FRONT

TICAGRELOR

CLEVERGE

90 mg Film-Coated Tablet

Antithrombotic Agent

(Platelet Aggregation Inhibitor excl. heparin)

℞

FORMULATION:
Each film-coated tablet contains:
Ticagrelor ..... 90 mg

PRODUCT DESCRIPTION:
Pale yellow to yellow, circular, biconvex, film-coated tablet, plain on both sides.

PHARMACOLOGIC PROPERTIES:
Pharmacodynamic Properties

Mechanism of action:
Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective, and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (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 cardiovascular events such as CV death, MI, or stroke.

Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration providing enhanced local adenosine responses. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet inhibition, modulation of inflammation, and induction of dyspnoea, which may contribute to the clinical profile of ticagrelor.

Pharmacokinetic Properties
General:
Ticagrelor demonstrates linear pharmacokinetics and exposure to Ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional.

Absorption:
Absorption of Ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite from Ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of Ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of Ticagrelor was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on Ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in Ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, Ticagrelor can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% 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%).

Metabolism:
CYP3A 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. Ticagrelor and the active metabolite are weak P-glycoprotein inhibitors.

The major metabolite of Ticagrelor is AR-C124910XX, which is also active as assessed by in vitro binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for Ticagrelor.

Excretion:
The primary route of Ticagrelor elimination is via hepatic metabolism. When radiolabeled Ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in feces, 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 mostly via biliary secretion. The mean $t_{\frac{1}{2}}$ was approximately 6.9 hours (range 4.5 – 12.8 hours) for Ticagrelor and 8.6 hours (range 6.5 – 12.8 hours) for the active metabolite.

Special Populations:
Elderly:
Higher exposures to Ticagrelor (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant.

Paediatric:
Ticagrelor has not been evaluated in a paediatric population.

Gender:
Higher exposures to Ticagrelor (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) 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 compared to subjects with normal renal function. The IPA effect of Ticagrelor was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment.

In patients with end stage renal disease on haemodialysis AUC and C_{max} of Ticagrelor 90 mg administered on a day without dialysis were 38% and 51% higher respectively compared to subjects with normal renal function. A similar increase in exposure was observed when Ticagrelor was administered immediately prior to dialysis showing that Ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of Ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function. No dosing adjustment is needed in patients with renal impairment.

Hepatic impairment:
C_{max} 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.

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 (C_{max} 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.

INDICATIONS:
Ticagrelor is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with *Acute Coronary Syndromes* ([ACS] unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

DOSAGE AND ADMINISTRATION:
In patients with Acute Coronary Syndromes, Ticagrelor treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment is recommended for at least 12 months unless discontinuation of Ticagrelor is clinically indicated. After one year, patients initiated on 90 mg twice daily may continue treatment with 60 mg twice daily without interruption.

Patients taking Ticagrelor should also take a daily low maintenance dose of acetyl-salicylic acid (ASA) of 75-150 mg, unless specifically contraindicated. An initial loading dose of ASA is recommended for patients with ACS.

Missed dose: Lapses in therapy should be avoided. A patient who misses a dose of Ticagrelor should take their next dose at its scheduled time.

Premature discontinuation: Premature discontinuation with any antiplatelet therapy, including Ticagrelor, could result in an increased risk of cardiovascular (CV) death, myocardial infarction (MI), or stroke due to the patient's underlying disease.

Switching: In patients having an ACS event, the loading dose of 180 mg should be given as soon as possible regardless of any previous antiplatelet treatment.

Physicians who, desire to switch patients, with a prior ACS event, to Ticagrelor should administer the first dose of Ticagrelor 24 hours following the last dose of the other anti-platelet medication.

Special Populations
Paediatric patients:
Safety and efficacy in children below the age of 18 have not been established.

Elderly patients:
No dose adjustment is required.

Patients with renal impairment:
No dose adjustment is necessary for patients with renal impairment.

Patients with hepatic impairment:
No dose adjustment is necessary for patients with mild hepatic impairment, Ticagrelor has not been studied in patients with severe hepatic impairment and there is limited information on treatment of patients with moderate hepatic impairment.

Administration:
For oral use. Ticagrelor can be taken with or without food.

For patients who are unable to swallow the tablet(s) whole, Ticagrelor 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.

CONTRAINDICATIONS:
Hypersensitivity to Ticagrelor or any of the excipients.
Active pathological bleeding.
History of intracranial haemorrhage.
Severe hepatic impairment.

WARNINGS AND PRECAUTIONS:
Bleeding risk
As with other antiplatelet agents, the use of Ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. 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, active or recent gastrointestinal bleeding, or moderate hepatic impairment). The use of Ticagrelor is contraindicated in patients with active pathological bleeding and in those with history of intracranial haemorrhage and 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 may augment haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.

Surgery:
• If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of Ticagrelor treatment should occur.

• Because of the reversible binding of Ticagrelor, restoration of platelet aggregation occurs faster with Ticagrelor compared to clopidogrel. In the OFFSET Study, mean Inhibition of Platelet Aggregation (IPA) for Ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g., in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

• In PLATO, patients undergoing CABG, Ticagrelor had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where Ticagrelor had a higher rate of major bleeding.

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

Patients at risk for bradyarrhythmia:
Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel, Bradyarrhythmic events have been reported in the postmarketing setting. In phase 3 studies evaluating the safety and efficacy of Ticagrelor, bradyarrhythmic events were reported in a similar frequency for ticagrelor and comparators (placebo, clopidogrel and ASA). 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 Ticagrelor outcome studies. Therefore, due to the limited clinical experience in these patients, caution is advised.

Dyspnoea:
Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with Ticagrelor (approximately 13.8%). The mechanism has not yet 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.

Thrombotic Thrombocytopenic Purpura (TTP):
Thrombotic Thrombocytopenic Purpura has been reported very rarely with the use of Ticagrelor. TTP is a serious condition and requires prompt treatment.

Interference with laboratory tests:
Platelet function tests to diagnose Heparin induced thrombocytopenia (HIT): False negative results in platelet function test for heparin induced thrombocytopenia (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.

Before considering discontinuation of ticagrelor, the benefit and risk of continued treatment 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 the PLATO Study 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.

Co-administration of Ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to Ticagrelor.

Discontinuations:
Patients who require discontinuation of Ticagrelor are at increased risk for cardiac events or stroke. Premature discontinuation of treatment should be avoided. If Ticagrelor must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

Effects on ability to drive and use machines:
No studies on the effects of Ticagrelor on the ability to drive and use machines have been performed. 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.

PREGNANCY AND LACTATION:

No clinical study has been conducted in pregnant or lactating women.

Limited clinical data on exposure to Ticagrelor during pregnancy are available.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development.

BACK

Because animal reproduction studies are not always predictive of a human response, Ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Lactation:
It is not known whether this medicinal product is excreted in human milk. Studies in rats have shown that Ticagrelor and active metabolites are excreted in the milk. The use of Ticagrelor during breastfeeding is not recommended.

DRUG INTERACTIONS:
Drug-Drug Interactions
Effects of Other Drugs on Ticagrelor:
Medicinal Products metabolised by CYP3A4

Ketoconazole (Strong CYP3A4 Inhibitors):
Co-administration of ketoconazole with Ticagrelor increased Ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} 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 should not be given concomitantly with Ticagrelor.

Diltiazem (Moderate CYP3A4 inhibitors):
Co-administration of Ticagrelor and diltiazem increased the C_{max} of Ticagrelor by 69% and AUC by 174%, and decreased the active metabolite C_{max} 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, fluconazole, and verapamil) can as well be co-administered with Ticagrelor.

Rifampin and Other CYP3A Inducers:
Co-administration of rifampin with Ticagrelor decreased Ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A4 inducers (e.g., phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to Ticagrelor as well and may result in reduced efficacy of Ticagrelor.

Cyclosporine (PgP and CYP3A inhibitor):
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

Others:
Clinical pharmacology interaction studies showed that co-administration of Ticagrelor with heparin, enoxaparin, and aspirin did not have any effect on Ticagrelor or the active metabolite plasma levels. Co-administration of Ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of Ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been reported in patients treated with morphine (approximately 35% reduction in ticagrelor). This interaction may be related to reduced gastrointestinal motility, and therefore apply to other opioids. The clinical relevance is unknown.

Effects of Ticagrelor on Other Drugs:
Medicinal Products metabolised by CYP3A4:
Simvastatin:
Co-administration of Ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on Ticagrelor plasma levels. Ticagrelor may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin:
Co-administration of atorvastatin and Ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Medicinal products metabolised by CYP2C9

Tolbutamide:
Co-administration of Ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that Ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

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

Digoxin (PgP substrate):
Concomitant administration of Ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with Ticagrelor.

Other Concomitant Therapy:
Ticagrelor was commonly administered with acetylsalicylic acid, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

ADVERSE DRUG SUBSTANCE:
Tabulated list of adverse drug reactions
Adverse drug reactions with Ticagrelor are listed by MedDRA System Organ Class (SOC) and frequency category. Within each SOC and frequency category, adverse drug reactions are presented in order of decreasing seriousness. Frequency categories are defined according to the following conventions: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

System Organ Classification	Very Common	Common	Uncommon	Rare
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[3]	
Blood and lymphatic system disorders	Blood disorders bleeding[1]			
Metabolism and nutrition disorders	Hyperuricaemia[4]	Gout		
Psychiatric disorders			Confusion	
Nervous system disorders		Dizziness Syncope	Intracranial haemorrhage	
Eye disorders			Eye haemorrhage[2]	
Ear and labyrinth disorders		Vertigo	Ear haemorrhage	
Vascular disorders		Hypotension		
Respiratory thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings[5]		
Gastrointestinal disorders		Gastrointestinal haemorrhage[1], Diarrhoea, Nausea	Retroperitoneal haemorrhage	
Skin and subcutaneous disorders		Subcutaneous or dermal bleeding[2], Pruritus		
Musculoskeletal connective tissue and bone disorders			Muscular bleedings[3]	
Renal urinary and disorders		Urinary tract bleeding[1]		
Reproductive system and breast disorders			Reproductive System bleedings[2]	
Investigations		Blood creatinine increased[4]		
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[6]		

[1]Frequencies derived from lab observations (Uric acid increases to >ULN from baseline below or within reference range, Creatinine increases of >50% from baseline) and not crude adverse event report frequency.
[2]e.g., bleeding from bladder cancer, gastric cancer, colon cancer.
[3]e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis.
[4]e.g., conjunctival, retinal, intraocular bleeding
[5]e.g., epistaxis, haemoptysis.
[6]e.g., gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage.
[1]e.g., ecchymosis, skin haemorrhage, petechiae.
[1]e.g., haemarthrosis, muscle haemorrhage.
[2]e.g., haematuria, cystitis haemorrhagic
[2]e.g., vaginal haemorrhage, haematospermia, postmenopausal haemorrhage.
[6]e.g., contusion, traumatic haematoma, traumatic haemorrhage.

OVERDOSE AND TREATMENT:
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. If bleeding occurs, appropriate supportive measures should be taken.

Ticagrelor is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
Alu/Clear PVC-PVdC Blister Pack x 10's (Box of 60's)

MANUFACTURED BY:
LLOYD LABORATORIES, INC.
No. 10 Lloyd Avenue, First Bulacan Industrial City,
Malolos, Bulacan

MANUFACTURED FOR:
ONE PHARMA
ONE PHARMA MARKETING INC.
L51, B21, Abel Nosce St., BF Resort Village, Talon II,
Las Piñas City, Metro Manila

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph". Seek medical attention immediately at the first sign of any adverse drug reaction.

REGISTRATION NUMBER:
DR-XY48422

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13 October 2022

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