310387-02

Metalyse®
Tenecteplase

Powder and solvent for solution for injection

Composition
METALYSE 10,000 units:
1 vial contains 10,000 units (50 mg) tenecteplase
1 pre-filled syringe contains 10 ml water for injections
Excipients:** L-arginine, phosphoric acid, polysorbate 20
trace residue: gentamicin from manufacturing process

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Indications
METALYSE is indicated for the thrombolytic treatment of acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after symptom onset

Dosage and administration
METALYSE should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of re-constituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10

The required dose should be administered as a single intravenous bolus over 5 to 10 seconds. A pre-existing intravenous line, which has been used for administration of 0.9% sodium chloride solution only, may be used for administration of METALYSE. If a line is used, this line should be flushed after METALYSE injection for proper delivery.
METALYSE is incompatible with dextrose solution. METALYSE should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line (not even with heparin).
ADJUNCTIVE THERAPY:
Antithrombotic adjunctive therapy is recommended according to the current international guidelines for the management of patients with ST-elevation myocardial infarction.

For coronary intervention please refer to section Special warnings and precautions.

Instructions for use/handling
METALYSE should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient. (see Dosage and Administration)
2. Check that the cap of the vial is still intact.
3. Remove the flip-off cap from the vial.
4. Remove the tip-cap from the syringe. Then immediately screw the pre-filled syringe on the vial adapter and penetrate the vial stopper in the middle with the spike of the vial adapter.
5. Add the water for injections into the vial by pushing the syringe plunger down slowly to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation is a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution is administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Transfer the appropriate volume of reconstituted solution of METALYSE into the syringe, based on the patient's weight.
10. Disconnect the syringe from the vial adapter.
11. METALYSE should be administered to the patient, intravenously over 5 to 10 seconds. It should not be administered into a line containing dextrose.
12. Any unused solution should be discarded.
13. Alternatively the reconstitution can be performed with the included needle.

Contraindications
Thrombolytic therapy is associated with a risk of bleeding. METALYSE is contraindicated in the following situations:

- significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
- patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (INR > 1.3) (please see section Special warnings and precautions, subsection "Bleeding")
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- severe uncontrolled arterial hypertension
- major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current AMI), recent trauma to the head or cranium
- prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- active peptic ulceration
- arterial aneurysm and known arterial/venous malformation
- neoplasm with increased bleeding risk
- acute pericarditis and/or subacute bacterial endocarditis
- acute pancreatitis
- hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients
- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months

Special warnings and precautions
METALYSE should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use. This does not preclude the pre-hospital use of METALYSE. As with other thrombolytics, it is recommended that when METALYSE is administered standard resuscitation equipment and medication be available in all circumstances.

Coronary intervention
Transfer to a coronary intervention capable facility for adjunctive Percutaneous Coronary Intervention (PCI):
Patients receiving METALYSE as primary coronary recanalization treatment should be transferred without delay to a coronary intervention capable facility for angiography and timely coronary intervention within 6-24 hours or earlier if medically indicated (please refer to section Pharmacological properties).

Primary Percutaneous Coronary Intervention (PCI)
If primary PCI is scheduled according to the current relevant treatment guidelines METALYSE as administered in the ASSENT-4 PCI study (please refer to section Pharmacological properties) should not be given.

Bleeding
The most common complication encountered during METALYSE therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during METALYSE therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including those following catheter insertions, arterial and venous puncture, cutdown and needle puncture). The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with METALYSE.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents should also be considered.

The use of METALYSE therapy has to be carefully evaluated in order to balance the potential risks of bleeding with expected benefits under the following conditions :

- Systolic blood pressure > 160 mm Hg
- Recent gastro-intestinal or genitourinary bleeding (within the past 10 days)
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg
- Cerebrovascular disease
- Patients receiving oral anticoagulants treatment: The use of METALYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.

Arrhythmias
Coronary thrombolysis may result in arrhythmia associated with reperfusion.
Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

Glyco-ProteinIIb/IIIa antagonists
The concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

Thrombo-embolism
The use of METALYSE can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g., mitral stenosis or atrial fibrillation.

Hypersensitivity
No antibody formation to the tenecteplase molecule has been observed after treatment. However, there is no experience with re-administration of METALYSE.

Anaphylactoid reactions associated with the administration of METALYSE are rare and can be caused by hypersensitivity to the active substance tenecteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. If an anaphylactoid reaction occurs, the injection should be discontinued and appropriate treatment should be initiated.

Interactions
No formal interaction studies with METALYSE and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with METALYSE.
Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after METALYSE therapy.

Fertility, pregnancy and lactation
Pregnancy
There is a limited amount of data from the use of METALYSE in pregnant women. Nonclinical studies performed with tenecteplase have shown bleeding with secondary mortality of dams due to the known pharmacological activity of the drug and in a few cases abortion and resorption of the foetus occurred (effects only have been observed with repeated dose administration). Tenecteplase is not considered to be teratogenic (see Toxicology).
The benefit of treatment must be evaluated against the potential risks in case of myocardial infarction during pregnancy.

Lactation:
It is not known if tenecteplase is excreted into human milk.

Fertility:
Clinical data as well as nonclinical studies on fertility are not available for tenecteplase (METALYSE).

Side effects
As with other thrombolytic agents, haemorrhage is the most common undesirable effect associated with the use of METALYSE. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.
The type of haemorrhage associated with thrombolytic therapy can be divided into two broad categories:
- Superficial bleeding, normally from injection sites.
- internal bleedings at any site or body cavity.

With intracranial haemorrhage neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion may be associated.

Immune system disorders
Rare: anaphylactoid reaction (incl. rash, urticaria, bronchospasm, laryngeal oedema)

Nervous system disorders
Uncommon: intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation stroke, intracranial haematoma, subarachnoid haemorrhage)

Eye disorders
Uncommon: eye haemorrhage.

Cardiac disorders
Uncommon: reperfusion arrhythmia (such as asystole, accelerated idioventricular arrhythmia, arrhythmia, extrasystoles, atrial fibrillation, atrioventricular block first degree - atrioventricular block complete, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia).

Occur in close temporal relationship to treatment with METALYSE.

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

Not known: cardiac arrest

Rare: pericardial haemorrhage

Vascular disorders
Very common: haemorrhage
Rare: embolism

Respiratory, thoracic and mediastinal disorders
Common: epistaxis.
Rare: pulmonary haemorrhage.

Gastrointestinal disorders
Common: gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage).

Not known: nausea

Not known: vomiting

Uncommon: retroperitoneal haemorrhage (such as retroperitoneal haematoma)

Skin and subcutaneous tissue disorders
Common: Ecchymosis.

Renal and urinary disorders
Common: urogenital haemorrhage (such as haematuria, haemorrhage urinary tract).

File information		Mandatory in	
		TD	Printfile
Issue date of TD:	15.11.2012	Yes	Yes
PPM SKU:	P014683	No	Yes
PPM SKU version:	005	No	Yes
Issue date of artwork:	24/JUN/2019	No	Yes
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Min. font size:	8,25 pt		
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Technical information			
a = Batch No.		b = Expiry date	
c = Manufacturing date		d = Price/Sample/Clinic	
Technical colors			
BI-Diecut-Legendcase	Free area		Gluepoints

Additional Requirements of Packaging site	
Template name: TD-PI_296x315	Index: b

59757-04
A
B
C

MASS A 8,5 mm
MASS B 2,2 mm
MASS C max. 42,5 mm

Example
Technical information
control code

DISETUJUI OLEH BPOM: 03/07/2019

No. ID: EREG10036411900019

General disorders and administration site conditions
Common: Injection site haemorrhage, puncture site haemorrhage.

Investigations
Rare: Blood pressure decreased.
Not known:Body temperature increased.

Injury, poisoning and procedural complications
Not known: Fat embolism, which may lead to corresponding consequences in the organs concerned.

Surgical and medical procedures
Not known: Transfusion.

Overdose
In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered.

Pharmacological properties
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

ASSENT 2 study
A large scale mortality trial (ASSENT 2) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% versus 28.9%, p = 0.0003). The reduction of the risk of bleeding is likely to be related to the increased fibrin specificity of tenecteplase and to its weight adapted regimen.

This translates into a significantly lower need of transfusions (4.3% versus 5.5%,p = 0.0002). Intracranial haemorrhage occurred at a rate of 0.93% versus 0.94% for tenecteplase and alteplase, respectively. In the 475 patients treated beyond 6 hours numerical differences in favour of tenecteplase were observed with regard to 30-day mortality (4.3% versus 9.6%), stroke (0.4% versus 3.3%) and ICH (0% versus 1.7%).

ASSENT-4 PCI study
The ASSENT-4 PCI study was designed to show if in 4000 patients with large myocardial infarctions pre-treatment with full dose tenecteplase and concomitant single bolus of up to 4,000 IU unfractionated heparin administered prior to primary Percutaneous Coronary Intervention (PCI) to be performed within 60 to 180 minutes leads to better outcomes than primary PCI alone. The trial was prematurely terminated with 1667 randomised patients due to a numerically higher mortality in the facilitated PCI group receiving tenecteplase. The occurrence of the primary endpoint, a composite of death or cardiogenic shock or congestive heart failure within 90 days, was significantly higher in the group receiving the exploratory regimen of tenecteplase followed by routine immediate PCI: 18.6% (151/810) compared to 13.4% (110/819) in the PCI only group, p = 0.0045. This significant difference between the groups for the primary endpoint at 90 days was already present in-hospital and at 30 days. Numerically, all of the components of the clinical composite endpoint were in favour of the PCI only regimen: death: 6.7% versus 4.9% p = 0.14; cardiogenic shock: 6.3% versus 4.8% p = 0.19; congestive heart failure: 12.0% versus 9.2% p = 0.06 respectively. The secondary endpoints re-infarction and repeat target vessel revascularisation were significantly increased in the group pre-treated with tenecteplase: reinfarction: 6.1% versus 3.7% p = 0.0279; repeat target vessel revascularisation: 6.6% versus 3.4% p = 0.0041.
The following adverse events occurred more frequently with tenecteplase prior to PCI: intracranial haemorrhage: 1% versus 0% p = 0.0037; stroke: 1.8% versus 0% p < 0.0001; major bleeds: 5.6% versus 4.4% p = 0.3118; minor bleeds: 25.3% versus 19.0% p = 0.0021; blood transfusions: 6.2% versus 4.2% p = 0.0873; abrupt vessel closure: 1.9% versus 0.1% p = 0.0001.

STREAM study
The STREAM study was designed to evaluate the efficacy and safety of a pharmaco-invasive strategy of early fibrinolytic treatment with tenecteplase and additional antiplatelet and anticoagulant therapy followed by angiography within 6-24 hours or rescue coronary intervention versus a strategy of standard primary PCI.

The study population consisted of patients with ST elevation acute myocardial infarction within 3 hours of onset of symptoms not able to undergo primary PCI within one hour of first medical contact.
A sample size of approximately 1000 patients per treatment group was planned for this exploratory study. After 382 patients had been enrolled (19.5 % of the planned study population), the dose of the tenecteplase bolus was reduced by half for the patients ≥ 75 years because of a higher incidence of intracranial haemorrhage (ICH) in this sub-group.

1892 patients were randomised by means of an interactive voice response system. The primary endpoint, a composite of death or cardiogenic shock or congestive heart failure or re-infarction within 30 days was observed in 12.4% (116/939) of the pharmaco-invasive arm versus 14.3% (135/943) in the primary PCI arm (relative risk 0.86 (0.68-1.09)). Single components of the primary composite endpoint for the pharmaco-invasive strategy versus primary PCI respectively were observed with the following frequencies:

	Pharmaco-invasive (n=944)	**Primary PCI (n=948)**	**P**
Composite death, shock, congestive heart failure, reinfarction	116/939 (12.4%)	135/943 (14.3%)	0.21
All-cause mortality	43/939 (4.6%)	42/946 (4.4%)	0.88
Cardiogenic shock	41/939 (4.4%)	56/944 (5.9%)	0.13
Congestive heart failure	57/939 (6.1%)	72/943 (7.6%)	0.18
Reinfarction	23/938 (2.5%)	21/944 (2.2%)	0.74
Cardiac mortality	31/939 (3.3%)	32/946 (3.4%)	0.92

The observed incidence of major and of minor non-ICH bleeds were similar in both groups:

	Pharmaco-invasive (n=944)	Primary PCI (n=948)	P
Major non-ICH bleed	61/939 (6.5%)	45/944 (4.8%)	0.11
Minor non-ICH bleed	205/939 (21.8%)	191/944 (20.2%)	0.40

Incidence of total strokes and intracranial haemorrhage

	Pharmaco-invasive (n=944)	**Primary PCI (n=948)**	**P**
Total stroke (all types)	15/939 (1.6%)	5/946 (0.5%)	0.03*
Intracranial haemorrhage	9/939 (0.96%)	2/946 (0.21%)	0.04**
Intracranial haemorrhage after protocol amendment to half dose in patients ≥ 75 years :	4/747 (0.5%)	2/758 (0.3%)	0.45

* the incidences in both groups are those expected in STEMI patients treated by fibrinolytics or primary PCI (as observed in previous clinical studies).
** the incidence in the pharmaco-invasive group is as expected for fibrinolysis with Metalyse (as observed in previous clinical studies).

None of the differences between groups displayed in the above tables reached the threshold of statistical significance except for the incidence of total strokes and ICH, however the incidences in the pharmaco-invasive group were as observed in previous clinical studies.
After the dose reduction of tenecteplase by half in patients ≥ 75 years there was no further intracranial hemorrhage (0 of 97 patients) (95% CI: 0.0- 3.7) versus 8.1% (3 of 37 patients) (95% CI: 1.7- 21.9) prior to the dose reduction. The bounds of the confidence interval of the observed incidences prior and after dose reduction are overlapping.
In patients ≥ 75 years the observed incidence of the primary efficacy composite end point for the pharmaco-invasive strategy and primary PCI were as follows: before dose reduction 11/37 (29.7%) (95% CI: 15.9- 47.0) vs. 10/32 (31.3%) (95% CI: 16.1-50.0), after dose reduction: 25/97 (25.8%) (95% CI: 17.4-35.7) vs. 25/88 (24.8%) (95% CI: 19.3-39.0). In both groups the bounds of the confidence interval of the observed incidences prior and post dose reduction are overlapping.

Pharmacokinetics
Absorption and distribution
Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Following i.v. bolus administration of 30 mg tenecteplase in patients with acute myocardial infarction, the initially estimated tenecteplase plasma concentration was 6.45 ± 3.60 µg/mL (mean ± SD). The distribution phase represents 31% ± 22% to 69% ± 15% (mean ± SD) of the total AUC following the administration of doses ranges from 5 to 50 mg.

Data on tissue distribution were obtained in studies with radioactively labelled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to which extent tenecteplase binds to plasma proteins in humans. The mean residence time (MRT) in the body is approximately 1 h and the mean (± SD) volume of distribution at the steady-state (Vss) ranged from 6.3 ± 2 L to 15 ± 7 L.

Metabolism
Tenecteplase is cleared from the circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life.

Elimination
After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half-life is 24 ± 5.5 (mean ± SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min. Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

Linearity/Non-Linearity
The dose linearity analysis based on AUC suggested that tenecteplase exhibits non-linear pharmacokinetics in the dose range studied, i.e. 5 to 50 mg.

Special populations
Renal and hepatic impairment
Because elimination of tenecteplase is through the liver, it is not expected that renal dysfunction will affect the pharmacokinetics of METALYSE. This is also supported by animal data. However, the effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans has not been specifically investigated.

Toxicology
Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by transient changes of ECG but these occurred at exposures that were considerably higher than the clinical exposure.
With regard to the indication and the single dose administration in humans, reproductive toxicity testing was confined to the rabbit, as a sensitive species. Tenecteplase induced no teratogenicity. Repeated dose administration resulted in bleeding with secondary mortality of dams. In a few cases abortion and resorption of the foetus occurred. Effects were not seen after single dose administration of tenecteplase.
Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.
No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

Incompatibilities
METALYSE is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution or infusion line.

Special precautions for storage
Do not store above 30°C. Keep the container in the outer carton in order to protect from light.

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 - 8°C and 8 hours at 30°C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C or 8 hours at 30°C.

Availability
Vial with 50 mg powder for solution for injection pre-filled syringe with 10 ml water for injections
Reg. No. DKI0252501844B1

Store below 30°C
Store in a safe place out of the reach of children!

Only on doctor's prescriptions
Harus dengan resep dokter

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG
Biberach/Riss, Germany
for Boehringer Ingelheim International GmbH, Germany

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Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

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