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 (RA), systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA)

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See final page for details on how to report.

Please see Important Safety Information starting on page 33 of this brochure

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This educational material is mandatory as a condition of the marketing authorisation of Actemra for intravenous infusion (Actemra IV) .

Please read this information carefully before administering the product.

Actemra IV (Actemra 20 mg/ml concentrate for solution for infusion):

Actemra, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more diseasemodifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

  In these patients, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

  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 methotrexate.

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Actemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Please see Important Safety Information starting on page 33 of this brochure

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

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 EMA website (www.ema.europa.eu)

RA: Dosing Preparation and Administration Guide with Actemra IV

Actemra, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more diseasemodifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to reduce the rate of progression of joint damage as measured by Xray and to improve physical function when given in combination with methotrexate.

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 information contained within the *Important Efficacy and Safety Information for Healthcare Professionals* for Actemra® (tocilizumab) intravenous (IV) and subcutaneous (SC) formulations and the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both. These educational tools contains valuable information that will help your patient, the patient's parents/guardians, or both understand what they may expect from the treatment of the patient's condition with Actemra.

Prior to each injection:

- it is important that you review the pre-administration checklist found in the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both.

Allow ample time to discuss any questions your patient, the patient's parents/guardians, or both may have.

Please see Important Safety Information starting on page 33 of this brochure

- 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 IV dosing in RA patients 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

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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 the patient:

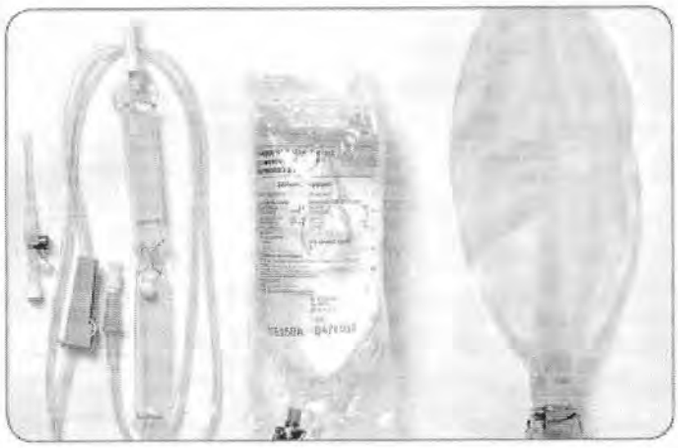
- Is taking other medicines (prescription and non-prescription medications, vitamins, herbals) such as:
    - Prescription medications to treat rheumatoid arthritis (RA) such as methotrexate (MTX), Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), MabThera® (rituximab), Orencia®

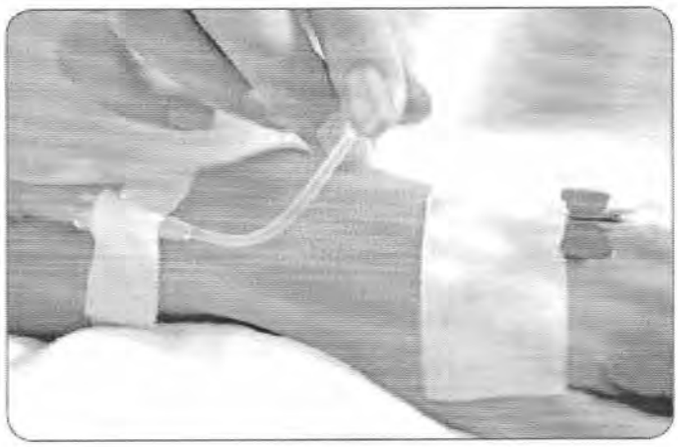
(abatacept), Kineret® (anakinra), Cimzia® (certolizumab pegol) and Simponi® (golimumab), Kevzara® (sarilumab), Olumiant® (baricitinib)[1]
    - Atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines
- Has had any allergic reactions to previous medications, including Actemra
- Is sexually active, pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
- Has 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 stomach ulcers or diverticulitis; have had or now have impaired lung function (e.g. interstitial lung disease)
- Has diabetes or other underlying conditions that may predispose them to infections
- Is planning or are scheduled to have surgery; have had a recent vaccination (such as flu shot) or are scheduled to have one
- Has 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. Answer any questions he or she might have
- Actemra does not require premedication

[1] Enbrel® is a registered trademark of Amgen Inc. and Pfizer Inc.; Humira® is a registered trademark of AbbVie; Remicade® is a registered trademark of Schering-Plough Corporation; MabThera® is a registered trademark of F. Hoffmann-La Roche Ltd; Orencia® is a registered trademark of Bristol-Myers Squibb; Kineret® is a registered trademark of Amgen Inc.; Cimzia® is a registered trademark of the UCB Group of Companies; Simponi® is a registered trademark of Centocor Inc. and Schering-Plough Corporation; Kevzara® (sarilumab) is a registered trademark of Genzyme Therapeutics; Olumiant® (baricitinib) is a registered trademark of Eli Lilly and Company Limited.





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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 by a healthcare professional using aseptic technique.

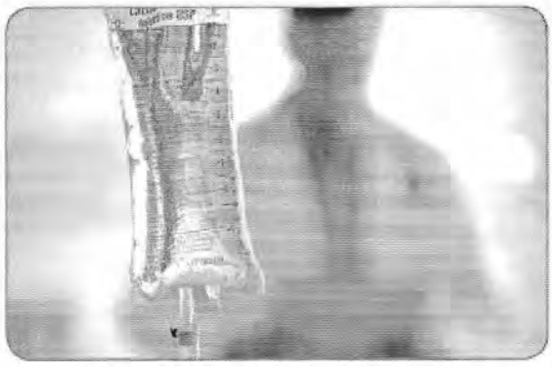
Please see Important Safety Information starting on page 33 of this brochure

- 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.

Please see Important Safety Information starting on page 33 of this brochure

pJIA: Dosing Preparation and Administration Guide with Actemra IV

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Actemra can be given as monotherapy in case of intoleranceto MTX or where continued treatment with MTX is inappropriate.

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 information contained within the *Important Efficacy and Safety Information for Healthcare Professionals* for Actemra® (tocilizumab) intravenous (IV) and subcutaneous (SC) formulations and the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both. These educational tools contains valuable information that will help your patient, the patient's parents/guardians, or both understand what they may expect from the treatment of the patient's condition with Actemra.

Prior to each injection:

- it is important that you review the pre-administration checklist found in the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both.

Allow ample time to discuss any questions your patient, the patient's parents/guardians, or both 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.

Actemra IV dosing in pJIA patients is calculated based on each patient's weight as follows:

For patients weighing <30 kg: Patient's weight (kg) x 10 mg/kg = Actemra dose

For patients weighing ≥30 kg: Patient's weight (kg) x 8 mg/kg = Actemra dose

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

For example, for a patient weighing 20 kg, the dose would be 200 mg (10 ml) and the provider could use one 200 mg vial.

As another **example, for a patient weighing 40 kg, the dose would be 320 mg (16 ml) and the provider could use four 80 mg 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 50 ml (patients <30 kg) or 100 ml (patients ≥30 kg) 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, patient's parents/guardians, or both if the patient:

- Is taking other medicines (prescription and non-prescription medications, vitamins, herbals) such as:
    - Prescription 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), Kevzara® (sarilumab), Olumiant® (baricitinib)[2]
    - Atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines
- Has had any allergic reactions to previous medications, including Actemra
- Is sexually active, pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
- Has 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 stomach ulcers or diverticulitis; have had or now have impaired lung function (e.g. interstitial lung disease)
- Has diabetes or other underlying conditions that may predispose them to infections
- Is planning or are scheduled to have surgery; have had a recent vaccination (such as flu shot) or are scheduled to have one
- Has 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, their parents/guardians, or both. Answer any questions they might have
- Actemra does not require premedication

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[2] Enbrel® is a registered trademark of Amgen Inc. and Pfizer Inc.; Humira® is a registered trademark of AbbVie; Remicade® is a registered trademark of Schering-Plough Corporation; MabThera® is a registered trademark of F. Hoffmann-La Roche Ltd; Orencia® is a registered trademark of Bristol-Myers Squibb; Kineret® is a registered trademark of Amgen Inc.; Cimzia® is a registered trademark of the UCB Group of Companies; Simponi® is a registered trademark of Centocor Inc. and Schering-Plough Corporation; Kevzara® (sarilumab) is a registered trademark of Genzyme Therapeutics; Olumiant® (baricitinib) is a registered trademark of Eli Lilly and Company Limited.

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 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

For patients <30 kg	**For patients ≥30 kg**
• From a **50 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 Actemra concentrate required for the patient's dose	• 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 Actemra concentrate required for the patient's dose
• The required amount of Actemra concentrate (**0.5 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml	• The required amount of Actemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- 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 and their parents/guardians 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 and their parents/guardians 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.

sJIA: Dosing Preparation and Administration Guide with Actemra IV

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Actemra can be given as monotherapy (in case of intolerance to methotrexate [MTX] or where treatment with MTX is inappropriate) or in combination with MTX.

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 information contained within the *Important Efficacy and Safety Information for Healthcare Professionals* for Actemra® (tocilizumab) intravenous (IV) and subcutaneous (SC) formulations and the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both. These educational tools contains valuable information that will help your patient, the patient's parents/guardians, or both understand what they may expect from the treatment of the patient's condition with Actemra.

Prior to each injection:

- it is important that you review the pre-administration checklist found in the *What You Should Know About Actemra* Patient Brochure with your patient, the patient's parents/guardians, or both.

Allow ample time to discuss any questions your patient, the patient's parents/guardians, or both may have.

1 Weigh patient and calculate Actemra dose

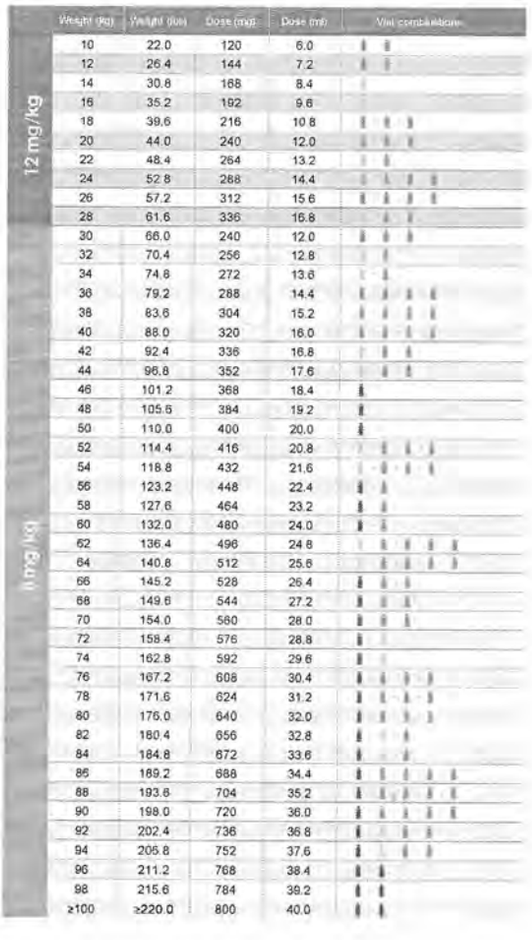
Actemra dosing is calculated based on each patient's weight. Verify the patient's weight, then locate it on the chart to find the corresponding dose and recommended vial combination.

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.

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

For patients weighing <30 kg: Patient's weight (kg) x 12 mg/kg = Actemra dose

For patients weighing ≥30 kg: Patient's weight (kg) x 8 mg/kg = Actemra dose



	Weight (kg)	Weight (lbs)	Dose (mg)	Dose (ml)	Vial combination
12 mg/kg	10	22.0	120	6.0	
	12	26.4	144	7.2	
	14	30.8	168	8.4	
	16	35.2	192	9.6	
	18	39.6	216	10.8	
	20	44.0	240	12.0	
	22	48.4	264	13.2	
	24	52.8	288	14.4	
	26	57.2	312	15.6	
	28	61.6	336	16.8	
	30	66.0	240	12.0	
	32	70.4	256	12.8	
	34	74.8	272	13.6	
	36	79.2	288	14.4	
	38	83.6	304	15.2	
	40	88.0	320	16.0	
	42	92.4	336	16.8	
	44	96.8	352	17.6	
	46	101.2	368	18.4	
	48	105.6	384	19.2	
	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	
8 mg/kg	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	

Please refer to the Actemra Paediatric Dosing Card for more details

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 50 ml (patients <30 kg) or 100 ml (patients ≥30 kg) 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

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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, patient's parents/guardians, or both if the patient:

- Is taking other medicines (prescription and non-prescription medications, vitamins, herbals) such as:
    - Prescription 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), Kevzara® (sarilumab), Olumiant® (baricitinib)[3]
    - Atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines
- Has had any allergic reactions to previous medications, including Actemra
- Is sexually active, pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
- Has 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 stomach ulcers or diverticulitis; have had or now have impaired lung function (e.g. interstitial lung disease)
- Has diabetes or other underlying conditions that may predispose them to infections
- Is planning or are scheduled to have surgery; have had a recent vaccination (such as flu shot) or are scheduled to have one
- Has cancer, cardiovascular risk factors, such as raised blood pressure and raised cholesterol levels, or moderate to severe kidney function problems
- Has a history of macrophage activation syndrome (MAS)

4 Prepare the patient for the infusion

- Review the What You Should Know About Actemra Patient Brochure with the patient, their parents/guardians, or both. Answer any questions they might have

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[3] Enbrel® is a registered trademark of Amgen Inc. and Pfizer Inc.; Humira® is a registered trademark of AbbVie; Remicade® is a registered trademark of Schering-Plough Corporation; MabThera® is a registered trademark of F. Hoffmann-La Roche Ltd; Orencia® is a registered trademark of Bristol-Myers Squibb; Kineret® is a registered trademark of Amgen Inc.; Cimzia® is a registered trademark of the UCB Group of Companies; Simponi® is a registered trademark of Centocor Inc. and Schering-Plough Corporation; Kevzara® (sarilumab) is a registered trademark of Genzyme Therapeutics; Olumiant® (baricitinib) is a registered trademark of Eli Lilly and Company Limited.

- RoActemra does not require premedication

These images are stock photography

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 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 2–8°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

For patients <30 kg	**For patients ≥30 kg**
• From a **50 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 Actemra concentrate required for the patient's dose	• 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 Actemra concentrate required for the patient's dose
• The required amount of Actemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml	• The required amount of Actemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- 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 and their parents/guardians 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 and their parents/guardians 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
    -

These images arestock photography

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 50 ml (for patients <30 kg) or 100 ml (for patients ≥30 kg) using aseptic technique.

- From a 50 or 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, their parents/guardians, or both 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.

In RA:

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.

In pJIA:

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. Following 184.4 patient-years of exposure with Actemra in pJIA patients, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension, and those within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (sJIA) patients. No clinically significant hypersensitivity reactions were reported during the clinical programme.

In sJIA:

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled clinical study, 4% of patients from the Actemra group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the Actemra group, 16% of patients experienced an event within 24 hours of infusion compared to 5.4% of patients in the placebo group during the 12-week clinical study. In the Actemra group, the events included, but were not limited to, rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation were reported in <1% (one out of 112) patients treated with Actemra during the controlled and open-label clinical study.

What should I do if the patient develops macrophage activation syndrome (MAS)?
MAS is a serious life-threatening disorder that may develop in sJIA patients. This syndrome is thought to be triggered by infections or changes in medications, but can occur without clear reasons or aetiology. In clinical trials, Actemra has not been studied in patients during an episode of active MAS. If your patient has a history of MAS, it is necessary to assess the risk and benefit to the patient before initiating Actemra therapy.

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 the patient, their parents/guardians, or both. This educational tool contains valuable information that will help your patient, their parents/guardians, or both fully understand what they may expect from their treatment.

Prior to each infusion, it is important that you review:

1. *The preadministration checklist* found in the *What You Should Know About Actemra* Patient Brochure (for all patients).
2. *The Important Efficacy and Safety Information* in the pJIA *Healthcare Professional Brochure* and particularly discuss with your patient, their parents/guardians, or both the information highlighted within the Patient Counselling Information and Laboratory Monitoring section (for pJIA patients).

Allow ample time to discuss any questions your patient, their parents/guardians, or both may have.

If the patient, their parents/guardians, or both would like more information about Actemra, please direct them to visit
[insert local affiliate Website] or to 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)

Actemra® (tocilizumab) Important Safety Information

Therapeutic Indications

Actemra (IV), in combination with methotrexate (MTX), is indicated for:

Rheumatoid Arthritis (RA):

- Actemra 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

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Actemra is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with MTX

Systemic Juvenile Idiopathic Arthritis (sJIA)

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or 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, or parents/guardians of paediatric 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 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.

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

In pJIA and sJIA patients, neutrophils and platelets should be monitored at the time of the second administration and thereafter according to good 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

The risk of cardiovascular disorders is increased in patients with RA. Patients receiving Actemra should have their 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.

Macrophage Activation Syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, Actemra has not been studied in patients during an episode of active MAS.

Sodium

Actemra IV 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 clearly 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 ADRs (occurring in ≥ 5% of patients treated with IV tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

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

The safety observed for Actemra SC in RA and GCA was consistent with the known safety profile of Actemra IV with a higher frequency of injection site reactions observed with Actemra SC.

In general, the ADRs observed with IV Actemra in sJIA patients were similar in type to those seen in RA patients. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

The types of ADRs in pJIA patients observed with IV Actemra were similar to those seen in RA and sJIA patients. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

In general, the safety profile observed with SC Actemra in patients with pJIA was consistent with the known safety profile of Actemra with the exception of injection site reactions (ISRs). A higher frequency of pJIA patients experienced ISRs following SC Actemra injections compared to adult RA.

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 via the national reporting system listed in Appendix V.

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.

Call for reporting

Consult the PIL/SmPC before prescribing, preparing or administering Actemra

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 at the website of Scientific Centre of Drug and Medical Technology Expertise after Academician Emil Gabrielyan" JSC via following address: www.pharm.am .

Adverse reactions should also be reported to Roche Medical Information via the Company contact point, that is provided below:

Drug Safety Department of Roche Moscow via contacts as follows: email: moscow.ds@roche.com, mobile phone: +7-495-229 2999, fax: +7-495- 229 7999 or try website: www.roche.ru

Company contact point:

Local Safety Responsible for Roche products in Armenia, Gayane Ghazaryan, via following contacts: +37491796688, email address: gayaneh.ghazaryan@gmail.com or Rima Davtyan tel: +010734643, email address: rima@pharmatech.am .

This educational material is mandatory as a condition of the marketing authorisation of Actemra in order to further minimise important selected risks.

Vahan Arushanyan

General Director, PharmaTech CJSC 27.11.18 _____

date / signature

Gayane Ghazaryan , Safety Responsible

for Roche products in Armenia, PharmaTech CJSC 26.11.18 _____

date / signature

RoACTEMRA
tocilizumab