For use in Ireland

Avtozma™ ▼
tocilizumab

Avtozma®▼ (tocilizumab) Healthcare Professional Brochure

Healthcare Professional Brochure for the following indications:

- Rheumatoid Arthritis (RA)
- Giant Cell Arteritis (GCA)
- Polyarticular Juvenile Idiopathic Arthritis (pJIA)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
- Chimeric Antigen Receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS)
- Coronavirus disease 2019 (COVID-19) in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

This Healthcare Professional Brochure is additional risk minimisation material and is provided by Celltrion Healthcare as a condition of the Avtozma marketing authorisation. It contains important safety information that you need to be aware of prior to prescribing Avtozma.

This Brochure must be read together with the Avtozma Summary of Product Characteristics (SmPC) and Package Leaflet, and the Avtozma Dosing Guide provided with this document (all of which are also available online at www.medicines.ie and www.hpra.ie) as they contain important safety information about Avtozma. Please read this information carefully before administering the product.

HEALTHCARE
CELLTRION

Important Risks of Avtozma (tocilizumab)

This section describes recommendations to minimise or prevent important risks of Avtozma in patients with RA, GCA, pJIA, sJIA, and CAR T cell-induced severe or life-threatening CRS.
Consult the SmPC before prescribing, preparing or administering Avtozma.

1. Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Avtozma treatment must not be initiated in patients with active or suspected infections. Inform patients and parents/guardians that Avtozma may lower their resistance to infections.

Exercise caution when considering the use of Avtozma 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.

All patients should be screened for latent tuberculosis (TB) prior to starting tocilizumab therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating therapy. 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.

Vigilance for the timely detection of serious infection is recommended for patients receiving tocilizumab as signs and symptoms of inflammation may be lessened due to suppression of acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Instruct patients and their parents/guardians to **seek immediate medical attention** if signs or symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment. Timely and appropriate measures should be implemented to address serious infections.

Patients and parents/guardians 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 Avtozma.

Administration of Avtozma should be interrupted if the patient develops a serious infection until the infection is controlled.

In COVID-19 patients, Avtozma should not be administered if they have any other concurrent severe active infection.

2. Complication of diverticulitis (including gastrointestinal perforation)

Inform patients and their parents/guardians that some patients who have been treated with Avtozma have had serious side effects in the stomach and intestines. Instruct the patient to **seek immediate medical attention** if signs or symptoms of severe, persistent abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever appear, to ensure rapid evaluation and appropriate treatment.

Avtozma should be used with caution in patients with previous history of intestinal ulceration or diverticulitis which can be associated with gastrointestinal perforation. Please refer to the Special Warnings and Precautions for use (SmPC section 4.4) for additional details.

3. Diagnosis of Macrophage Activation Syndrome in sJIA

Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. There are currently no universally accepted definitive diagnostic criteria, although preliminary criteria have been published.[1]

The differential diagnosis of MAS is broad because of the variable and multi-system abnormalities of the disorder and the non-specific nature of the most prominent clinical features, which include fever, hepatosplenomegaly and cytopenia. As a result, achieving a rapid clinical diagnosis is often difficult. Other features of MAS include neurologic abnormalities, and laboratory abnormalities such as hypofibrinogenaemia. Successful treatment of MAS has been reported with cyclosporine and glucocorticoids.[1,2,3,4]

The severity and life-threatening nature of this complication, coupled with the frequent difficulties in achieving a rapid diagnosis, necessitate appropriate vigilance and careful management of patients with active sJIA.

[1] Ravelli A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; 146: 598-604. [2] Sawhney S, et al. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001; 85: 421-6. [3] Behrens EM, et al. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007; 34: 1133-8. [4] Stéphan JL, et al. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford) 2001; 40: 1285-92.

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3.1. IL-6 inhibition and MAS

Some of the laboratory features associated with tocilizumab administration, related to IL-6 inhibition, are similar to some of the laboratory features associated with the diagnosis of MAS (such as a decline in leukocyte count, neutrophil count, platelet count, serum fibrinogen and erythrocyte sedimentation rate; all of which occur most notably within the week following tocilizumab administration). Ferritin levels frequently decrease with tocilizumab administration, but often increase with MAS and therefore, may be a useful differential laboratory parameter.[1,3]

Characteristic clinical findings of MAS (central nervous system dysfunction, haemorrhage and hepatosplenomegaly), if present, are useful in establishing the diagnosis of MAS in the context of IL-6 inhibition. Clinical experience and the clinical status of the patient, coupled with the timing of the laboratory specimens in relation to tocilizumab administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS.

4. Haematological abnormalities: thrombocytopenia and the potential risk of bleeding and/or neutropenia

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

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

Monitoring:

- **In RA and GCA patients,** neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.
- **In sJIA and pJIA patients,** neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice.

Additional recommendation for neutropenia and thrombocytopenia can be found in Special warnings and precautions for use section 4.4 of the SmPC.

Details on dose modification and additional monitoring can be found in the Posology and Method of administration section 4.2 of the SmPC.

In COVID-19 patients who develop an ANC < 1 x 10^9 / L or a platelet count < 50 x 10^3/µL, administration of treatment is not recommended. Neutrophil and platelet counts should be monitored according to current standard clinical practices, see section 4.2 of the SmPC.

5. Hepatotoxicity

Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with tocilizumab treatment (see Undesirable effects section 4.8 of the SmPC). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with tocilizumab. When clinically indicated, other liver function tests including bilirubin should be considered.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 4.8 of the SmPC). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of tocilizumab. Cases of liver failure resulting in liver transplantation have been reported. The frequency of serious hepatic injury is considered rare.

Advise patients to **seek medical help immediately** if they experience signs and symptoms of liver injury, such as tiredness, abdominal pain and jaundice.

Caution should be exercised when considering initiation of Avtozma treatment in patients with elevated ALT or AST > 1.5 times the upper limit of normal (x ULN). In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

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Monitoring:

- **In RA, GCA, pJIA and sJIA 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, Avtozma treatment should be interrupted.
- For recommended modifications, including Avtozma discontinuation, based on transaminase levels, consult the table below or see section 4.2 of the SmPC.
- When clinically indicated, other liver function tests, including bilirubin should be considered.

Patients hospitalised with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognised as a complication of severe COVID-19.

The decision to administer tocilizumab should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with tocilizumab. In COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of tocilizumab treatment is not recommended.
In COVID-19 patients, ALT/AST should be monitored according to current standard clinical practices.

5.1. Dose adjustments due to liver enzyme abnormalities

The dose adjustments due to liver enzyme abnormalities are recorded in the table below.

Laboratory value of ALT or AST	Action in patients with RA and GCA treated with pre-filled pens or syringes	Action in patients with RA treated with infused solution	Action in patients with pJIA and sJIA
>1–3-times Upper Limit of Normal (ULN)	Modify the dose of concomitant disease-modifying anti-rheumatic drugs (DMARDs) (for RA) or immunomodulatory for agents for (GCA) if appropriate. For persistent increases in this range, reduce Avtozma dose frequency to every other week injection or interrupt Avtozma until ALT or AST have normalised. Restart with weekly or every other week injection, as clinically appropriate	Modify the dose of the concomitant methotrexate if appropriate. For persistent increases in this range, reduce Avtozma dose to 4 mg/kg or interrupt Avtozma until ALT or AST have normalised. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate	Modify the dose of the concomitant metho-trexate if appropriate. For persistent increases in this range, interrupt Avtozma until ALT or AST have normalised
>3–5-times ULN	Interrupt Avtozma dosing until lower than 3-times ULN and follow recommendations for ALT/AST >1–3-times ULN. For persistent increases higher than 3 times the ULN (confirmed by repeat testing), discontinue Avtozma	Interrupt Avtozma dosing until lower than 3-times ULN and follow recommendations above for >1–3-times ULN. For persistent increases higher than 3-times ULN, discontinue Avtozma	Modify the dose of the concomitant methotrexate if appropriate. Interrupt Avtozma dosing until lower than 3-times the ULN and follow recommendations for >1–3-times ULN
Higher than 5-times ULN	Discontinue Avtozma	Discontinue Avtozma	Discontinue Avtozma. The decision to discontinue Avtozma in pJIA and sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient

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6. Elevated lipid levels and potential risk of cardiovascular/ cerebrovascular events

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

Monitoring:

- Assessment of lipid parameters should be performed in RA, GCA, sJIA and pJIA patients 4 to 8 weeks following initiation of Avtozma therapy.

Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. Please see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable Effects of the SmPC for further information.

7. Malignancies

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

Healthcare professionals should be aware of the need for timely and appropriate measures to diagnose and treat malignancies.
Please see sections 4.4 Special Warnings and Precautions for use and 4.8 Undesirable Effects of the SmPC for further information.

8. Demyelinating disorders

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

Healthcare providers should be aware of the need for timely and appropriate measures to diagnose and treat demyelinating disorders. Please see sections 4.4 Special warnings and precautions for use of the SmPC for further information.

9. Infusion/injection reactions

Serious injection/infusion site reactions may occur when administering Avtozma.

Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab.
Recommendations for management of infusion/injection reactions can be found in Special Warnings and Precautions for Use, section 4.4 of the Avtozma SmPC, as well as the Avtozma Dosing Guide.

10. Dose interruption in sJIA and pJIA

Dose adjustments due to laboratory abnormalities (sJIA and pJIA)

If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many comorbid conditions that may affect laboratory values in sJIA or pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Liver enzyme abnormalities

Laboratory Value	Action
>1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt Avtozma until ALT/AST have normalised.
>3 x ULN to 5 x ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt Avtozma dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN.
>5 x ULN	Discontinue Avtozma. The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

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Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC >1	Maintain dose.
ANC 0.5 to 1	Interrupt Avtozma dosing. When ANC increases to >1 x 10^9/L resume Avtozma.
ANC <0.5	Discontinue Avtozma. The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Low platelet count

Laboratory Value (cells x 10^3/µL)	Action
50 to 100	Modify the dose of the concomitant MTX if appropriate. Interrupt Avtozma dosing. When platelet count is >100 x 10^3/µL resume Avtozma.
<50	Discontinue Avtozma. The decision to discontinue Avtozma in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dosing frequency due to laboratory abnormalities has not been studied in sJIA or pJIA patients.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients. Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with tocilizumab. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities. Available data suggest that clinical improvement is observed within 6 weeks of initiation of tocilizumab. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

11. Dosage and administration

Dose calculations for all indications and formulations (IV and SC) can be found in the Avtozma Dosing Guide as well as section 4.2 of the SmPC.

Paediatric Patients

- The safety and efficacy of Avtozma subcutaneous formulation in children from birth to less than 1 year have not been established. No data are available.
- A change in dose should only be based on a consistent change in the patient's body weight over time.
- The pre-filled pen (PFP) should not be used to treat paediatric patients less than 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.

sJIA Patients

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General Recommendations

Before you administer Avtozma, ask the patient or parents/guardians if the patient:

- Has an infection, is being treated for an infection or has a history of recurring infections
- Has signs of an infection, such as a fever, cough or headache, or is feeling unwell
- Has herpes zoster or any other skin infection with open sores
- Has had any allergic reactions to previous medications, including Avtozma
- Has diabetes or other underlying conditions that may predispose him or her to infection
- Has tuberculosis (TB), or has been in close contact with someone who has had TB
  - As recommended for other biologic therapies in RA, sJIA, pJIA or GCA, patients should be screened for latent TB infection prior to starting Avtozma therapy. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating Avtozma
- Is taking other biological drugs to treat RA, sJIA, pJIA, GCA, or receiving atorvastatin, simvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, methylprednisolone, dexamethasone, or benzodiazepines
- Has had or currently has viral hepatitis or any other hepatic disease
- Has a history of gastrointestinal ulcers or diverticulitis
- Has recently received a vaccination or is scheduled for any vaccination
- Has cancer, cardiovascular risk factors such as raised blood pressure and raised cholesterol levels or moderate-to-severe kidney function problems
- Has persistent headaches

Pregnancy:
Female patients who are of childbearing potential must use effective contrazception during (and up to 3 months after) treatment. Avtozma should not be used during pregnancy unless clearly necessary.

Breast-feeding:
It is unknown whether Avtozma is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Avtozma should be made taking into account the benefit of breast-feeding to the child and the benefit of Avtozma therapy to the woman.

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.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events to HPRA Pharmacovigilance via www.hpra.ie. You should also report side effects to Celltrion by emailing medinfoie@celltrionhc.com or calling (01) 564 5074.
By reporting side effects you can help provide more information on the safety of this medicine.

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