Avtozma®▼ (tocilizumab) Dosing Guide

Avtozma® (tocilizumab) intravenous (IV) and subcutaneous (SC) formulations

A guide to assist healthcare professionals with the dose preparation and administration of Avtozma therapy in patients with:

Rheumatoid Arthritis (RA) (IV or SC)

Giant Cell Arteritis (GCA) (SC)

Polyarticular Juvenile Idiopathic Arthritis (pJIA) (IV or SC)

Systemic Juvenile Idiopathic Arthritis (sJIA) (IV or SC)

Chimeric Antigen Receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS) in adults and paediatric patients 2 years of age and older (IV)

Coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation (IV)

This Avtozma Dosing Guide is additional risk minimisation material and is provided by Mint Health Ltd as a condition of the Avtozma marketing authorisation. It contains important safety information that you need to be aware of when administering Avtozma.

This Avtozma Dosing Guide must be read together with the Avtozma Healthcare Professional and Patient Brochures (available online at https://medicinesauthority.gov.mt/rmm), the Avtozma Summary of Product Characteristics and the Package Leaflet that comes with Avtozma (and is also available on https://www.ema.europa.eu/en/medicines/human/EPAR/avtozma) as it contains important information about Avtozma. Please read this information carefully before administering the product.

Indications and Usage

Avtozma Intravenous (IV)

Avtozma 20mg/ml concentrate for solution for infusion

Avtozma, 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 disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

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

Avtozma 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. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (polyarticular Juvenile Idiopathic Arthritis, 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. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

Avtozma is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Avtozma Subcutaneous (SC)

Avtozma 162mg solution for injection in pre-filled syringe

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

- the treatment of severe, active and progressive 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 disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

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

Avtozma 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.

Avtozma is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (polyarticular Juvenile Idiopathic Arthritis, 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. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Avtozma 162mg solution for injection in pre-filled pen

Avtozma, 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 disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists

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

Avtozma is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 12 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids

Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Avtozma 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 12 years of age and older, who have responded inadequately to previous therapy with MTX.

Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate

Avtozma is indicated for the treatment of GCA in adult patients.

Tocilizumab SC formulation is administered with a single-use pre-filled pen. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA and/or GCA.

General Information

The pre-filled pen should not be used to treat paediatric patients < 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.

The first injection should be performed under the supervision of a qualified health care professional. A patient or parent/guardian can inject Avtozma only if the physician determines that it is appropriate and the patient or parent/guardian agrees to medical follow-up as necessary and has been trained in proper injection technique.

Patients who transition from tocilizumab IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified health care professional.

All patients treated with Avtozma should be given the Patient Alert Card.

Suitability of the patient or parent/guardian for subcutaneous home use should be assessed.

Prior to starting treatment with Avtozma

- It is important that you review the baseline checklist found under section “General Recommendations” in the Healthcare Professional (HCP) 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.
- It is important that you review the information contained within the Avtozma Healthcare Professional (HCP) Brochure for Avtozma® (tocilizumab) intravenous (IV) and subcutaneous (SC) formulations and the Avtozma Patient Brochure with your patient, the patient’s parents/guardians, or both. These will help them understand what they may expect from the treatment of the patient’s condition with Avtozma.

Avtozma Patient Alert Cards and other information can be requested from your sales representative or Medical Information. If you have questions or concerns, please email or call

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For full information, see the Summary of Product Characteristics (SmPC) and the Package Leaflet, which can be found on the https://www.ema.europa.eu/en/medicines/human/EPAR/avtozma.

Intravenous (IV) administration of Avtozma by infusion

This section will walk you through the Avtozma infusion process in 6 steps

1. Weigh patient and calculate Avtozma dose

Avtozma dosing is calculated based on each patient's weight and the indication for which they are treated. The treatment frequency varies by indication. Verify the patient's weight and indication, then locate it on the charts (included on the following pages) 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 again 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.

Once the dose is calculated, choose the vial combination of Avtozma that best matches the patient's needs.

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

RA: Dosing Preparation and Administration Guide with Avtozma IV

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

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

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

Doses above 1.2 g have not been evaluated in clinical studies.

Dosing should take place at 4-week intervals.

8 mg/kg				
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	@+@

@ [400 mg (20 ml) vials], # [200 mg (10 ml) vials], * [80 mg (4 ml) vials]

pJIA: Dosing Preparation and Administration Guide with Avtozma IV

Avtozma 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 = Avtozma dose

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

Dosing should take place at 4-week intervals.

The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. 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.

10 mg/kg	Weight (kg)	Weight (lbs)	Dose (mg)	Dose (ml)	Vial combinations
	10	22.0	100	5.0	*+*
	12	26.4	120	6.0	*+*
	14	30.8	140	7.0	*+*
	16	35.2	160	8.0	*+*
	18	39.6	180	9.0	#
	20	44.0	200	10.0	#
	22	48.4	220	11.0	*+*+*
	24	52.8	240	12.0	*+*+*
	26	57.2	260	13.0	#+*
	28	61.6	280	14.0	#+*
8 mg/kg	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	@+*

	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	@+@

@ [400 mg (20 ml) vials], # [200 mg (10 ml) vials], * [80 mg (4 ml) vials]

sJIA: Dosing Preparation and Administration Guide with Avtozma IV

Avtozma IV 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 = Avtozma dose

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

Dosing should take place at 2-week intervals.

The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. 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.

12 mg/kg	Weight (kg)	Weight (lbs)	Dose (mg)	Dose (ml)	Vial combinations
	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	#+*+*
8 mg/kg	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	@+*

	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	@+@

@ [400 mg (20 ml;) vials], # [200 mg (10 ml) vials], * [80 mg (4 ml) vials]

CRS: Dosing Preparation and Administration Guide with Avtozma IV

Avtozma dosing in CRS patients is calculated based on each patient's weight as follows:

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

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

If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of Avtozma may be administered. The interval between consecutive doses should be at least 8 hours.

Doses exceeding 800 mg per infusion are not recommended in CRS patients.

Subcutaneous administration is not approved for CRS.

COVID-19: Dosing Preparation and Administration Guide with Avtozma IV

The recommended posology for treatment of COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation, see section 5.1 of the Avtozma 20 mg/mL concentrate for solution for infusion Summary of Product Characteristics (SmPC). If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of Avtozma 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2 of the SmPC).

Administration of Avtozma is not recommended in patients with COVID-19 who have any of the following laboratory abnormalities:

Laboratory test type	**Laboratory value**	**Action**
Liver enzyme	>10 x ULN	Administration of Avtozma is not recommended
Absolute neutrophil count	< 1 x 10^9 /L	
Platelet count	< 50 x 10^3 /μL	

2. Gather all necessary supplies

You will need:

- Avtozma 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 IV catheter
- Gauze
- Tourniquet
- Gloves
- Alcohol/cleansing wipes
- Appropriate treatment to manage an anaphylactic reaction

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

Follow the recommended baseline patient questions as described in the Avtozma Healthcare Professional Brochure (General Recommendation) as well as the Summary of Product Characteristics (Section 4.4 – Warnings and Precautions).

4. Prepare the patient for the infusion

Avtozma does not require premedication.

Review the Package Leaflet and the Patient Brochure with the patient and answer any questions he or she might have.

5. Prepare the Avtozma infusion

Avtozma is a ready-mix solution and requires no reconstitution. The expiry date should always be checked before use. The Avtozma concentrate for IV infusion should be diluted to a final volume of 100 ml (patients ≥ 30 kg) and to a final volume of 50 ml (patients< 30 kg), by a healthcare professional using aseptic technique.

- Avtozma should be refrigerated for storage and the fully diluted Avtozma solution should be allowed to reach room temperature before it is infused.
- The fully diluted Avtozma solutions for infusion may be stored at 2°C–8°C for a month or 30°C (if diluted under controlled and validated aseptic conditions) for up to 48 hours and should be protected from light.
- From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the

responsibility of the user and would normally not be longer than 24 housr at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

- Avtozma solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.

- **Weight-/indication-based dosing:**

- **For RA, CRS, sJIA, COVID-19 and pJIA (≥30 kg):**

  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 Avtozma solution required for the patient's dose.

  Withdraw the required amount of Avtozma concentrate (0.4 mL/kg) from the vial and place in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

- **For sJIA and CRS 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 the Avtozma solution required for the patient's dose.

  Withdraw the required amount of Avtozma concentrate (0.6 mL/kg) from the vial and place in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

- **For pJIA 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 the Avtozma solution required for the patient's dose.

  Withdraw the required amount of Avtozma concentrate (0.5 mL/kg) from the vial and place in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming

- Avtozma 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 Avtozma with other medications.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to slightly opalescent, colourless to pale yellow and free of visible particles should be diluted.
- Dispose of the needle and syringe in a sharps container when finished.

6. Begin the Avtozma infusion

The infusion should be administered over one hour. It must be administered with an infusion set and should never be administered as an IV push or bolus.

Monitor the patient for infusion related reactions.

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.

Dosing administration guide with Avtozma SC using either the Pre-filled Syringe or Pre-filled Pen (Avtozma devices)

The pre-filled syringe is used in RA (162 mg once per week), GCA (162 mg once every week in combination with a tapering course of glucocorticoids), pJIA (162 mg once every 2 weeks in patients weighing ≥ 30 kg or once every 3 weeks in patients weighing < 30kg), and sJIA (162 mg once every week in patients weighing ≥ 30 kg or 162 mg once every 2 weeks in patients < 30 kg) indications only.

The pre-filled pen is used in the following indications only:

- RA (162 mg once per week)

- GCA (162 mg once every week in combination with a tapering course of glucocorticoids)

- In patients 12 years of age and older for the treatment of active systemic juvenile idiopathic arthritis (sJIA) (162 mg subcutaneously once every week in patients weighing greater than or equal to 30 kg or 162 mg subcutaneously once every 2 weeks in patients weighing less than 30 kg)

- In patients 12 years of age and older for the treatment of juvenile idiopathic polyarthritis (pJIA, rheumatoid factor positive or negative and extended oligoarthritis) (162 mg subcutaneously once every 2 weeks in patients weighing greater than or equal to 30 kg or 162 mg subcutaneously once every 3 weeks in patients weighing less than 30 kg).

Patients must have a minimum body weight of 10 kg when receiving Avtozma subcutaneously.

The pre-filled pen should not be used to treat paediatric patients < 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.

Instructions apply to both devices.

Monitor the patient for injection related reactions.

This guide will walk you through the Avtozma SC injection process in 7 steps.

1. Gather all necessary supplies

You will need:

- One Avtozma Pre-filled Syringe OR Pre-filled pen at room temperature
- A well-lit, clean, flat surface
- Puncture-resistant container/sharps container for disposal
- Alcohol pad/cleansing wipes
- Sterile cotton ball or gauze
- Clock or watch
- Adhesive bandage

Avtozma Pre-filled Syringe

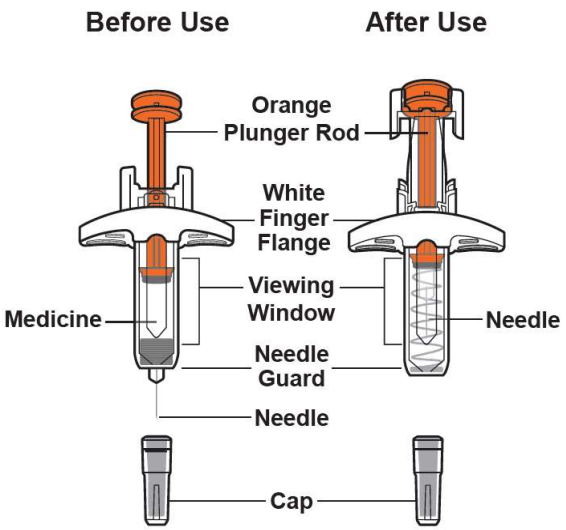

Figure A

Avtozma Pre-filled Pen

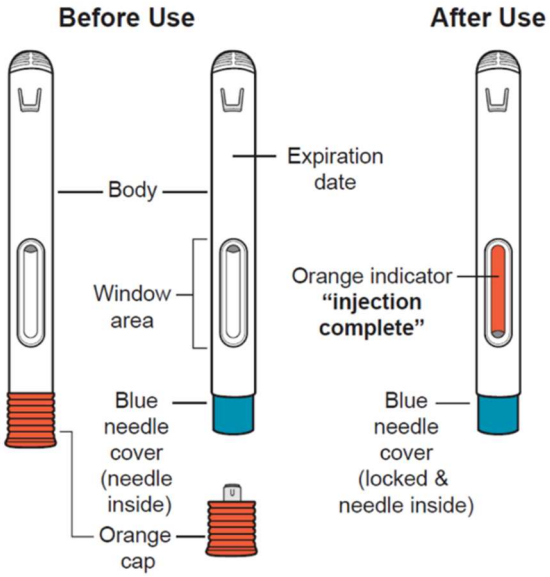

Figure B

2. Take baseline assessments

The first injection using the Avtozma device should be performed under the supervision of a qualified healthcare professional.

The healthcare professional should take baseline assessments to ensure the patient is healthy enough to receive the injection.

Vital signs may include:

- Blood pressure
- Temperature
- Pulse

Follow the recommended baseline patient questions as described in the Avtozma Healthcare Professional Brochure (General Recommendation) as well as the Summary of Product Characteristics (Section 4.4 – Warnings and Precautions).

3. Prepare for injection

- Store the Avtozma SC device in the refrigerator at 2°C – 8°C. Do not freeze.
- Allow the device to reach room temperature **(18°C to 28°C)** after removing it from the refrigerator. Do not warm up the device in any other way.
  – **Do not** speed up the warming process in any way, such as using the microwave or placing in warm water.
  – **Do not** leave the device to warm up in direct sunlight.
- Do not shake the device.
- Do not reuse the device.
- Do not try to take apart the device at any time.
- Do not use the device through clothing.

Before every use:

– **Check the Avtozma SC device to make sure it is not damaged.** Do not use if it appears to be damaged or if you have accidentally dropped it.
– If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the device if the box looks like it has already been opened.
– Check that the device box is not damaged. **Do not** use device if the box looks damaged.
– **Check the expiration date on device. Do not** use the Avtozma SC device if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the device in a sharps container and get a new one.
– **Inspect the Avtozma SC device visually for particulate matter and discolouration** prior to administration and check the expiration date. Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or if any part of it appears to be damaged.

- Do not leave the Avtozma SC device unattended. Keep out of the reach of children.
- Stop administration of Avtozma immediately if an anaphylactic reaction or other serious hypersensitivity reaction occurs. Initiate appropriate therapy and permanently discontinue Avtozma.

Injection Preparation: Avtozma Pre-filled Syringe

Avtozma 162 mg is supplied in 0.9 ml of solution for injection as a pack of 1 or 4 single-use pre-filled syringes, and multipacks containing 12 (3 packs of 4) pre-filled syringes. Not all pack sizes may be marketed.

- They should be kept in the outer carton to protect them from light and should be kept dry. The pre-filled syringes should be kept out of sight and reach of children.

- Administer Avtozma 162 mg/0.9 ml within 3 weeks once you remove it from the refrigerator and do not keep it above 30°C.
- Allow the Pre-filled Syringe to reach room temperature and wait for 30 minutes before injecting Avtozma 162 mg/0.9 ml.
- Start the injection within 5 minutes after removing the cap, to prevent the medicine from drying out and blocking the needle.

Injection Preparation: Avtozma Pre-filled Pen

- Administer Avtozma pre-filled pen within 3 weeks once you remove it from the refrigerator and do not keep it above 30°C.
- Do not remove the pre-filled pen cap until you are ready to inject Avtozma.
- Take the box containing the pre-filled pen out of the refrigerator.
- Open the box and remove one single-use Avtozma pre-filled pen from the box.
- Return any remaining pre-filled pens in the box to the refrigerator.
- Place the pre-filled pen on a clean, flat surface and let it warm up for 45 minutes to allow it to reach room temperature. If the pre-filled pen does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.

4. Choose and prepare an injection site

- Wash your hands with soap and water.
- Clean the chosen injection site area using the alcohol pad to reduce the risk of infection. Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. Let the skin dry for approximately 10 seconds. Do not touch the injection site again before giving the injection.
- Do not fan or blow on the clean area.

Injection site for the Pre-filled Syringe and Pre-filled Pen are as follows:

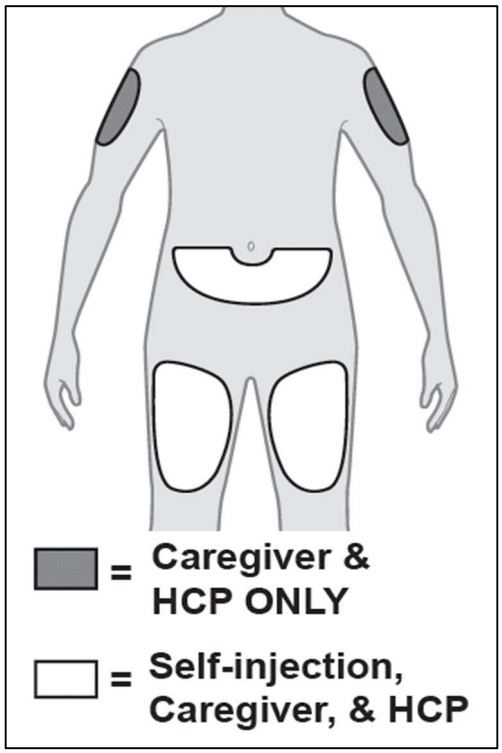

Figure C

Pre-filled Syringe:

The recommended injection sites are the front and middle of your thighs and the lower part of the abdomen below the navel (belly button) except for the 2 inch (5 cm) area directly around the navel (**See Figure C**).

If a caregiver is giving the injection, the outer area of the upper arms may also be used (**See Figure C**).

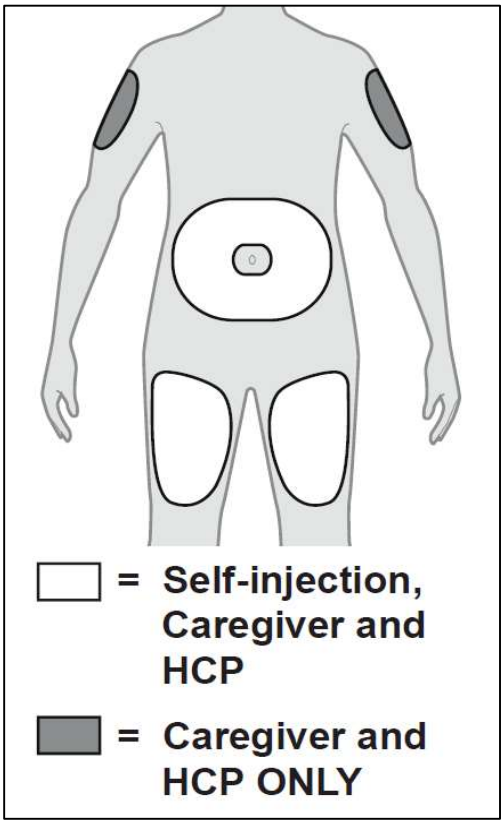

Figure D

Pre-filled Pen:

The front of your thigh or your abdomen except for the 2 inch (5 cm) area around your navel are the recommended injection sites (**See Figure D**).

The outer area of the upper arms may also be used only if the injection is being given by a caregiver and health care professional (HCP). Do not attempt to use the upper arm area by yourself (**See Figure D**).

- **Rotate Injection Site**

  Choose a different injection site for each new injection, at least:

  – Pre-filled Syringe: 1 inch (2.5 cm) from the area you used for your previous injection.
  – Pre-filled Pen: 1 inch (2.5cm) from the last area you injected.

- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.
  Do not inject into areas that could be bothered by a belt or waistband.

5. Administering the injection

Administration: Avtozma Pre-filled Syringe

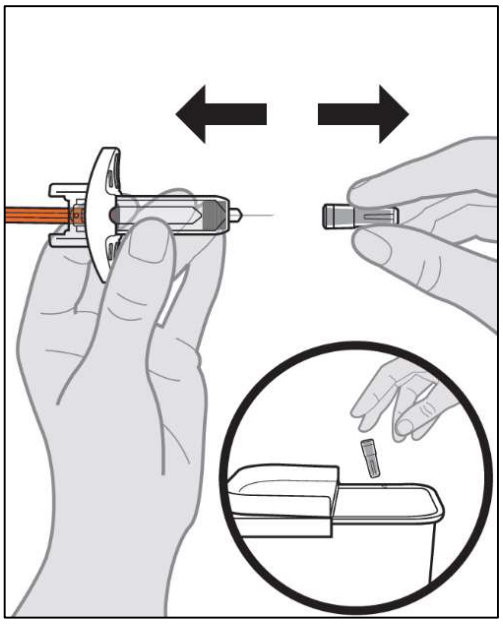

Figure E

1. Do not shake the pre-filled syringe. Hold the needle guard of the syringe firmly with one hand and pull off the needle-cap with the other. Do not pull or press the plunger. Do not touch the needle or let it touch any surface. After removing the needle-cap, the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled syringe. Never re-attach the needle-cap after removal.

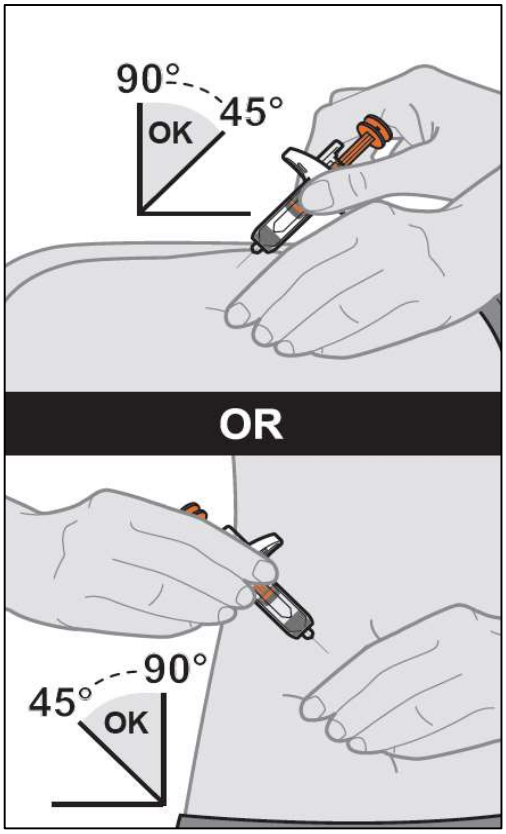

Figure F

2. Pinch a fold of loose skin at the injection site to provide a firm surface for injection. Insert the needle with a quick, firm action. The needle may be inserted at an angle between 45° to 90° (See Figure F).
It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful, and the medicine may not work.
Insert the needle all the way in. Then keep the syringe in position and let go of the pinched skin.

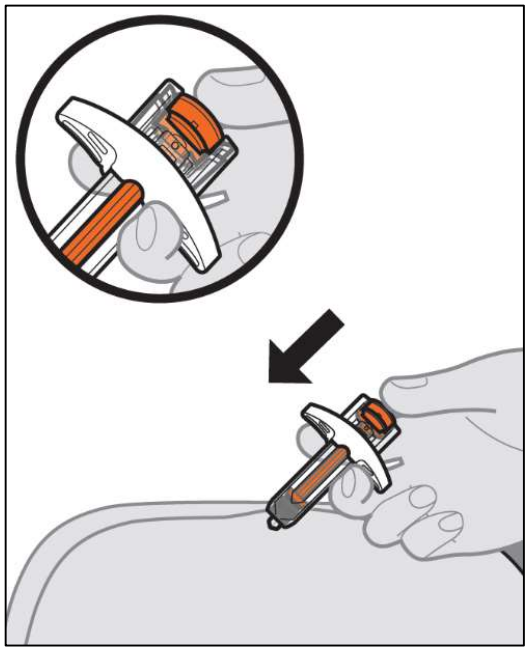

Figure G

3. Slowly inject all the medicine by gently pushing the plunger all the way down. When the plunger is all the way down, keep pressing down to be sure all the medication has been injected. If you cannot depress the plunger after you insert the needle, dispose of the pre-filled syringe in a puncture-resistant container and use a new pre-filled syringe.

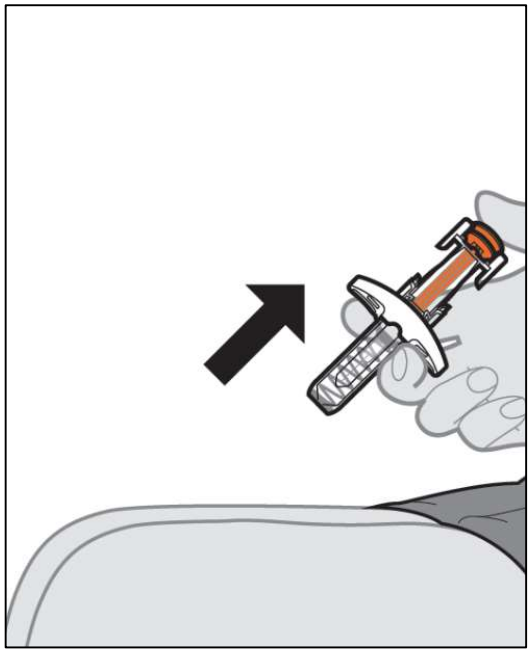

Figure H

4. Keep the plunger pushed down while you take the needle out of the skin at the same angle it was inserted.
5. Release the plunger, once the needle is completely removed from the skin, allowing the needle guard to protect the needle. Throw away the used syringe in a puncture-resistant container or sharps container.

After the Injection

There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection site with a small bandage.

Administration: Avtozma Pre-filled Pen

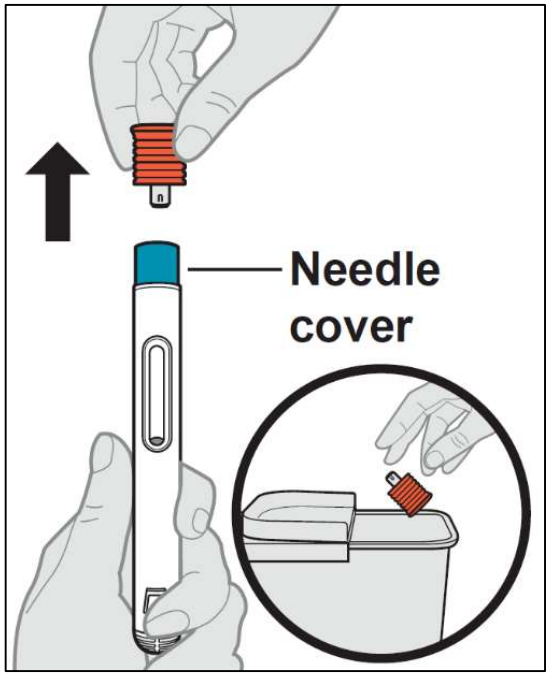

Figure I

- Hold the pre-filled pen by the injector body with the cap on top using one hand. Gently pull the cap straight off with the other hand (**See Figure I**). Dispose of the cap right away in your sharps disposal container.
- **Do not** touch the needle shield at the tip of the pre-filled pen to avoid accidental needle stick injury.
- After you remove the orange cap, the pre-filled pen is ready for use. If the pre-filled pen is not used within 3 minutes of the cap removal, the pre-filled pen should be disposed of in the sharps container and a new pre-filled pen should be used.

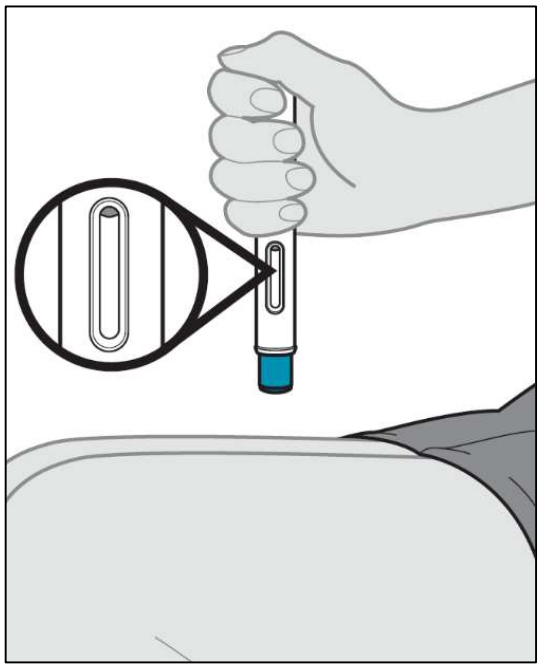

Figure J

- **Do not** re-cap the pre-filled pen.
- Hold the pre-filled pen by the injector body with the cap on top using one hand (**See Figure J**).

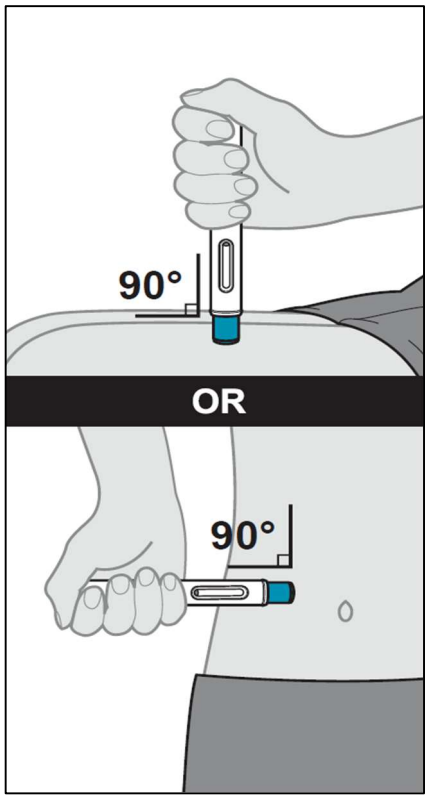

Figure K

- Without pinching or stretching the skin, place the pre-filled pen against the skin at a 90-degree angle (**See Figure K**).
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful, and the medicine may not work
- **Do not** administer into muscle or a blood vessel.

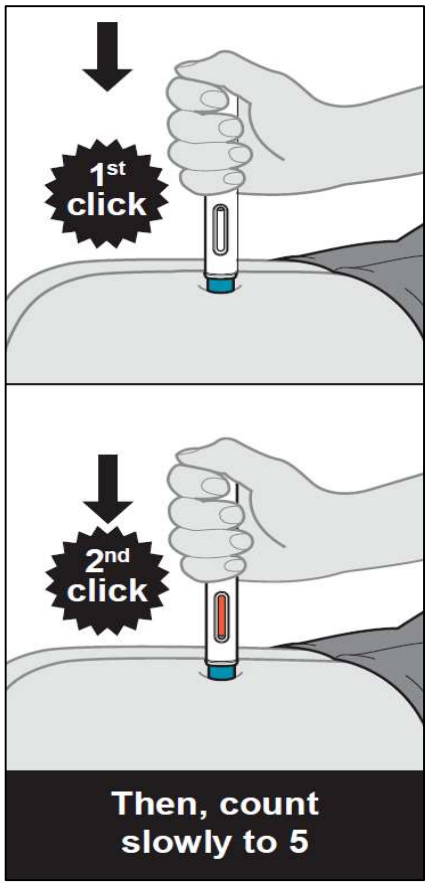

Figure L

- Firmly press the pre-filled pen into the skin to begin the injection.
- When the injection starts you will hear the 1st "click" and the orange indicator will begin to fill the window (**See Figure L**).
- Keep holding the pre-filled pen firmly against the skin and listen for the 2nd "click".
- After you hear the 2nd "click", continue to hold the pre-filled pen firmly against the skin and **count slowly to 5** to make sure you inject the full dose (**See Figure L**).
- Watch the orange indicator until it stops moving and has reached the end of the window to be sure the full dose of medicine is injected.

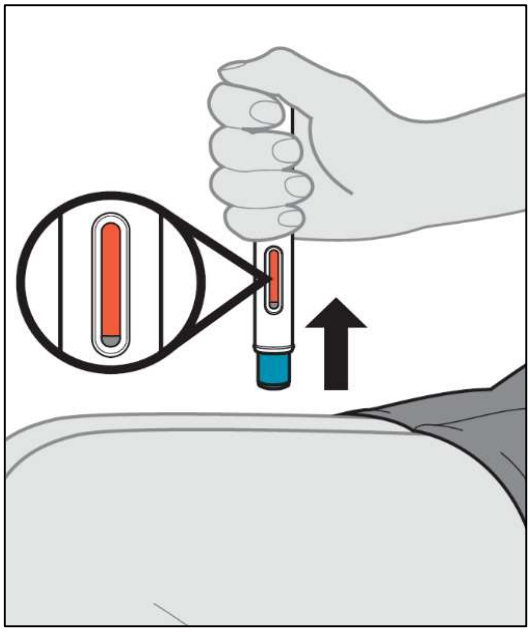

Figure M

- When the orange indicator has stopped moving, lift the pre-filled pen straight off of the injection site at a 90-degree angle to remove the needle from the skin.
- The needle cover will automatically move out and lock into place covering the needle (**See Figure M**).
- If the window has not turned completely orange or if the medicine is still injecting, this means you have not received a full dose. Carefully place the pre-filled pen into the sharps disposal container and call your healthcare provider immediately.
- **Do not** touch the needle cover of the pre-filled pen.
- **Do not** try to re-use the pre-filled pen.
- **Do not** repeat the injection with another pre-filled pen.

After the Injection:

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

6. Dispose of the Avtozma device

- **Do not** put the cap back on the Avtozma device.
- Put the used uncapped Avtozma device directly into the sharps container right away after use.
- **Do not throw away (dispose of) the device in the household trash and do not recycle it.**
- Always keep the sharps container and Avtozma device out of the sight and reach of children.

7. Record your injection

Write the date, time, and specific part of your body where you injected yourself.

Product traceability

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

Reporting of side effects

Reporting suspected adverse events or reactions after authorisation 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 (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:

Mint Health Ltd, 3/4 Cantrija Complex, Triq it-Targa,Il-Maghtab, Naxxar NXR6613 Malta

Telephone: +356 2093 9800

Email: pharmacovigilancemt@mint.com.mt

Alternatively, suspected adverse reactions should be reported to:

Malta Medicines Authority, ADR reporting form is available online at: http://www.medicinesauthority.gov.mt/adrportal, and by post or email to:

Post: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta.

Email: postlicensing.medicinesauthority@gov.mt.