APPROVED
The Order of Ministry of Health of Ukraine
02.12.2020 № 2779
Registration certificate
№ UA/11433/01/01

AMENDED
The Order of Ministry of Health of Ukraine
07.09.2023 № 1593

INSTRUCTION
for medical use

PLATOGREL®

Composition:
active substance: clopidogrel;
1 tablet contains clopidogrel bisulfate equivalent to clopidogrel 75 mg;
excipients: povidone K-30, mannitol (E 421), microcrystalline cellulose, low-substituted hydroxypropyl cellulose, hydrogenated castor oil, iron oxide red (E 172); coating Opadry Y-1-7000 white: hypromellose, polyethylene glycol, titanium dioxide (E 171).

Pharmaceutical form. Film-coated tablets.
Basic physico-chemical properties: pink film-coated round biconvex tablets, smooth on both sides.

Pharmacotherapeutic group. Platelet aggregation inhibitors excluding heparin.
ATC code B01A C04.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized by CYP 450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptors and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation.
As a result of the irreversible binding, platelets exposed to clopidogrel are affected for the remainder of their lifespan (approximately 7–10 days) and recovery of normal platelet function corresponds to the rate of platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by the released ADP.
Since the active metabolite is formed by CYP 450 enzymes, some of which are polymorphic or inhibited by other medicinal products, not all patients will have adequate inhibition of platelet aggregation.
Pharmacodynamic effects.
From the first day of the use of repeated daily drug doses of 75 mg, a significant slowdown of ADP-induced platelet aggregation is observed. This effect progressively increases and is stabilized

between day 3 and day 7. At steady state, the mean level of aggregation inhibition under the effect of the daily dose of 75 mg is 40 % to 60 %. Platelet aggregation and bleeding time return to the baseline level on average 5 days after discontinuation of the treatment.

Pharmacokinetics.

Absorption.

After oral administration of a single and multiple doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma concentrations of unchanged clopidogrel (approximately 2,2−2,5 ng/mL after a single dose of 75 mg orally) are reached approximately 45 minutes after dosing. Absorption is at least 50 % based on the urinary excretion of clopidogrel metabolites.

Distribution.

Clopidogrel and the main (inactive) metabolite circulating in the blood bind reversibly *in vitro* to human plasma proteins (98 % and 94 % respectively). This binding is non-saturable *in vitro* within a wide concentration range.

Metabolism.

Clopidogrel is extensively metabolized in the liver. *In vitro* and *in vivo*, there are two main metabolic pathways: one takes place with the participation of esterases and leads to hydrolysis with the formation of an inactive derivative of carboxylic acid (which is 85 % of all metabolites circulating in blood plasma), and the other one involves the enzymes of the P450 cytochrome system. First clopidogrel is transformed into an intermediate metabolite 2-oxo-clopidogrel. As a result of further metabolism of 2-oxo-clopidogrel a thiol derivative of clopidogrel, an active metabolite, is formed. This active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active metabolite of clopidogrel (thiol derivative) which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. The C_{max} of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after 4 days of 75 mg maintenance dose. C_{max} is reached approximately 30 to 60 minutes after dosing.

Excretion.

120 hours after oral administration of the labeled ^{14}C-clopidogrel, in humans approximately 50 % of the dose is excreted with the urine and approximately 46 % with the feces. After oral administration of a single dose of 75 mg, the half-life of clopidogrel is approximately 6 hours. The half-life of the main (inactive) metabolite circulating in blood is 8 hours after a single or multiple use of the drug.

Pharmacogenetics.

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. The pharmacokinetics of the active metabolite of clopidogrel and antiplatelet effects, according to *ex vivo* platelet aggregation measurements, differ according to the CYP2C19 genotype.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles correspond to nonfunctional metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Mongoloid (99%) patients with poor metabolism. Other alleles associated with absent or reduced metabolism are less frequent. These include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolism possesses two loss-of-function alleles as defined above. According to the published data, CYP2C19 genotypes associated with poor metabolism are present in 2 % of Caucasian patients, 4 % of Negroid patients and 14 % of Mongoloid patients. Tests are currently available to determine a patient's CYP2C19 genotype.

A crossover study involving healthy subjects with certain types of CYP2C19 metabolism (ultrarapid, extensive, intermediate and poor) evaluated the pharmacokinetics and antiplatelet effects using a dose of 300 mg followed by a dose of 75 mg per day, as well as a dose of 600 mg followed by a dose of 150 mg per day. Each of these was used for a total of 5 days (until steady state was reached). No significant differences were found in the concentrations of the active metabolite in the blood and the mean inhibition of platelet aggregation (IPA) between individuals with ultrarapid, extensive and intermediate metabolism. The blood concentration of the active metabolite decreased by 63−71 % in the poor metabolizers as compared to the subjects with extensive metabolism. After

the use of the 300 mg /75 mg dose regimen, antiplatelet effects were less pronounced in individuals with poor metabolism, with the mean IPA (5 μM ADP) of 24 % (24 hours) and 37 % (day 5), as compared to an IPA of 39 % (24 hours) and 58 % (day 5) in subjects with extensive metabolism and 37 % (24 hours) and 60 % (day 5) in those with intermediate metabolism. When individuals with poor metabolism received the 600 mg/150 mg dose regimen, blood concentrations of the active metabolite were greater than with the 300 mg/75 mg dose regimen. In addition, IPA was 32 % (24 hours) and 61 % (day 5), which was greater than in subjects with poor metabolism receiving the 300 mg/75 mg dose regimen, and similar to the indicators in other CYP2C19 metabolizer groups receiving the 300 mg/75 mg regimen. Based on clinical effects studies, no appropriate dose regimen for this patient group has been established.
Consistent with the above results, there is additional data on the reduction of blood concentrations of the active metabolite by 28 % in individuals with intermediate metabolism and by 72 % in individuals with poor metabolism; platelet aggregation inhibition (5 μM ADP) was also decreased, with differences in IPA of 5,9 % and 21,4 %, respectively, when compared to individuals with extensive metabolism.
There is evidence that the incidence of cardiovascular events (death, myocardial infarction and stroke) or stent thrombosis was significantly higher in individuals with intermediate and poor metabolism receiving clopidogrel than in those with extensive metabolism. According to other data, the incidence of cardiovascular events did not differ significantly depending on the peculiarities of metabolism.
Therefore, it can be concluded that none of the known analyzes included a sufficient number of patients to be able to reveal a difference in the clinical outcomes in patients with poor metabolism.
Special patient groups.
The pharmacokinetics of the active metabolite of clopidogrel has not been studied in the following special patient groups.
Renal impairment.
After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance 5−15 ml per minute), inhibition of ADP-induced platelet aggregation was less pronounced (25 %) than that observed in healthy volunteers, and the prolongation of bleeding time was similar to that seen in healthy volunteers receiving 75 mg of clopidogrel per day. Clinical tolerance was good in all patients.
Hepatic impairment.
After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy volunteers. The mean bleeding time prolongation was also similar in the two groups.
Race. The prevalence of CYP2C19 alleles that cause intermediate and poor CYP2C19 metabolism activity differs according to the race/ethnicity (see section “Pharmacogenetics”). There is limited data on Mongoloid patients that makes it possible to assess the clinical implication of genotyping of this CYP.

Clinical characteristics.
Indications.
Secondary prevention of manifestations of atherothrombosis in adults:
- patients who have suffered myocardial infarction (the treatment is started after a few days, but not later than 35 days after the occurrence), ischemic stroke (the treatment is started after 7 days, but not later than 6 months after the occurrence), or those with diagnosed peripheral arterial disease;
- patients with acute coronary syndrome:
  – with acute coronary syndrome without ST-segment elevation (unstable angina or non-Q-wave myocardial infarction), including patients who have undergone stent placement in the process of percutaneous coronary angioplasty, in combination with acetylsalicylic acid (ASA);
  – with acute myocardial infarction with ST-segment elevation in combination with ASA (in patients receiving standard medical therapy for whom thrombolytic therapy is indicated).

Moderate- and high-risk transient ischemic attack (TIA) or minor ischemic stroke (IS).
Clopidogrel in combination with ASA is indicated in adult patients with moderate- or high-risk TIA (ABCD score 2[1] ≥ 4) or minor ischemic stroke (NIHSS score [2] ≤ 3) within 24 hours of the TIA or IS event.

[1] Age, blood pressure, clinical signs, duration and diagnosis of diabetes mellitus.
[2] National Institute of Health Stroke Scale.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation. Clopidogrel in combination with ASA is indicated in adult patients with atrial fibrillation who have at least one risk factor for vascular events, who have contraindications to treatment with vitamin K antagonists (VKA) and who have a low risk of bleeding, for the prevention of atherothrombotic and thromboembolic events, including stroke.
For further information see section "Pharmacological properties".

Contraindications.
- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic insufficiency.
- Acute bleeding (e.g., peptic ulcer or intracranial hemorrhage).

Interaction with other medicinal products and other forms of interaction.
Medicinal products associated with an increased risk of bleeding.
There is an increased risk of hemorrhagic complications due to the potential additive effect, therefore, concomitant administration of such medicinal products with clopidogrel should be undertaken with caution (see section "Administration details").
Oral anticoagulants.
Concomitant use of clopidogrel with oral anticoagulants is not recommended because the combination can enhance the intensity of bleeding (see section "Administration details"). Although the use of clopidogrel at a dose of 75 mg per day does not alter the pharmacokinetic profile of S-warfarin or international normalized ratio (INR) in patients who receive long-time treatment with warfarin, concomitant use of clopidogrel and warfarin increases the risk of bleeding because of the existence of independent effects on hemostasis.
Inhibitors of glycoprotein receptors IIb/IIIa.
Clopidogrel should be used with caution in patients receiving concomitant inhibitors of glycoprotein receptors IIb/IIIa (see section "Administration details").
Other antiplatelet agents.
Concomitant use of antiplatelet drugs increases the risk of bleeding due to the additive effect. Any signs or symptoms of blood loos should be evaluated immediately if the patient is concomitantly treated with other antiplatelet drugs (see section "Administration details").
Acetylsalicylic acid (ASA).
Acetylsalicylic acid does not alter the inhibitory action of clopidogrel on ADP-induced platelet aggregation, but clopidogrel increases the effect of ASA on collagen-induced platelet aggregation. However, concomitant use of 500 mg of ASA two times a day for one day caused no significant increase in bleeding time, which was prolonged as a result of using clopidogrel. As there is a possible pharmacodynamic interaction between clopidogrel and ASA with an increased risk of bleeding, concomitant use of these drugs requires caution (see section "Administration details"). In spite of this, there is experience of concomitant use of clopidogrel and ASA for up to 1 year (see section "Pharmacological properties").
Heparin.
According to the existing data, the use of clopidogrel did not require dose adjustment for heparin and did not alter the effect of heparin on coagulation. Concomitant administration of heparin did not alter the inhibitory effect of clopidogrel on platelet aggregation. As pharmacodynamic interaction is possible between clopidogrel and heparin with increased risk of bleeding, concomitant use of these drugs requires caution (see section "Administration details").
Thrombolytic agents.

The safety of concomitant administration of clopidogrel, fibrin specific or non-fibrin specific thrombolytic agents and heparin was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin were co-administered with ASA (see section "Adverse reactions").

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Concomitant use of clopidogrel and naproxen increased the number of occult gastrointestinal bleedings. However, due to the lack of research on the interaction of the drug with other NSAIDs, it is unknown whether the risk of gastrointestinal bleeding increases when using the drug with other NSAIDs. Therefore, caution is required during concomitant use of NSAIDs, particularly COX-2 inhibitors, with clopidogrel (see section "Administration details").

Selective serotonin reuptake inhibitors (SSRIs).

SSRIs affect platelet activation and increase the risk of bleeding, therefore, caution must be exercised during their concomitant use with clopidogrel.

Concomitant use of other medicinal products.

CYP2C19 inducers.

Since clopidogrel is metabolized partly by CYP2C19, the use of medicinal products that induce the activity of this enzyme is expected to result in higher concentrations of the active metabolite of clopidogrel.

Rifampicin is a strong CYP2C19 inducer, therefore its use results in increased levels of the active metabolite of clopidogrel as well as in platelet inhibition, which, in particular, may increase the risk of bleeding. As a precautionary measure, simultaneous use of strong CYP2C19 inducers with clopidogrel should be avoided (see section "Administration details").

CYP2C19 inhibitors.

Since clopidogrel is metabolized to its active metabolite partly under the influence of CYP2C19, the use of drugs that inhibit the activity of this enzyme is likely to result in reduced plasma concentrations of the active metabolite of clopidogrel. The clinical significance of this interaction is not clear. Therefore, as a precautionary measure, concomitant use of strong and moderate CYP2C19 inhibitors should be avoided (see sections "Pharmacokinetics" and "Administration details").

Moderate or strong CYP2C19 inhibitors include omeprazole, esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine and efavirenz.

Proton pump inhibitors (PPIs).

Omeprazole at a dose of 80 mg once daily administered concomitantly with or at a 12-hour interval between the administrations of these two drugs decreased the blood concentration of the active metabolite by 45 % (loading dose) and by 40 % (maintenance dose). The decrease was associated with a reduction of the inhibition of platelet aggregation by 39 % (loading dose) and 21 % (maintenance dose). Esomeprazole is expected to give a similar interaction with clopidogrel. Data on the clinical consequences of these pharmacokinetic and pharmacodynamic interactions in terms of major cardiovascular events is disputable. As a precaution, omeprazole or esomeprazole should not be used concomitantly with clopidogrel (see section "Administration details").

A less pronounced decrease in blood concentrations of the metabolite has been observed with the use of pantoprazole or lansoprazole.

Plasma concentrations of the active metabolite were reduced by 20 % (loading dose) and by 14 % (maintenance dose) during concomitant use of pantoprazole at a dose of 80 mg once daily. This reduction was associated with a decrease of the mean inhibition of platelet aggregation by 15 % and by 11 %, respectively. These results indicate the possibility of concomitant use of clopidogrel and pantoprazole.

There is no evidence that other medicinal products which reduce gastric acid production, such as H_2-blockers or antacids have effect on the antiplatelet activity of clopidogrel.

Boosted anti-retroviral therapy.

HIV patients treated with boosted anti-retroviral therapy (ART) are at high risk of vascular events.

Significantly reduced platelet inhibition has been shown in HIV patients treated with ritonavir- or cobicistat-boosted ART. Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with ritonavir-boosted ART, who have

experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Average platelet inhibition may be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with boosted ART should be discouraged.

Combination with other medicinal products.

A number of other clinical studies have been conducted with clopidogrel and other medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with *atenolol, nifedipine*, or both drugs. Furthermore, the pharmacodynamic activity of clopidogrel remained practically unchanged upon co-administration with *phenobarbital* and *estrogen*.

The pharmacokinetics of *digoxin* or *theophylline* were not modified by the co-administration of clopidogrel.

Antacids.

Antacids did not modify the extent of clopidogrel absorption.

Data from studies indicate that *phenytoin* and *tolbutamide* which are metabolized by the CYP2C9 enzyme can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products.

Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have demonstrated that the increase in repaglinide exposure is due to inhibition of the CYP2C8 enzyme by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section "Administration details").

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients taking clopidogrel and receiving other concomitant medicinal products including diuretics, beta blockers, ACE inhibitors, calcium antagonists, cholesterol-lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, and GPIIb/IIIa antagonists showed no evidence of clinically significant adverse interactions.

As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. The use of a parenteral antiplatelet agent should be considered in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Rosuvastatin.

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of a 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on C_{max} after repeated administration of a 75 mg clopidogrel dose.

Administration details.

Overall risk of bleeding and hematological disorders.

Due to the risk of bleeding and hematological adverse reactions, full blood count determination and/or other appropriate testing should be promptly considered whenever symptoms suggestive of bleeding arise during the course of treatment with the drug (see section "Adverse reactions"). As with other antiplatelet agents, clopidogrel should be used with caution in patients with an increased risk of bleeding.

Risk factors for bleeding include trauma, surgery or other pathological conditions, concomitant use of other medicinal products (e.g., anticoagulants including heparin; antiplatelet drugs including pentoxifylline and glycoprotein IIb/IIIa inhibitors; NSAIDs used on regular basis including COX-2 inhibitors and ASA; selective serotonin reuptake inhibitors (SSRIs); strong CYP2C19 inducers, or other medicinal products associated with an increased risk of hemorrhagic events (see section "Interaction with other medicinal products and other forms of interaction").

Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section "Interaction with other medicinal products and other forms of interaction").
If a patient is to undergo elective surgery and the antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians (including dentists) that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should therefore be used with caution in patients with an increased risk of bleeding (particularly gastrointestinal and intraocular).
Patients should be warned that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (in terms of site or duration) to their physician.
The use of clopidogrel 600 mg loading dose is not recommended in patients with non-ST segment elevation acute coronary syndrome and ≥ 75 years of age due to increased bleeding risk in this population.
Thrombotic thrombocytopenic purpura (TTP).
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes even after a short exposure. TTP is characterized by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially dangerous condition requiring prompt treatment including plasmapheresis.
Acquired hemophilia.
Acquired hemophilia has been reported following the use of clopidogrel. In cases of confirmed isolated prolongation of aPTT (activated partial thromboplastin time) with or without bleeding, acquired hemophilia should be considered. Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists; clopidogrel should be discontinued in such patients.
Recent ischemic stroke.
Initiation of therapy.

- In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
- There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
- In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.

Non-minor IS patients (NIHSS score > 4)
In view of the lack of data, use of dual antiplatelet therapy is not recommended (see section "Indications").
Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned
There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.
Cytochrome P450 2C19 (CYP2C19).
Pharmacogenetics: patients who are poor CYP2C19 metabolizers demonstrate lower plasma concentrations of the active metabolite of clopidogrel and a smaller antiplatelet effect when using clopidogrel at recommended doses. Tests are available to identify a patient's CYP2C19 genotype.
Since clopidogrel is metabolized to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme is expected to result in reduced plasma

concentrations of the active metabolite of clopidogrel. However, the clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be avoided (see section "Interaction with other medicinal products and other forms of interaction"; for a list of CYP2C19 inhibitors, see section "Pharmacokinetics").
Use of medicinal products that induce the activity of CYP2C19 is expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be avoided (see section "Interaction with other medicinal products and other forms of interaction").
CYP2C8 substrates.
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section "Interaction with other medicinal products and other forms of interaction").
Cross-reactions among thienopyridines.
Patients should be evaluated for history of hypersensitivity to other thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section "Adverse reactions"). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or hematological cross-reactions such as thrombocytopenia and neutropenia. Patients with a history of allergic reaction and/or hematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.
Renal impairment.
Therapeutic experience with clopidogrel is limited in patients with renal impairment, therefore clopidogrel should be used with caution in such patients (see section "Dosage and administration").
Hepatic impairment.
Experience is limited in patients with moderate hepatic disease who may have hemorrhagic diathesis, therefore, clopidogrel should be used with caution in this population (see section "Dosage and administration").
Excipients
Platogrel® contains hydrogenated castor oil which may cause indigestion and diarrhea.
Special precautions for disposal of residues and waste
Dispose of the unused product or waste in accordance with the local requirements.

Use during pregnancy or breast feeding.
Pregnancy.
Due to the absence of clinical data on the use of clopidogrel during pregnancy, it is undesirable to prescribe the drug to pregnant women (precautionary measure).
Animal studies have not revealed any direct or indirect adverse effect on pregnancy, embryonal/fetal development, childbirth and postnatal development.
Breastfeeding.
It is unknown whether clopidogrel is excreted in breast milk. Animal studies have shown that it is excreted in breast milk, therefore, breastfeeding should be discontinued during treatment with the drug Platogrel®.
Fertility.
Animal studies have revealed no adverse effect of clopidogrel on fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.
Clopidogrel has no or negligible effect on the reaction rate when driving motor transport or using other mechanisms.

Dosage and administration.
Adults including elderly patients.
Platogrel® should be given as a single daily dose of 75 mg, regardless of meals.

For patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), treatment with clopidogrel should be initiated with a single 300 mg or 600 mg loading dose. A 600 mg loading dose may be considered in patients under 75 years of age when percutaneous coronary intervention is intended (see section "Administration details"). Clopidogrel treatment should be continued with the dose of 75 mg 1 time per day (with acetylsalicylic acid (ASA) at a dose of 75-325 mg per day). Since the use of higher ASA doses increases the risk of bleeding, it is not recommended to exceed the 100 mg dose of ASA. The optimal treatment duration has not been formally established. Clinical data support the benefits of using the drug up to 12 months, and the maximum effect was observed after 3 months of treatment.
In patients with ST-segment elevation acute myocardial infarction, clopidogrel should be taken at a dose of 75 mg 1 time per day, starting with a single loading dose of 300 mg in combination with ASA, with or without thrombolytic drugs. The treatment of patients over 75 years of age should be started without the loading dose of clopidogrel. The combined therapy should be started as soon as possible after the emergence of symptoms and continued at least for 4 weeks. The benefit from using the combination of clopidogrel and ASA for more than four weeks has not been studied for this disease.
Adult patients with moderate to high-risk TIA or minor IS.
Adult patients with moderate to high-risk TIA (ABCD2 score ≥ 4) or minor IS (NIHSS score ≤ 3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA at a dose of 75–100 mg once daily. Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by antiplatelet monotherapy.
In patients with atrial fibrillation, clopidogrel should be used as a single daily dose of 75 mg. ASA at a dose of 75-100 mg per day should be started and continued along with clopidogrel (see section "Pharmacological properties").
If a dose is missed:
– if less than 12 hours have passed from the moment when it was necessary to take the next dose, the patient should immediately take the missed dose, and the next dose can be taken at the usual time;
– if more than 12 hours have passed, the patient should take the next dose at the usual time and should not double the dose in order to compensate the missed dose.
Renal impairment. The therapeutic experience of using the drug in patients with renal impairment is limited (see section "Administration details").
Hepatic impairment. The therapeutic experience of using the drug in patients with moderate hepatic disease and risk of hemorrhagic diathesis is limited (see section "Administration details").

Children.
Clopidogrel should not be administered to children (under 18 years of age) as there is no data regarding the efficacy of the drug in this age group.

Overdose.
Symptoms: prolongation of bleeding time with further complications may be observed.
Treatment: symptomatic.
No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

Adverse reactions.
Bleeding, mostly reported during the first month of treatment, is the most common adverse reaction reported both in clinical studies as well as in post-marketing experience.
Adverse reactions occurred either during clinical studies or were spontaneously reported when clopidogrel was used. Adverse reactions are classified according to the defined frequency: very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), frequency unknown (cannot be estimated from the available data).

Within each system organ class, adverse reactions are presented in order of decreasing seriousness.
Blood and lymphatic system disorders. Uncommon: thrombocytopenia, leukocytopenia, eosinophilia. Rare: neutropenia including severe neutropenia. Very rare: TTP (see section "Administration details"), aplastic anemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired hemophilia A, granulocytopenia, anemia.
Immune system. Very rare: serum sickness, anaphylactoid reactions. Frequency unknown: cross-hypersensitivity between thienopyridines (such as ticlopidine, prasugrel) (see section «Administration details»), insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with the HLA DRA4 subtype.
Psychiatric disorders. Very rare: hallucinations, confusion.
Nervous system disorders. Uncommon: intracranial bleeding (in some cases with fatal outcome), headache, paresthesia, dizziness. Very rare: taste disturbances, ageusia.
Organs of vision. Uncommon: eye bleeding (conjunctival, ocular, retinal).
Ear and labyrinth disorders. Rare: vertigo (dizziness).
Cardiac disorders. Frequency unknown: Kounis syndrome ("vasospastic allergic angina" or "allergic myocardial infarction") in the context of a hypersensitivity reaction due to clopidogrel.
Vascular disorders. Common: hematoma. Very rare: serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension.
Respiratory, thoracic and mediastinal disorders. Common: nosebleed. Very rare: respiratory tract bleeding (hemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia.
Gastrointestinal disorders. Common: gastrointestinal bleeding, diarrhea, abdominal pain, dyspepsia. Uncommon: gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence. Rare: retroperitoneal hemorrhage. Very rare: gastrointestinal and retroperitoneal bleeding/hemorrhage (with fatal outcome), pancreatitis, colitis (in particular ulcerative or lymphocytic), stomatitis.
Hepatobiliary disorders. Very rare: acute liver failure, hepatitis, abnormal results of liver function tests.
Skin and subcutaneous tissue disorders. Common: subcutaneous bleeding/bruising. Uncommon: rash, pruritus, skin hemorrhage (purpura). Very rare: bullous dermatitis (toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme, acute generalized exanthematous pustulosis (AGEP)), angioedema, maculopapular, erythematous or exfoliative rash, urticaria, eczema, lichen planus, drug-induced hypersensitivity, drug rash with eosinophilia and systemic symptoms (DRESS-syndrome).
Musculoskeletal system. Very rare: musculoskeletal bleeding (hemarthrosis), arthritis, arthralgia, myalgia.
Renal and urinary tract disorders. Uncommon: hematuria. Very rare: glomerulonephritis, blood creatinine increased.
General disorders. Common: bleeding at the injection site. Very rare: fever.
Reproductive system and breast disorders. Rare: gynecomastia.
Investigations. Uncommon: prolonged bleeding time, decreased neutrophil and platelet count.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua/

Shelf-life.
3 years.

Storage conditions.

Store at a temperature not more than 25 °C in the original package.
Keep out of reach of children.

Package.
14 tablets are in a blister; 2 or 4 or 6 blisters are in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

Last revision date.
07.09.2023 № 1593