STEP-BY-STEP DOSING AND ADMINISTRATION GUIDE

A guide to assist healthcare professionals with the dose preparation and administration of ACTEMRA therapy in patients with rheumatoid arthritis

Contents

Part I – Intravenous (IV) administration of Actemra by infusion

For RA

This guide will walk you through the Actemra infusion process in 6 steps.

Before therapy begins

Before beginning Actemra therapy, it is important that you review the *What You Should Know About Actemra* Patient Brochure with each patient. This educational tool contains valuable information that will help your patients fully understand what they may expect from their treatment.

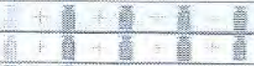
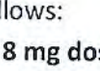
Prior to each infusion, it is important that you review the pre-administration checklist found in the *What You Should Know About Actemra* Patient Brochure with your patient and allow ample time to discuss any questions he or she may have.

- Actemra patient brochures and other information can be requested from your sales representative. If you have questions or concerns, please visit [insert local affiliate Website] or call [insert affiliate contact number].
- For full information, see the Summary of Product Characteristics (SmPC) and the Patient Leaflet, which can be found on the European Medicines Agency website (www.ema.europa.eu)

1. Weigh patient and calculate Actemra dose

Actemra dosing is calculated based on each patient's weight. Verify the patient's weight, then locate it on the chart to find the corresponding dose and recommended vial combination.

If the patient's dose has been calculated prior to the infusion date, take his or her weight to make sure that it has not changed from the time of the original calculation to require a change in dose. If the patient's weight has changed, contact the prescriber to discuss whether a dosing change is needed. Refer to the chart to check whether a dosing adjustment is necessary.

8 mg/kg dose				
Weight (kg)	Weight (lbs)	Dose (mg)	Dose (mL)	Vial combinations
50	110.0	400	20.0	
52	114.4	416	20.8	
54	118.8	432	21.6	
56	123.2	448	22.4	
58	127.6	464	23.2	
60	132.0	480	24.0	
62	136.4	496	24.8	
64	140.8	512	25.6	
66	145.2	528	26.4	
68	149.6	544	27.2	
70	154.0	560	28.0	
72	158.4	576	28.8	
74	162.8	592	29.6	
76	167.2	608	30.4	
78	171.6	624	31.2	
80	176.0	640	32.0	
82	180.4	656	32.8	
84	184.8	672	33.6	
86	189.2	688	34.4	
88	193.6	704	35.2	
90	198.0	720	36.0	
92	202.4	736	36.8	
94	206.8	752	37.6	
96	211.2	768	38.4	
98	215.6	784	39.2	
≥100	≥220.0	800	40.0	

Actemra dosing is calculated based on each patient's weight as follows:

For the 8 mg/kg dose: Patient weight (kg) x 8 (mg/kg) = Actemra 8 mg dose.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended.

Once the dose is calculated, choose the vial combination of Actemra that best matches the patient's needs. Actemra is available in three different dosing vials:

 400 mg (20 ml) vials  200 mg (10 ml) vials  80 mg (4 ml) vials

Inspect the vials for particulate matter and discolouration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be used.

2. Gather all necessary supplies

You will need:

- Actemra, at room temperature
- Syringes and large-bore needles
- One primary infusion set
- One 100 ml bag of 0.9% (9 mg/mL) sterile,non-pyrogenic sodium chloride solution for injection
- One intravenous (IV) catheter
- Gauze
- Tourniquet
- Gloves
- Alcohol/cleansing wipes

These images are stock photography

3. Take baseline assessments

Take baseline assessments to ensure the patient is healthy enough to receive the infusion.

Vital signs may include:

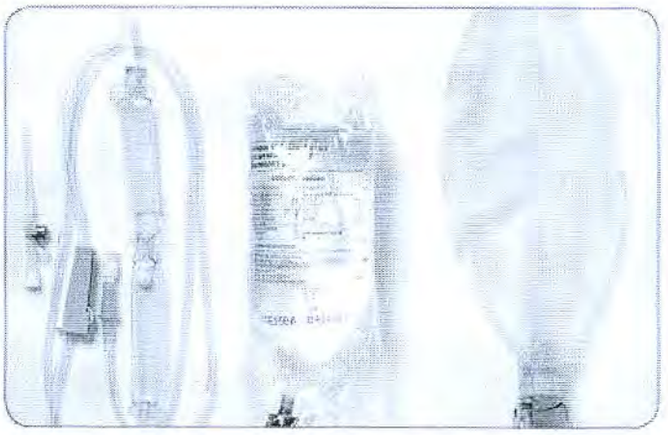
- Blood pressure
- Temperature
- Pulse

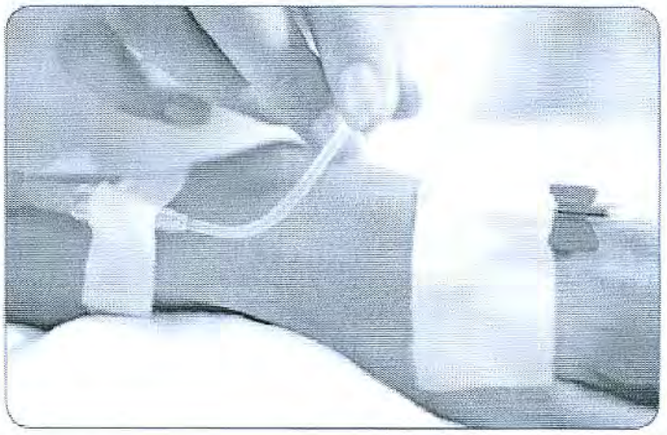
Also ask the patient if they:

- Are taking other medicines. This includes prescription and non-prescription medications, vitamins and herbals
- Are taking any other medications to treat rheumatoid arthritis (RA) such as methotrexate (MTX), Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), MabThera® (rituximab), Orencia® (abatacept), Kineret® (anakinra), Cimzia® (certolizumab pegol) and Simponi® (golimumab)
- Have had any allergic reactions to previous medications, including Actemra
- Are pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
- Have an infection or are being treated for an infection; have had or now have hepatitis or any disease of the liver; have a history of gastrointestinal ulcers or diverticulitis; have had or now have impaired lung function (e.g. interstitial lung disease)
- Have diabetes or other underlying conditions that may predispose them to infections
- Are planning or are scheduled to have surgery; have had a recent vaccination (such as flu shot) or are scheduled to have one
- Have cancer, cardiovascular risk factors, such as raised blood pressure and raised cholesterol levels, or moderate-to-severe kidney function problems

4. Prepare the patient for the infusion

- Review the *What You Should Know About Actemra* Patient Brochure with the patient and answer any questions he or she might have
- Actemra does not require premedication





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5. Prepare the Actemra infusion

Actemra should not be infused concomitantly in the same IV line with other medications. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Actemra with other medications.

Actemra is a ready-mix solution and requires no reconstitution. The expiry date should always be checked before use. The Actemra concentrate for IV infusion should be diluted to 100 ml by a healthcare professional using aseptic technique.

- Actemra should be refrigerated for storage and the fully diluted Actemra solution should be allowed to reach room temperature before it is infused. The fully diluted Actemra solutions for infusion may be stored at 2°C–8°C or room temperature (if diluted under controlled and validated

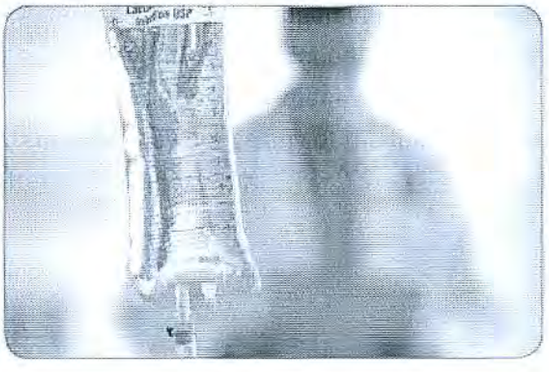
aseptic conditions) for up to 24 hours and should be protected from light. Actemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of the Actemra solution required for the patient's dose
- Slowly add Actemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- Dispose of needle and syringe in sharps containers when finished

6. Begin the Actemra infusion

The infusion should be administered over 60 minutes. **It must be administered with an infusion set and should never be administered as an IV push or bolus.**

- Prior to the infusion, inform the patient that serious allergic reactions including anaphylaxis have been reported in association with Actemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced allergic reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. Most allergic reactions occur during infusion or within 24 hours of Actemra administration, although allergic reactions can occur at any time. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued. Fatal anaphylaxis has been reported after marketing authorisation during treatment with IV Actemra.
- Instruct the patient to **seek immediate medical attention** if they notice any of the following signs or symptoms of systemic allergic reactions after receiving Actemra:
    - Rash, itching or hives
    - Shortness of breath or trouble breathing
    - Swelling of the lips, tongue or face
    - Chest pain
    - Feeling dizzy or faint
    - Severe stomach pain or vomiting
    - Hypotension



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Once the infusion is completed, remove the catheter and dispose of all supplies properly, clean and bandage the infusion site and check the patient's vital signs.

FREQUENTLY ASKED QUESTIONS – Actemra vials for IV Infusion

How do I store Actemra vials?

Actemra must be refrigerated at 2°C–8°C. Do not freeze. Protect the vials from light by storing in the original package until time of use.

What vial sizes are available, and which should we stock?

Actemra is available in three different dosing vials: 400 mg (20 ml), 200 mg (10 ml) and 80 mg (4 ml). As the dosing of Actemra IV is calculated based upon patient weight, you may need a supply of all three dosing vials on hand in order to select the correct vial combination for each patient.

Do I need to administer premedication?

No premedication is required before administering Actemra. However, an IV of medication-free 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution should be administered to open and prepare the patient's vein for the infusion.

How do I prepare Actemra for infusion? What diluents can I use?

Actemra concentrate for IV infusion should be diluted to 100 ml using aseptic technique.

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of the Actemra concentrate required for the patient's dose, under aseptic conditions
- Slowly add Actemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Actemra should be refrigerated for storage and the fully diluted Actemra solution should be allowed to reach room temperature before it is infused
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted. The expiry date should always be checked before use
- Dispose of needle and syringe in sharps containers when finished

What is the infusion duration?

Actemra is administered over 60 minutes. It must be administered with an infusion set and should never be administered as an IV push or bolus.

How do I store the diluted infusion? What is the stability of Actemra?

The fully diluted Actemra solutions for infusion may be stored at 2°C–8°C or room temperature (if diluted under controlled and validated aseptic conditions) for up to 24 hours, and should be protected from light. Actemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.

What should I look for during the infusion?

Watch the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis. Most allergic reactions occur during infusion or within 24 hours of Actemra administration, although allergic reactions can occur at any time. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued.

Instruct the patient to **seek immediate medical attention** if they notice any of the following signs or symptoms of systemic allergic reactions after receiving Actemra:

- Rash, itching or hives
- Shortness of breath or trouble breathing
- Swelling of the lips, tongue or face
- Chest pain
- Feeling dizzy or faint
- Severe stomach pain or vomiting
- Hypotension

What kinds of side effects and reactions can occur during or after the infusion, and how common are they?
The most common side effects with Actemra are upper respiratory tract infections (common cold, sinus infections), headache, temporary increases in blood pressure, rash and dizziness.

Adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the Actemra 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment-limiting.

The rate of anaphylactic reactions, occurring in a total of six out of 3778 patients (0.2%), was several-fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with Actemra during the controlled and open-label clinical studies. These reactions were generally observed during the second to fifth infusions of Actemra. Fatal anaphylaxis has been reported after marketing authorisation during treatment with Actemra IV.

How frequently should I monitor the patient's vital signs?
Take the patient's vital signs before and after each infusion.

What if patients cannot schedule their infusion in exactly 4 weeks?
Actemra should be administered once every 4 weeks. Contact the prescriber for any deviations from that schedule.

What information do I need to provide the patient about Actemra?
Before beginning Actemra therapy, it is important that you review the *What You Should Know About Actemra* Patient Brochure with each patient. This educational tool contains valuable information that will help your patients fully understand what they may expect from their treatment.

Prior to each infusion, it is important that you review the preadministration checklist found in the *What You Should Know About Actemra* Patient Brochure. The patient should be allowed ample time to review and discuss any questions he or she may have.

If the patient would like more information about Actemra, please direct him or her to visit
If the patient would like more information about Actemra, please direct him or her to visit *«SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC* website: www.pharm.am.

For full information, see the Summary of Product Characteristics (SmPC) and the Patient Leaflet, which can be found on the www.pharm.am

Actemra® (tocilizumab) Important Safety Information

Therapeutic indications

Actemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Actemra can be used alone or in combination with methotrexate (MTX) and/or other diseasemodifying anti-rheumatic drugs (DMARDs). Actemra has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function,:

In these patients, Actemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active, severe infections.

Special warnings and precautions for use

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as Actemra for moderate-to-severe RA or GCA as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of Actemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biological treatments all patients should be screened for latent tuberculosis (TB) infection prior to starting Actemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating Actemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be advised to **seek medical advice** if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a TB infection occur during or after therapy with Actemra.

Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with immunosuppressive biologic therapies for RA. In clinical studies with Actemra, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis

Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with Actemra. Actemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued.

Active hepatic disease and hepatic impairment

Treatment with Actemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment.

Hepatic transaminase elevations

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA and GCA patients, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For ALT or AST elevations > 3 to 5 x ULN, Actemra treatment should be interrupted.

Haematological abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with Actemra 8 mg/kg IV in combination with MTX. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with Actemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µl). In patients who develop an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/µl, continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with Actemra to date. Infections have been reported in patients with neutropenia in clinical trials.

In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

Lipid parameters

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with Actemra. In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid-lowering agents.

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with Actemra is currently unknown.

Malignancy

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with Actemra as clinical safety has not been established. It is recommended that all patients, particularly elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Actemra therapy. The interval between live vaccinations and initiation of Actemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

Combination with TNF antagonists

There is no experience with the use of Actemra with TNF antagonists or other biological treatments for RA. Actemra is not recommended for use with other biological agents.

Sodium

This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of Actemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk for humans is unknown.

Actemra should not be used during pregnancy unless absolutely necessary.

Breast-feeding

It is unknown whether Actemra is excreted in human breast milk. The excretion of Actemra in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra to the woman.

Fertility

Available non-clinical Actemra data do not suggest an effect on fertility.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC website (www.pharm.am) Pharmacovigilance department via email: vigilance@pharm.am or hotline telephone: (+374 10) 237265, (+374 98) 773368 .

You can also report side effects directly to PharmaTech Safety department via mobile phone: +37491796688, or email: gayaneh.ghazaryan@gmail.com or direct your report to Drug Safety Department of Roche Moscow via contacts below: email: moscow.ds@roche.com, mobile phone: +7-495-229 2999, fax: +7-495- 229 7999 or try website: www.roche.ru.

Product traceability

In order to improve the traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.

For full information on all possible adverse events please see the Summary of Product Characteristics (SmPC) or the Patient Leaflet, which can be found at the «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC website (www.pharm.am)

Vahan Arushanyan, director of Pharmatech CJSC

Signature:_____

Date: 22.03.18

Gayane Ghazaryan, Safety Responsible for Roche Products in Armenia,

PharmaTech CJSC

Signature:_____

Date: 22.03.18