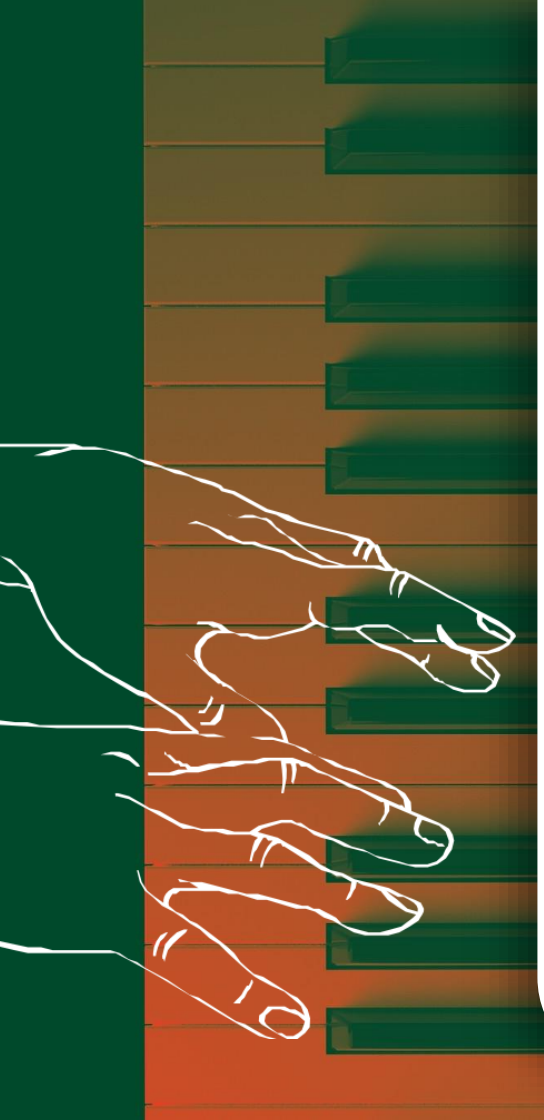


PATIENT CARE
IS THE FINEST OF ARTS

R-PHARM
Innovative health technologies

OLOKIZUMAB

FULL PRESCRIBING INFORMATION

INITIAL APPROVAL IN RUSSIA: 21.05.2020 (ЛП-006218). INCL. CHANGES №1 OF 04.09.2020, №2 OF 05.03.2021, №3 OF 10.11.2020, №4 OF 03.06.2021, №5 OF 01.06.2021, №7 OF 14.09.2021, №8 OF 29.11.2021, №9 OF 01.11.2022

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

INSTRUCTIONS
FOR MEDICAL USE OF THE MEDICINAL PRODUCT
OLOKIZUMAB

Marketing Authorization in Russia: ЛП-006218

International nonproprietary name: Olokizumab

Pharmaceutical form: solution for subcutaneous injection

Composition per 1 mL:
Active substance: Olokizumab – 160.0 mg;
Excipients: sodium chloride, polysorbate 80, L-histidine hydrochloride monohydrate, sorbitol, water for injection.

APPEARANCE
Clear or slightly opalescent, colorless to light yellow solution.

Pharmacotherapeutic group: monoclonal antibodies

ATC code: L04AC

Pharmacological properties:

Olokizumab is a humanized (containing grafted complementarity determining regions (CDRs)) monoclonal antibody of the immunoglobulin (Ig) G4/kappa isotype. Olokizumab selectively binds to human IL-6 and effectively neutralizes the effects of IL-6 in vivo and in vitro. Obtained data indicate that olokizumab does not significantly bind to other molecules of the IL-6 family and does not affect their functioning, nor does it activate the IL-6 signaling pathway.

Pharmacodynamics:

In the RA0010 phase 2a clinical trial, a single subcutaneous administration of olokizumab at a dose of 1 mg/kg and 3 mg/kg in patients with rheumatoid arthritis (RA) caused a decrease in mean (±SD) plasma C-reactive protein (CRP) levels within 24 hours after the drug administration, continuing for 7 days from the start of treatment (the respective CRP levels were 9.4 (±11.1) mg/L and 3.4 (±2.7) mg/L at baseline, 5.7 (±6.8) mg/L and 2.9 (±3.1) mg/L 24 hours after the administration, and 0.6 (±0.6) mg/L and 0.5 (±0.4) mg/L 7 days after the administration). CRP levels following a single administration remained low for 10 weeks. The sustained decrease in plasma CRP levels was also shown in RA0056 and RA0083 phase 2 studies in patients with moderate to severe rheumatoid arthritis treated with multiple administrations of olokizumab at a dose of 60 to 480 mg/month for 12 weeks. The geometric mean plasma CRP level ranged from 5.0 to 11.3 mg/L by treatment groups at the baseline and did not exceed 1 mg/L for all tested doses one week after the initiation of treatment and throughout the entire treatment period thereafter.

In the CREDO1 and CREDO2 double-blind, controlled phase 3 trials in patients with moderate to severe rheumatoid arthritis inadequately controlled by methotrexate therapy, as well as in CREDO3 trial in patients with moderate to severe rheumatoid arthritis with inadequate response to tumor necrosis factor (TNF) inhibitor therapy, the subcutaneous olokizumab administration at a dose of 64 mg every 2 weeks (Q2W) or 64 mg every 4 weeks (Q4W) led to the reduction in the mean plasma CRP level to normal 2 weeks after the initiation of therapy. Low CRP levels persisted for 24 weeks throughout the entire treatment period.

Clinical efficacy:

The efficacy of subcutaneous olokizumab administration was studied in three randomized, double-blind, controlled, multicenter phase 3 studies.

The CREDO1 and CREDO2 studies involved 428 and 1648 patients with moderate to severe rheumatoid arthritis inadequately controlled by methotrexate. Patients received olokizumab at a dose of 64 mg every 2 weeks (Q2W) and every 4 weeks (Q4W) or placebo in combination with background methotrexate therapy at a dose of 15 to 25 mg/week (or ≥10 mg/week in case of documented intolerance to higher doses) for 24 weeks. If no response to therapy was observed after 14 weeks of treatment, patients could be additionally treated with sulfasalazine and/or hydroxychloroquine.

The CREDO3 study involved 368 patients with moderate to severe rheumatoid arthritis who did not respond adequately to prior TNF inhibitor therapy. The patients received olokizumab at a dose of 64 mg Q2W and Q4W for 24 weeks or placebo for 16 weeks. After 16 weeks of treatment, placebo patients were re-randomized to receive olokizumab at a dose of 64 mg Q2W and Q4W until the end of the 24-week treatment period. All patients received background methotrexate therapy at a dose of 15 to 25 mg/week (or ≥10 mg/week in case of documented intolerance to higher doses). If no response to therapy was observed after 14 weeks of treatment, patients could be additionally treated with sulfasalazine and/or hydroxychloroquine.

The efficacy of combination therapy with methotrexate and olokizumab at both tested doses was significantly superior to that with methotrexate and placebo and led to a decrease in the

severity of rheumatoid arthritis symptoms, also helping to reduce its activity or achieve remission in a larger number of patients. When analyzing the efficacy of olokizumab in the CREDO1, CREDO2 and CREDO3 studies, the response rate measured using ACR20 (American College of Rheumatology response criteria) was assessed by region, sex, age, weight and body mass index at the time of enrollment, the severity of the disease, the duration from the time of diagnosis, the duration of the previous methotrexate therapy, and antibody status. None of the above parameters had a significant effect on the response to olokizumab therapy. Olokizumab therapy showed a noticeable effect after 4 weeks of treatment, a pronounced effect that persisted for at least 24 weeks developed approximately 12 weeks after the initiation of therapy.

Pharmacokinetics

Absorption

Bioavailability of olokizumab was evaluated based on the data obtained for 173 patients with mild to moderate rheumatoid arthritis who received olokizumab at various doses for 12 weeks, combined with the data from 40 patients with mild to moderate rheumatoid arthritis treated with a single injection of various doses of olokizumab and the data obtained from 41 healthy volunteers after a single injection of various doses of olokizumab. The bioavailability after subcutaneous administration is 63%.

After a single subcutaneous injection of olokizumab 0.3 to 6 mg/kg in patients with mild to moderate rheumatoid arthritis, the maximum concentration of the drug in the blood (C_{max}) increased dose-dependently. The time to C_{max} ranged from 4 to 12 days, with measurable olokizumab levels lasting for approximately 16 weeks.After a single subcutaneous administration of olokizumab 64 mg to patients with moderate and severe rheumatoid arthritis inadequately controlled by methotrexate, C_{max} was achieved on average within 7-10 days (Table 1).

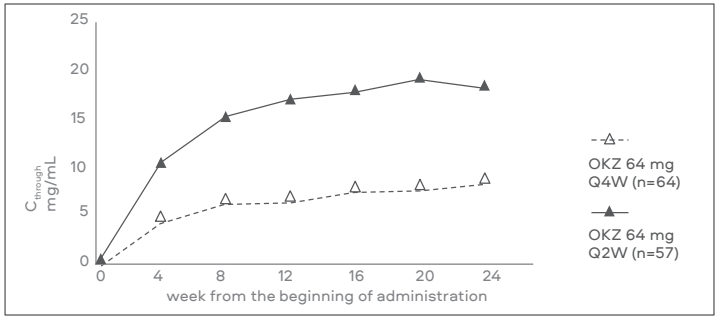
With multiple administrations, the concentration of olokizumab in the blood increased during the initial treatment period and reached the steady state within 16 (64 mg Q4W) and 14 (64 mg Q2W) weeks from the beginning of treatment (see Table 1, Figure 1).

Table 1. Pharmacokinetic parameters of Olokizumab after subcutaneous injection to patients with moderate to severe RA

PK parameter	Baseline		Week 20	
	OKZ 64 mg Q4W N = 18	OKZ 64 mg Q2W N = 18	OKZ 64 mg Q4W N = 18	OKZ 64 mg Q2W N = 18
C_{max} (µg/mL)	6.18	6.22	17.00	21.55
%CV	50.0	39.2	55.7	25.0
$AUC_{0\text{-}tau}$* (µg*h/mL)	2886	1556	8411	5485
%CV	45.3	38.9	29.9	31.8
t_{max} (h)	190.2	234.4	244.5	127.8
Median	166.5	236.7	167.6	96.7
Min - Max	92.8 – 402.3	95.8 – 359.2	95.4 – 670.7	0.0 – 334.7

RA - rheumatoid arthritis; OKZ - Olokizumab; Q2W - every 2 weeks; Q4W - every 4 weeks; C_{max} - maximum plasma concentration of the drug; $AUC_{0\text{-}tau}$ - area under the concentration-time curve; t_{max} - time to maximum concentration of the drug; *$AUC_{0\text{-}tau}$ for Q4W administration was calculated for a period of 672 hours (28 days), and for Q2W administration for a period of 336 hours (14 days)

Figure 1. Increase in the trough concentration (C_{trough}) with repeated subcutaneous administration in patients with moderate to severe rheumatoid arthritis



Biotransformation

In an in vitro study on human cryopreserved hepatocytes, olokizumab reversed the inhibitory effect of IL-6 on CYP1A1/2, 2B6, 2C9, 3A4/5 and 2C19 activity, as well as on NTCP activity.

Elimination

Estimates of the clearance of olokizumab in patients with mild to moderate rheumatoid arthritis were 0.17 L/day (relative standard deviation [% RSD] = 4.9%) with low or medium individual variability.

Pharmacokinetic-pharmacodynamic relationship

The magnitude of a CRP level decrease in patients with active rheumatoid arthritis who received olokizumab was not dose-dependent. In addition, in patients with mild to moderate rheumatoid arthritis, a positive correlation was found between the concentration of olokizumab in the plasma and neutropenia, increases in plasma AST, ALT and triglyceride levels, although the effect size was small. Also, by day 14 after the administration of olokizumab, a steady decrease in the VEGF and amyloid serum protein A levels was observed in all therapeutic groups, independently of the dose.

Therapeutic Indications

Treatment of patients aged 18 years or older with moderate to severe rheumatoid arthritis in combination with methotrexate and who have an inadequate response to methotrexate or tumor necrosis factor inhibitor (TNFi) therapy.

Pathogenesis-based therapy of cytokine release syndrome in patients with moderate to severe new coronavirus infection (COVID-19).

Contraindications

A history of hypersensitivity to olokizumab or any component of the drug.

Active infectious diseases (including tuberculosis).

Children under 18 years of age.

Hereditary fructose intolerance (the drug contains sorbitol).

Breastfeeding..

Use with Caution

- In patients with a history of serious or opportunistic infections; with concomitant diseases and conditions that are risk factors for developing infections (diabetes, renal failure, use of immunosuppressive drugs, elderly age, etc.).
- In patients exposed to tuberculosis. The risk-benefit ratio of the drug should be evaluated before using Olokizumab in such patients.
- In patients with a history of diverticulitis or intestinal perforations and other risk factors for intestinal perforation.
- In patients with hepatic impairment or hepatic failure.

Use during Pregnancy and Breastfeeding

Pregnancy

The safety and efficacy of Olokizumab during pregnancy are not well established. In animal studies, reproductive toxicity was not ruled out. It is assumed that IL-6 plays an important role in the cervix opening and, possibly, in the delivery of the placenta. Thus, the use of Olokizumab may interfere with labor. In particular, an increase in the frequency of difficulty in labor with retained placenta and, in some cases, with significant vaginal bleeding was observed in animals. The significance of this information for humans is not known.

Six pregnancies were reported in clinical studies, in 5 of which patients received concomitant therapy with methotrexate. Out of the 6 cases of pregnancy, 2 pregnancies were terminated by the decision of the patient or physician (abortion), 2 pregnancies ended with the birth of a live child at term (one spontaneous vaginal birth, one delivery by cesarean section), 1 pregnancy was ectopic and therefore was also terminated, and the outcome of 1 pregnancy was a spontaneous abortion (miscarriage).

Before treatment with Olokizumab, women of reproductive age should have a pregnancy test. The attending physician should explain in.

detail the risks of using Olokizumab during pregnancy and instruct the patient of childbearing potential about the need to use highly effective methods of contraception and perform regular pregnancy tests during treatment and for at least 6 months after the last dose of Olokizumab. In the event that a patient receiving Olokizumab becomes pregnant, she should immediately stop using the drug and consult a doctor.

Olokizumab should not be used during pregnancy unless there is a clear clinical need.

Lactation

The penetration of olokizumab into breast milk has not been studied. There are no clinical data on risks for a breastfed baby. Since Olokizumab is indicated for use in combination with methotrexate, which is secreted into breast milk, it is recommended to stop breastfeeding when using the drug.

Fertility

There are no clinical data on the effect of olokizumab on human fertility.

During animal studies, no negative effects of olokizumab on fertility in male and female cynomolgus monkeys were found.

Posology and method of administration

Rheumatoid arthritis

Olokizumab should be administered as a subcutaneous injection, into the thigh or anterior abdominal wall, the total content of 0.4 mL of 160 mg/mL solution at once. Before administration, the solution should be warmed to room temperature. Storage at > 8 °C must not exceed 4 hours.

The first administration must be supervised by a qualified healthcare professional. The patient should be monitored for 30 minutes after the first injection. After learning the subcutaneous injection technique under the supervision of a healthcare professional, the patient (or patient's caregiver) may self-administer the drug. A doctor experienced in the diagnosis and treatment of rheumatoid arthritis determines whether self-administration of Olokizumab by the patient or patient's caregiver is appropriate.

Only single-use syringes should be used to administer Olokizumab.

Missed dose

If a scheduled injection is missed, the missed dose should be administered as soon as possible; the interval between any two injections should be at least half of the interval of the selected dose frequency (see Table 2).

Table 2. Missed Dose Instructions

Dose frequency	Interval from the date of missed injection	Action
OKZ 64 mg Q4W	≤ 14 days	*Perform an injection instead of the missed one and continue according to the schedule*
	> 14 days	*Skip the missed injection*
OKZ 64 mg Q2W	≤ 7 days	*Perform an injection instead of the missed one and continue according to the schedule*
	> 7 days	*Skip the missed injection*

OKZ - Olokizumab; Q2W - every 2 weeks; Q4W - every 4 weeks

Discontinuation of treatment

Treatment with Olokizumab should be discontinued if the patient has:

Elevated liver enzymes meeting the following criteria:

– increased AST or ALT >8 x upper limit of normal (ULN) at any time, regardless of total bilirubin levels or concomitant symptoms.
– increased AST or ALT >5 x ULN for ≥2 weeks after injection, regardless of total bilirubin levels or concomitant symptoms.
– increased AST or ALT >3 x ULN and total bilirubin >2 x ULN.
– increased AST or ALT >3 x ULN with symptoms of liver damage (fatigue, nausea, vomiting, pain or tenderness in the upper right quadrant of the abdomen, fever or rash).

The patient has any of the following laboratory abnormalities:

– absolute neutrophil count <500×106/L (<500/mm3).

– two consecutive lymphocyte counts <500×106/L (<500/mm3).
– platelet count <50×109/L (<50,000/mm3 or <50,000×106/L).

Confirmed pregnancy while using Olokizumab (see Use during pregnancy and breastfeeding).

Gastrointestinal perforation (see Special warnings).

Severe or life-threatening infection (see Special warnings).

Posology:

The recommended dose is 64 mg once every 4 weeks. In patients with severe rheumatoid arthritis and DAS28 ≥ 6.9, an increase in the dosing frequency to 64 mg once every 2 weeks subcutaneously may be considered.

Pathogenesis-directed therapy for cytokine release syndrome in new coronavirus infection (COVID-19)

Olokizumab should be administered as a subcutaneous injection, into the thigh or anterior abdominal wall, the total content of 0.4 mL of 160 mg/mL solution at once. Before administration, the solution should be warmed to room temperature. Storage of the drug at > 8 °C must not exceed 4 hours.

Posology:

The recommended dose is 64 mg as a single dose.

Pediatric population

The safety and efficacy of Olokizumab in children and adolescents aged below 18 years have not been established. No data are available.

Special populations

Elderly patients (> 65 years): no dose adjustment is required.

Patients with renal impairment: the safety and efficacy of Olokizumab in patients with renal impairment have not been studied. No data are available.

Patients with hepatic impairment: the safety and efficacy of Olokizumab in patients with hepatic impairment have not been studied. No data are available.

Instructions for preparing and injecting the drug

Take the Olokizumab vial or pre-filled syringe out of the refrigerator in advance: wait for approximately 30 minutes for it to warm to room temperature before preparing the injection**. Do not heat up the product.**

Get ready for the injection

Step 1

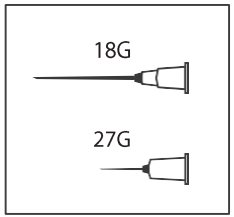
Wash your hands with warm water and soap, choose a flat, clean surface, carefully inspect the drug vial or pre-filled syringe and do not use it if:

- it has been out of the refrigerator for more than 4 hours,
- it contains the wrong medication name,
- the shelf life indicated on the package has expired,
- the vial or pre-filled syringe is cracked, damaged or leaking,
- the solution is cloudy, discolored, or contains flakes or particles.

The drug in a pre-filled syringe is ready for use.

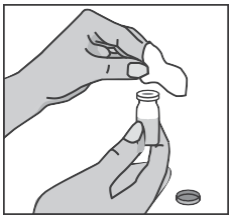
Prepare the drug in a vial for use following the instructions

Prepare a 1-2 mL disposable hypodermic syringe, two disposable sterile needles (it is recommended to use an 18G needle to draw the drug from the vial and a 27G needle to perform a subcutaneous injection), 2 sterile alcohol wipes.

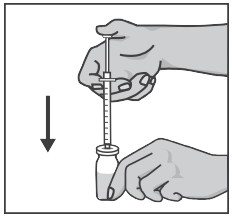


Step 2

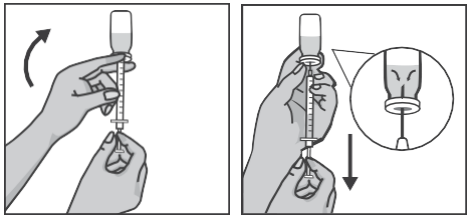
Join the capped thicker drawing needle with the syringe. Remove the plastic protective cap from the vial, clean the top of the rubber stopper with a sterile alcohol wipe.



Take the syringe in your right hand, remove the cap from the needle and insert the needle vertically into the center of the vial stopper so that the tip of the needle appears on the other side of the stopper.



Holding the syringe with your right hand, take the vial with your left hand and turn it upside down so that all the liquid collects over the stopper. Pulling the plunger of the syringe down, draw the entire contents of the vial into the syringe.

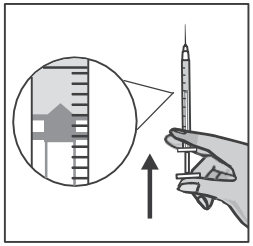


Pull the needle out of the vial and place the cap back on it. Without removing the cap, replace it with a hypodermic needle. Dispose of the used drawing needle into the sharps container

Important! Do not perform the injection with the drawing needle as this may cause pain and damage at the injection site.

Step 3

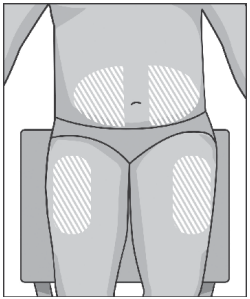
Carefully remove the cap from the hypodermic needle. Do not touch it and be careful not to stick yourself with the tip of the needle. Hold the syringe upright and flick it with your finger to make any air bubbles go to the top. Holding the syringe upright, push the plunger slowly up to expel air and excess fluid from the syringe so that the syringe plunger stops at the 0.4 mL mark.



Place the syringe on the carton so that the needle stays on top of the package and does not touch other surfaces.

Select an injection site

Select an injection site on the upper thighs or abdomen, at least 5 cm from the navel. If the injection is performed by a healthcare professional, other sites for subcutaneous injections may be selected. The drug should not be injected into moles, scars, lesions or indurations, areas of redness, skin hypersensitivity reactions.

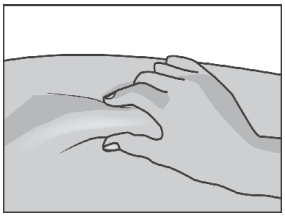


It is recommended to change the injection site regularly. The new injection site should be at least 2.5 cm from the previous one. You can alternate injection sites between the thighs and abdomen.

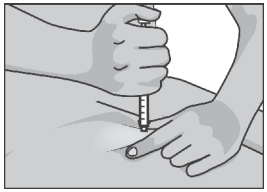
Perform the injection

Clean the skin of the selected injection site with a new sterile alcohol wipe. Allow the injection site to dry and do not touch it prior to injection.

Gently squeeze the skin around the injection site with your non-dominant hand (for example, if you are right-handed, use your left hand) and hold it firmly.



Hold the syringe in your dominant hand over the raised area of skin at a 90 degree angle. Insert the needle into the skin with a quick, smooth thrusting motion. If there is a low amount of subcutaneous fat on the abdomen, a 45-degree angle may be used..



Do not move the needle relative to the tissue and push the plunger down slowly until the entire volume of the drug from the syringe is injected under the skin. The plunger should reach the bottom of the syringe. Wait a few seconds before removing the needle.

Pull the needle out of the skin at the same angle at which it was inserted. There may be slight bleeding at the injection site. If necessary, place a sterile wipe on the injection site.

Remember!

Dispose of used syringes in the sharps container immediately after injection. When the container is full, close it carefully and tightly and discard it in a trash can.

Always use a new syringe, do not reuse syringes.

Side Effects

The safety of Olokizumab was evaluated in randomized, controlled clinical trials CREDO1, CREDO2, and CREDO3. A total of 2440 patients with moderate to severe rheumatoid arthritis participated in the studies, of whom 1582 patients received olokizumab and 454 patients received placebo. All patients received background methotrexate therapy.

The pooled analysis of safety data from studies CREDO1, CREDO2 and CREDO3 showed that the most common adverse reactions were elevated hepatic transaminase levels, hyperlipidemia, and leukopenia.

Adverse reactions are listed according to MedDRA system organ class (SOC). Within each class, adverse reactions are categorized by frequency of occurrence: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and unknown frequency.

Table 3. Adverse drug reactions observed with Olokizumab therapy

	Frequency class		
System organ class	Very common	Common	Uncommon
Infections and parasitic diseases		latent tuberculosis, pharyngitis, conjunctivitis	sepsis, phlegmon[1], pneumonia, subcutaneous abscess, limb abscess, ear infection[2], folliculitis, fungal infection of the skin, *H. pylori* infection, hordeolum, paronychia, onychomycosis, periodontitis, respiratory tract infection, tooth infection, fungal vulvovaginitis
Blood and lymphatic system disorders		leukopenia, neutropenia, thrombocytopenia	lymphocytosis, lymphadenopathy; eosinophilia, erythrocytosis
Immune system disorders			drug hypersensitivity
Endocrine disorders			hypothyroidism
Metabolism and nutrition disorders		hypercholesterolemia, hypertriglyceridemia, hyperlipidemia	diabetes mellitus, hyperkalemia, hypernatremia, obesity, vitamin D deficiency
Psychiatric disorders			insomnia
Nervous system disorders			cervicobrachial syndrome, migraine, paresthesia, sciatica, vertebrobasillar insufficiency

Eye disorders			cataract, allergic conjunctivitis, eyelid swelling, keratitis
Ear and labyrinth disorders			tinnitus
Cardiac disorders			angina pectoris, atrial fibrillation, atrial tachycardia, sinus tachycardia, bradycardia, ventricular extrasystoles, extrasystoles, mitral valve regurgitation, tricuspid valve regurgitation
Vascular disorders		hypertension	aortic atherosclerosis, deep vein thrombosis, diabetic angiopathy, hematoma, thrombophlebitis, varicose vein
Respiratory, thoracic and mediastinal disorders			pulmonary fibrosis, asthma, atelectasis, dysphonia, dyspnea, nasal bleeding, interstitial lung disease, oropharyngeal pain, rhinorrhea, airway congestion, vasomotor rhinitis
Gastrointestinal disorders		diarrhea, abdominal pain	stomatitis, abdominal distension, constipation, dental caries, gastric polyps, gastritis, gastrooesophageal reflux disease, hemorrhoids, odynophagia; toothache
Hepatobiliary disorders	ALT increased	AST increased, hepatic enzymes increased, transaminases[3] increased, liver function test increased, direct and indirect bilirubin increased	cholelithiasis, hepatic disorder
Skin and subcutaneous tissue disorders		rash, dermatitis	actinic keratosis, blister, dry skin, ecchymosis, erythema, hyperhidrosis, hyperkeratosis, photosensitivity reaction, pruritus, skin lesion, urticaria
Musculoskeletal and connective tissue disorders		musculoskeletal pain[4]	myositis, muscle spasms, intervertebral disc disorder, joint effusion, osteochondrosis, osteopenia, osteoporosis, plantar fasciitis, rotator cuff syndrome, spinal osteoarthritis
Renal and urinary disorders			chronic kidney disease, hematuria, nephrolithiasis, nephropathy, proteinuria, renal colic
Reproductive system and breast disorders			metrorrhagia
Congenital, familial and genetic disorders			type V hyperlipidemia
General disorders and administration site reactions		injection site reaction	asthenia; drug intolerance; fatigue; pain
Laboratory tests and investigations		GGT increased	hemoglobin increased, hematocrit increased, adiponectin increased, weight gain, positive mycobacterium tuberculosis test

GGT, gammaglutamyltransferase.

[1] - phlegmon term also includes erysipelas

[2] - ear infection term also includes otitis media and otitis externa

[3] - increased transaminase activity term also includes hypertransaminasemia

[4] - musculoskeletal pain term also includes musculoskeletal chest pain, back pain, neck pain, spinal pain, and myalgia

Gastrointestinal perforations

Gastrointestinal (GI) perforations can develop with the use of IL-6 signaling pathway inhibitors. They are mostly associated with the previous diverticulitis or other inflammatory gastrointestinal diseases. In the population of patients with moderate to severe rheumatoid arthritis, who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, gastrointestinal perforations were not observed during the double-blind treatment period (24 weeks). Cases of diverticular perforation in the same patient population were reported in patients who continued olokizumab therapy for 2 years in an open-label, long-term study. The frequency of this adverse reaction is unknown.

Hypersensitivity reactions

In the population of patients with moderate to severe rheumatoid arthritis who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, 145 (9.2%) of 1582 patients who received olokizumab experienced systemic adverse drug reactions and hypersensitivity reactions, the most of them being mild to moderate. In all the studies, the percentage of patients who experienced at least one adverse event related to hypersensitivity reactions during treatment was higher in patients receiving olokizumab, regardless of the dosing regimen, than in patients receiving placebo. The most common reactions in the

pooled olokizumab group that included 1582 patients were rash (28 patients, 1.77%), dermatitis (16 patients, 1.01%), and eosinophilia (9 patients, 0.57 %). In a population of patients from the CREDO3 study, who had had an inadequate response to TNF inhibitors, one case of anaphylactic reaction was reported in a patient who received olokizumab at a dose of 64 mg Q4W.

Infections

In the population of patients with moderate to severe rheumatoid arthritis who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, at least one case of infection was reported in 446 (28.2%) of 1582 participants treated with olokizumab; the frequency of infections was slightly higher than in the placebo group (125 patients (27.5%)). The most common infections with the higher rates in the olokizumab group were latent tuberculosis (45 (2.84%) and 9 (1.98%) patients in olokizumab and placebo groups, respectively), pharyngitis (22 (1.39%) patients and 4 (0.88%) patients, respectively), and conjunctivitis (16 (1.01%) patients and 0 patients, respectively). Overall, opportunistic infections were more common in patients treated with olokizumab (9 patients, 0.57%) than in patients who received placebo (1 patient, 0.22%). Among opportunistic infections reported in more than one patient, Herpes zoster was observed in 6 (0.38%) patients from the olokizumab group and in 1 (0.22%) patient from the placebo group. Pulmonary tuberculosis was observed in 2 (0, 13%) patients from the olokizumab group and was not observed in the placebo group.

In the population of patients with moderate to severe rheumatoid arthritis, who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, and received olokizumab, the following serious infections, which occurred in more than two patients and were more frequent in the olokizumab group, have been reported: sepsis, including staphylococcal sepsis (5 patients, 0.32%), cellulitis (4 patients, 0.25%) and erysipelas (2 patients, 0.13%), pneumonia (3 patients, 0.19%), subcutaneous abscess (2 patients, 0.13%), and two cases of pulmonary tuberculosis (2 patients, 0.13%) were regarded as serious AEs.

Neutropenia

Neutropenia

In the population of patients with moderate to severe rheumatoid arthritis who participated in CREDO1, CREDO2, and CREDO3 placebo-controlled trials, the decrease in the mean absolute neutrophil count after 12 weeks of therapy was more pronounced in patients receiving Olokizumab (1582 patients) versus placebo (454 patients) and then remained stable until the end of the treatment period (see Table 4).

Table 4. The mean absolute neutrophil count dynamic during 24 weeks of therapy

Duration of treatment	Mean absolute neutrophil count ×10⁹/L									
	CREDO1			CREDO2				CREDO3*		
	OKZ 64 mg Q4W	OKZ 64 mg Q2W	Place-bo	OKZ 64 mg Q4W	OKZ 64 mg Q2W	Place-bo	ADA	OKZ 64 mg Q4W	OKZ 64 mg Q2W	Place-bo
0	5,9	5,2	5,7	5,9	6,0	6,1	5,9	6,1	5,6	5,7
12 weeks	3,9	3,4	5,6	3,9	3,9	5,7	4,7	4,2	3,9	6,0
24 weeks	3,7	3,2	5,3	3,8	3,8	4,6	5,6	-	-	-

*The data were represented only for the period before re-randomization of patients receiving placebo to Olokizumab therapy Q4W or Q2W.

OKZ, Olokizumab; ADA, adalimumab

Therefore, neutropenia developed at least once during the treatment in 66 (4.17%) and 7 (1.54%) patients from the olokizumab and placebo groups, respectively.

Increased hepatic transaminases and bilirubin

In the population of patients with moderate to severe rheumatoid

arthritis who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, an elevation in ALT considered by investigators an adverse event was observed in 11.4% of patients receiving olokizumab and in 3.9% of patients receiving placebo. An elevation in AST, considered by investigators an adverse event was observed in 105 (6.9%) and 15 (3.3%) patients from the olokizumab and placebo groups, respectively.

In the majority of patients, the transaminases elevation was asymptomatic and did not lead to treatment discontinuation.

An increase in bilirubin level considered by the investigators an adverse event was observed in 24 patients (1.52%) from the olokizumab group and in 1 patient (0.22%) from the placebo group.

In most patients, an elevation in transaminases was not accompanied by an increase in bilirubin concentration. A simultaneous increase in ALT and AST >3×ULN with an increase in bilirubin >2×ULN was observed in one patient receiving olokizumab 64 mg Q2W.

Overall, the fluctuations in the individual ALT levels were observed during the entire treatment period. The number of patients who had an increase in ALT levels above the upper limit of normal (1×ULN) at least once during the treatment period (24 weeks) was approximately 2 times higher in the olokizumab group than in the placebo group (see Table 5).

Table 5. Frequency of adverse event “ALT increased” in patients from CREDO1, CREDO2, and CREDO3 clinical studies

ALT level	Number of patients (%)					
	Baseline			During treatment period*		
	OKZ 64 mg Q4W	OKZ 64 mg Q2W	Placebo	OKZ 64 mg Q4W	OKZ 64 mg Q2W	Placebo
CREDO1 (N = 438)						
n	142	143	142	140	141	141
> 1×ULN ≤ 3×ULN	14 (9,9 %)	12 (8,4 %)	14 (9,9 %)	74 (52,9 %)	67 (47,5 %)	38 (27,0 %)
> 3×ULN ≤ 5xULN	0	0	0	8 (5,7 %)	9 (6,4 %)	6 (4,3 %)
> 5×ULN	0	1 (0,7 %)	0	8 (5,7 %)	4 (2,8 %)	1 (0,7 %)
CREDO2 (N=1648)						
n	477	463	243	477	463	243
> 1×ULN ≤ 3×ULN	58 (12,2 %)	43 (9,3 %)	21 (8,6 %)	250 (52,4 %)	247 (53,3 %)	75 (30,9 %)
> 3×ULN ≤ 5xULN	0	1 (0,2 %)	1 (0,4 %)	30 (6,3 %)	34 (7,3 %)	2 (0,8 %)
> 5×ULN	0	1 (0,2 %)	0	10 (2,1 %)	8 (1,7 %)	3 (1,2 %)
CREDO3 (N = 368)**						
N	186	171	69	186	170	67
> 1×ULN ≤ 3×ULN	16 (8,6 %)	19 (11,1 %)	6 (8,7 %)	80 (43,0 %)	96 (56,5 %)	17 (25,4 %)
> 3×ULN ≤ 5xULN	0	1 (0,6 %)	0	12 (6,5 %)	8 (4,7 %)	0
> 5×ULN	0	1 (0,6 %)	0	5 (2,7 %)	4 (2,4 %)	0

N, number of patients in the group; n, number of patients with the available results
*the highest ALT value was taken into account for each patient during the 24-week treatment period. ULN, upper Limit of Normal; OKZ, Olokizumab.
**Olokizumab groups also included patients from the placebo group that were re-randomized to receive Olokizumab at Week 16.

Hyperlipidemia

In the population of patients with moderate to severe rheumatoid arthritis who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled studies, an increase in blood lipids during treatment considered by investigators an adverse event was observed in 100 (6.32%) patients receiving olokizumab and in 11 (2.42%) patients receiving placebo.

On average, total cholesterol, LDL, and HDL levels increased in the groups of patients receiving olokizumab during the first 4 weeks of therapy, and then remained stable until the end of the treatment period.

Injection site reactions

In the population of patients with moderate to severe rheumatoid arthritis who participated in the CREDO1, CREDO2, and CREDO3 placebo-controlled trials, injection site reactions were reported in 58 (3.67%) patients receiving olokizumab. The most frequent reactions were erythema, pruritus, and bleeding at the injection site.

Overdose

Overdose cases were not observed during clinical trials. However, additional clinical data show that the overall safety profile of olokizumab in patients receiving the drug at a dose of 240 mg Q2W (480 mg per month) for 12 weeks is comparable to the overall safety profile in patients receiving the drug at the recommended dose.

Pediatric population

There is no data on overdose in pediatric population.

Interaction with other medicinal products

Concomitant use with methotrexate did not affect the olokizumab exposure. The effect of olokizumab on the methotrexate exposure is not expected with their simultaneous use, clinical data are not available. In all clinical trials in patients with their simultaneous use, clinical data are not available. In all clinical trials in patients with rheumatoid arthritis, olokizumab was used in conjunction with methotrexate.

Special clinical studies of drug interactions of olokizumab have not been conducted. According to the results of the CREDO1 clinical trial, no cases of clinically significant drug interactions of olokizumab with other drugs were reported.

In an in vitro study on human cryopreserved hepatocytes, olokizumab reversed the inhibitory effect of IL-6 on CYP1A1/2, 2B6, 2C9, 3A4/5 and 2C19 activity, as well as on NTCP activity. Thus, it should be considered that in patients with active rheumatoid arthritis, dose adjustment of drugs metabolized by these CYP isoforms may be necessary after beginning the treatment with Olokizumab.

The concentration of the following drugs may decrease when used together with Olokizumab (including, but not limited to): statins (simvastatin, lovastatin, atorvastatin); oral contraceptives; calcium channel blockers; glucocorticoids (dexamethasone, methylprednisolone); warfarin; quinidine; theophylline; tizanidine; phenytoin; pimozide; cyclosporine; sirolimus; tacrolimus; benzodiazepines (e.g. diazepam, alprazolam, triazolam, midazolam, bromazepam).

Special warnings

Anaphylactic or anaphylactoid reactions: administration of protein-containing may be associated with the occurrence of immunological/allergic or non-immunological hypersensitivity reactions, which can be severe. These reactions can manifest as acute infusion reactions, allergic reactions, or delayed-type hypersensitivity reactions. Thus, the first administration of Olokizumab should be performed in a healthcare institution where appropriate medicinal products and equipment for the relief of anaphylactic and anaphylactoid reactions are available. A case of serious anaphylactic reaction to Olokizumab has been reported in a clinical study.

Infections: increased incidence of infections is common for patients receiving immunosuppressants, including IL-6 signaling pathway blockers. The use of Olokizumab is associated with an increased risk of developing or intensifying infections. Patients with active infections should not start therapy with Olokizumab. Caution should be exercised when using Olokizumab in patients with risk factors for the development of infections. With the development of a serious infection, therapy with Olokizumab should be discontinued. Patients should be instructed about possible signs and symptoms of infection, requiring immediate medical attention.

Tuberculosis: before starting therapy for rheumatoid arthritis with Olokizumab, the patient should be examined/tested for the presence of latent tuberculosis infection. Patients with an identified latent tuberculosis infection should undergo a standard course of anti-tuberculosis therapy before starting therapy with Olokizumab.

Care should be exercised when using Olokizumab in patients who are in close contact (living together or being in other confined spaces, for example, in the workplace, at public meetings, or in a building for long periods during the day) with a person suffering from active tuberculosis. Before using Olokizumab in such patients, carefully assess the balance of risk and benefit of using the product.

Risk of gastrointestinal perforation: cases of gastrointestinal perforation have been reported with the use of IL-6 signaling pathway inhibitors, mainly in patients with diverticulitis. Caution should be exercised when using Olokizumab in patients with a history of diverticulitis or bowel perforation and other risk factors for bowel perforation. In case of gastrointestinal symptoms, such as abdominal pain, that develop during the treatment with Olokizumab, the patient should be examined immediately.

Renal impairment: patients with renal impairment were not included in the clinical study of Olokizumab. Due to the lack of data, caution should be exercised when using Olokizumab in patients with renal impairment. .

Hepatic impairment: the use of Olokizumab, as well as other IL-6 inhibitors, is associated with elevated levels of ALT, AST, and gamma-glutamyl transferase (see Section “Elevated levels of hepatic transaminases"). Patients with ALT or AST ≥1.5×ULN were not included in the clinical study. Caution should be exercised when using Olokizumab in patients with hepatic impairment and liver failure.

Monitoring of laboratory blood parameters: in clinical studies, a decrease in the neutrophil and leukocyte counts have been reported during the treatment with Olokizumab and other IL-6 inhibitors. According to the data on the use of other IL-6 inhibitors, neutropenia did not lead to an increase in the frequency of infections. Patients with leukocyte count <3.5 × 109/L, neutrophil count <2000 × 106/L (<2000/mm3) were not included in the clinical study.

Vaccination: the safety of immunization with live vaccines in patients treated with IL-6 inhibitors, including olokizumab, has not been established. Patients requiring vaccination with live vaccines were not included in the clinical study.

Malignant neoplasms: there are no data on the safety of olokizumab in patients with malignant neoplasms. The risk of malignant tumors in patients treated with Olokizumab is not known.

Effects on ability to drive and operate machines
Studies on the effect of the drug on the ability to drive vehicles and operate machines have not been conducted. Although there are currently no adverse reactions associated with dizziness during olokizumab therapy, dizziness has often been observed with other IL-6 inhibitors. Patients experiencing dizziness during Olokizumab therapy should be advised not to drive vehicles or operate machines until dizziness stops.

Presentation
Solution for subcutaneous injection, 160 mg/mL.
0.4 mL of the drug per 2 mL transparent borosilicate glass (type I) vials sealed with chlorobutyl rubber or bromobutyl rubber stoppers and crimped with a combination aluminum cap with a plastic flip off cover.
1 vial with the package leaflet per carton.
1 vial with one 1 mL sterile syringe and 2 stainless chromium-nickel steel needles (G18 and G27), protected by plastic caps, 2 sterile alcohol wipes with the package leaflet per carton.
0.4 mL of the drug in a 1 mL prefilled syringe made of transparent glass (type I), with a plastic finger flange and a steel needle protected by a plastic cap and closed with an elastomeric (chlorobutyl) stopper with a FluroTec coating (with B2-40 applied for lubrication) into which the polypropylene plunger rod is screwed.
1 pre-filled syringe per carton insert intended to minimize plunger rod movement.
1 insert with a pre-filled syringe along with 1 individually packaged alcohol wipe and the package leaflet per carton.

Storage conditions
Store at 2 to 8 °C protected from light.
Keep out of the reach of children.
Do not freeze

Shelf-life
3 years.
Do not use after the expiry date indicated on the package.

Pharmacy terms of sale
Prescription drug.

Manufacturer
R-Pharm JSC, Russian Federation, Yaroslavskaya obl., g.o. g. Yaroslavl, g.
Yaroslavl, Ul. Gromova 15.
Tel./fax: +7 (4852) 40-30-20
Ajinomoto Althea, Inc., 11040 Roselle Street, San Diego (CA) 92121,
United States of America
* *When packaged at ORTAT JSC, additionally indicate*:

Packed:
ORTAT JSC,
157092, Russian Federation, Kostromskaya obl., Susaninsky raion, s.
Severnoye, mkr. Kharitonovo.

Marketing authorization owner/ organization receiving customer claims:
R-Pharm JSC, Russian Federation
19, Berzarina str., bldg. 1, Moscow, 123154
Tel. +7 (495) 956-79-37, fax +7(495) 956-79-38
E-mail: info@rpharm.ru