetic analysis, the mean AUC ranged from 1095 ng*h/mL to 1458 ng*h/mL and the mean Cmax ranged from 143 ng/mL to 206 ng/mL at steady state.

Gender

Higher exposures to ticagrelor and the active metabolite were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment

Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment (creatinine clearance <30 ml/min) compared to subjects with normal renal function.

In patients with end stage renal disease on haemodialysis AUC and Cmax of ticagrelor 90 mg administered on a day without dialysis were 38% and 51% higher compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis (49% and 61%, respectively) showing that ticagrelor is not dialysable.

Exposure of the active metabolite increased to a lesser extent (AUC 13-14% and Cmax 17-36%). The inhibition of platelet aggregation (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function.

Hepatic impairment

Cmax and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment.

Ethnicity

Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. In clinical pharmacology studies, the exposure (Cmax and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical Particulars:

6.1 List of excipients

Core tablet:
Mannitol (Pearlitol 160C)
Calcium hydrogen phosphate dihydrate
Hydroxy propyl cellulose
Croscarmellose sodium
Magnesium stearate
Coating ingredient:
Hypromellose
Titanium dioxide
Macrogol
Iron oxide red
Black iron oxide

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30° C.

6.5 Nature and contents of container

Tablets are available in Alu-PVC/PVDC Film clear blister pack of 10's & 14's tablets.
Pack size: 6x10 & 1x14 Tablets Alu-PVC/PVDC Film clear

7. Marketing Authorization Holder

Healol Pharmaceuticals SDN BHD
74-3, Jalan Wangsa Delima 6, Klsc Wangsa Maju,
53300 Kuala Lumpur, Malaysia

8. Manufacturer Name

Unison Pharmaceuticals Pvt. Ltd.
Unit-III, C-7,8,9, Steel Town, Opp. Nova
Petrochemicals, Village Moraiya, Sanand,
Ahmedabad, Gujarat 382213, INDIA

9. Date of revision of the text

January 2026

XXXXXXXXXX

400 mm

Size: 520 x 400 mm
Colour: P P Black C

Pharmacode: XXXX

Back

Note: Position of box is not fixed. it might be change as per machine suitability. Tape should be use for folding.

Font Type : Times New Roman
Font Size : 10 & 12 pt

DATE: 17/01/2026 VERSION: 11
DATE: 12/01/2026 VERSION: 10
DATE: 09/01/2026 VERSION: 09
DATE: 11/08/2025 VERSION: 08
DATE: 21/05/2025 VERSION: 07
DATE: 03/05/2025 VERSION: 06
DATE: 21/04/2025 VERSION: 05
DATE: 10/06/2024 VERSION: 04
DATE: 31/05/2024 VERSION: 03
DATE: 30/01/2024 VERSION: 02
DATE: 08/01/2024 VERSION: 01
DATE: 16/12/2023 VERSION: 00

INSERT/PIL/OUTSERT SPECIFICATION

Artwork Code XX XXX XXXX XX **Open Size** 520 x 400 mm **Close Size** 60 x 31 mm **Folding Condition** Folded **Type of Paper** Bible

GSM of Paper 40 gsm **Colour of Paper** White **Colour of Matter** P P Black C **Pharmacode** XXXX **Any other special process** Final fold by Tape

Old Artwork Code N.A. **Old Pharmacode** N.A. **Reference Change Control no.** N.A. **of Plant** N.A.

Review & Approved By Contract Giver/Customer/Authority/MA Holder (If Applicable) :

Sign & Date :	
Name :	
Designation :	
Department :	

Z:\General Export\MALAYSIA\HEALOL PHARMA\TGSON\TGSON-60\XX XXX XXXX XX_TGSON-60_Outsert_Malaysia_17-01-2026.cdr