SUMMARY OF PRODUCT CHARACTERISTICS
(Prescribing Information)

CYTOFLAVIN®

(Inosine + Nicotinamide + Riboflavin sodium phosphate+ Succinic acid)
concentrate for solution for infusion

BRAND NAME: CYTOFLAVIN®
DOSAGE FORM: concentrate for solution for infusion
COMPOSITION: each ampoule contains:

Active ingredients:	
Succinic acid	– 1.00 g
Nicotinamide	– 0.10 g
Inosine	– 0.20 g
Riboflavin sodium phosphate	– 0.02 g
Excipients:	
Meglumine	– 1.65 g
Sodium hydroxide	– 0.34 g
Water for injections	- up to 10 mL

DESCRIPTION: A clear yellow solution.
THERAPEUTIC CATEGORY: Other nervous system drugs
ATC CODE: N07XX

INDICATIONS

CYTOFLAVIN® is indicated for adults as adjunctive to standard therapy for the treatment of:

1. Moderate acute ischemic stroke in the first 6-24 hours from the onset of stroke.
2. Sequelae due to ischemic stroke that occurred in the previous 25-30 days.

ADMINISTRATION AND DOSAGE

In adults:

CYTOFLAVIN® is administered intravenously by drop infusion only. Prior to administration, a single dose of CYTOFLAVIN® (10 mL) must be diluted with 200 mL of 5 % glucose or 0.9 % sodium chloride. Recommended infusion rate is 3 – 4 mL (60-80 drops/min).

1. In moderate acute ischemic stroke, CYTOFLAVIN® should be administered as early as possible after the stroke onset at a single dose 10 mL at 8-12 h intervals for 10 consecutive days.

2. In sequelae due to ischemic stroke that occurred in the previous 25-30 days, CYTOFLAVIN® is administered once a day at a single dose 10 mL and given for 10 consecutive days.

CONTRAINDICATIONS

- Known sensitization to any of the component of CYTOFLAVIN®,
- Pregnancy,
- Breastfeeding,
- Childhood (age 0-18),
- Not indicated to critically ill patients until the normalization of central hemodynamic parameters and/or if arterial oxygen partial pressure is below 60 mm Hg.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The prepared solution of CYTOFLAVIN® is administered at infusion rate of 3-4 mL/min. If the infusion rate is exceeded, adverse drug reactions that do not require the medicinal product withdrawal (hyperemia, feeling of heat, bitter taste, dryness, sore throat) may occur.

In critically ill patients CYTOFLAVIN® can be administered only following the normalization of central hemodynamic parameters.
In diabetes therapy is carried out under the control of blood glucose level.
Use cautiously in patients with nephrolithiasis, gout, hyperuricemia.
Intense yellow coloration to the urine following the infusion may occur.
The data on the treatment of elderly patients with CYTOFLAVIN® is limited. No special clinical studies for elderly patients have been carried out. CYTOFLAVIN® should be used with caution in patients aged 65 years and older.
The data on the treatment of patients with renal/hepatic insufficiency is limited. No special clinical studies for patients with renal and hepatic insufficiency have been carried out. According to the mechanism of action, dose adjustment in patients with renal/hepatic insufficiency is not required. Nevertheless, due to insufficient evidence, CYTOFLAVIN® should be used with caution in patients with renal/hepatic insufficiency.

DRUG INTERACTIONS
Succinic acid, Inosine, Nicotinamide are compatible with other medicines used as a standard therapy for the treatment of acute ischemic stroke; or sequelae due to ischemic stroke.
To present day, no data on incompatibilities of CYTOFLAVIN® with drugs with hemopoiesis-stimulating effect, anti-hypoxants, anabolic steroids is available.
Chlorpromazine, imipramine, amitriptyline block adjoining of riboflavin to flavin adenine mononucleotide and flavin adenine dinucleotide due to blockade of flavinkinase and increase its excretion in urine.
Thyroid hormones intensify the metabolism of Riboflavin sodium phosphate.
Riboflavin reduces the activity of doxycycline, tetracycline, oxytetracycline, erythromycin and lincomycin. Not compatible with streptomycin.
CYTOFLAVIN® is not recommended to be administered in one syringe or vial with the other medicinal products, besides indicated in “Administration and Dosage” section.

PREGNANCY AND LACTATION
No studies of CYTOFLAVIN® in pregnant and lactating women have been performed. CYTOFLAVIN® is not recommended for use during periods of pregnancy and breastfeeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
To drive and operate machinery with care due to the possible development of side effects (dizziness, psychomotor agitation). To stop driving and operating machinery is required in case of development of these side effects.

SIDE EFFECTS
According to the WHO classification, adverse reactions are classified according to their frequency of development as follows:
- *very common (frequency of adverse drug reaction is* ≥1/10);
- *common (frequency of adverse drug reaction is ≥1/100 – <1/10);*
- *uncommon (frequency of adverse drug reaction is ≥1/1000 – <1/100);*
- *rare (frequency of adverse drug reaction is ≥1/10000 – <1/1000);*
- *very rare (frequency of adverse drug reaction is <1/10000);*
- *rate is unknown (frequency of adverse drug reaction can’t be determined on the basis of the obtained data).*

SAC classification system	Frequency of adverse drug reactions	Symptoms
Immune disorders	very rare	hypersensitivity reaction (HSR), anaphylactic shock

Nervous system disorders	very rare	headache, dizziness, paresthesia, tremor, hypoesthesia
Mental disorders	very rare	psychomotor agitation (anxiety, increased motor activity)
Cardiac disorders	very rare	tachycardia, short-term chest pain, feeling of increasing frequency or enhancing of heartbeats
Vascular disorders	very rare	arterial hypotension/hypertension, hyperaemia or paleness of skin of varying severity
Respiratory disorders, thoracic organs and mediastinal disorders	very rare	respiratory affection (dyspnea), asthma, throat irritation, dry cough, hoarseness, paresthesia in the nose, dysosmia, bronchospasm
Gastrointestinal disorders	very rare	bitter taste, dryness, metallic taste in the mouth, short-term epigastric pain, nausea, vomiting, oral hypoesthesia, dyspepsia
Skin and subcutaneous tissue disorders	very rare	itch, rash, facial swelling, urticaria, angioedema, sweating
Metabolic disorders	very rare	transient hypoglycemia, hyperuricemia, exacerbation of gout
Systemic disturbances and local injection site abnormalities	rare	shivering, hyperthermia, weakness, fervescence, sweating, pain and erythema
Laboratory and instrumental data	very rare	hyperpnea

To avoid adverse reactions, it is recommended to comply with the dosing regimen and the rate of drug administration.
Symptoms of hypersensitivity (anaphylaxis, angioedema) were rarely reported in patients, received CYTOFLAVIN®. In case of these drug adverse reactions, CYTOFLAVIN® should be withdrawn and the corresponding alternative therapy should be recommended. Patients should be notified not to administer CYTOFLAVIN® any longer.

OVERDOSE AND TREATMENT

No cases of overdose with CYTOFLAVIN® were registered or reported. Symptomatic therapy should be provided at overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacological effects of CYTOFLAVIN® are conducted by the synergistic combined action of its ingredients.
CYTOFLAVIN® improves cerebral blood flow; activates metabolic processes in central nervous system; facilitates recovery from altered state of consciousness, promotes reduction of neurological deficit, and improves brain cognitive functions. CYTOFLAVIN® reduces arousal time after general anesthesia in case of prolonged postanesthetic clouding of consciousness.
Administration of CYTOFLAVIN® within 12 hours after onset of acute ischemic stroke has beneficial impact on ischemic and necrotic lesions (which results in reduction of infarct size), promotes recovery of neurological deficit, and significantly reduces the degree of disability in a long-term perspective.

Pharmacokinetics
Succinic acid and Inosine (calculated with reference to undiluted medicine) are utilized virtually immediately when CYTOFLAVIN® is given by intravenous infusion at infusion rate 2 mL/min and, therefore, the components of CYTOFLAVIN® are soon indeterminable in plasma.
Succinic acid – peak of concentration is determined within the first minute after administration of the medicine, with further rapid decrease without accumulation and immediate return to the background level due to fast enzymatic degradation to water and carbon dioxide.
Inosine is metabolized in liver to inosine monophosphate, followed by its subsequent acidification to uric acid. Only minor quantities of Inosine are excreted by kidneys.
Nicotinamide is metabolized in liver to N-methylnicotinamide and excreted by kidneys. The plasma half-life is about 1.3 hours, apparent volume of distribution - about 60 L, total clearance - about 0.6 L/min.
Riboflavin sodium phosphate. The plasma half-life is about 2 hours, apparent volume of distribution - about 40 L, total clearance - about 0.3 L/min.

HOW SUPPLIED
10 mL of concentrate for solution for infusion per amber glass ampoules. Each pack has 5 ampoules per one-sided blister pack, heat-sealed with cover film. 1 blister pack per carton package with package insert enclosed.

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL
As CYTOFLAVIN® is a light sensitive medicine, please keep in the commercial package in a light protected place.
If you have unused or expired CYTOFLAVIN® you should dispose of the medicine in the following manner. Please open an ampoule, dispose of the content via wastewater and the glass ampoule via special household waste for glass.

TERMS AND STORAGE
- Shelf life: 2 years. Administration of the medicinal product with expired date is prohibited.
- Store in a light protected place at temperature below 30 ºC.

Prescription only medicine.

Manufactured by: “Scientific Technological Pharmaceutical Firm “POLYSAN” Ltd.
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HARUS DENGAN RESEP DOKTER

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Reg. number:

Revision date: