For use in Ireland

Tyenne®
tocilizumab

Healthcare Professional Brochure

TYENNE for the following indications:

- Rheumatoid Arthritis [Intravenous or subcutaneous
- Giant Cell Arteritis [Subcutaneous]
- Polyarticular Juvenile Idiopathic Arthritis (also referred to as Juvenile Idiopathic Polyarthritis) [Intravenous or subcutaneous]
- Systemic Juvenile Idiopathic Arthritis [Intravenous or subcutaneous
- Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome [Intravenous]
- Treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation [Intravenous].

TYENNE 20mg/ml concentrate solution for infusion

TYENNE 162 mg solution for injection in pre-filled syringe.

TYENNE 162 mg solution for injection in pre-filled pen.

This Healthcare Professional Brochure is additional risk minimisation material and is provided by Fresenius Kabi (Ireland) Limited and is mandatory as a condition of the Marketing Authorisation in order to minimise important selected risks. It contains important safety information that you need to be aware of prior to prescribing TYENNE.

This Healthcare Professional Brochure must be read together with the TYENNE Summary of Product Characteristics and the TYENNE Dosing Guide provided with this document (and also available on www.hpra.ie) as it contains important safety information about TYENNE including Instructions for Use.

Full prescribing information can be found in the TYENNE® Summary of Product Characteristics (SmPC): **www.medicines.ie** (Ireland)

FRESENIUS KABI
caring for life

Indications and usage

TYENNE Intravenous IV

- TYENNE IV, 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, TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. TYENNE 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.
- TYENNE 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. TYENNE can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- TYENNE in combination with 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. TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- TYENNE 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.
- TYENNE 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.
- TYENNE 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

TYENNE Subcutaneous (SC) – Pre-Filled syringe (PFS)

- TYENNE SC, in combination with 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, TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. TYENNE 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.
- TYENNE 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. TYENNE can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- TYENNE in combination with 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. TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- TYENNE is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

TYENNE SC – Pre-filled pen

- TYENNE, in combination with 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, TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. TYENNE 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.
- TYENNE is indicated for the treatment of GCA in adult patients.
- TYENNE 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 (see Section 4.2 of the SmPC).
- TYENNE can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- TYENNE in combination with MTX is indicated for the treatment of 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 (see Section 4.2 of the SmPC).
- TYENNE can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Important Risks of TYENNE

Objective

This section describes recommendations to minimise or prevent important risks of TYENNE in patients with rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Consult the SmPC before prescribing, preparing or administering TYENNE.

1. Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including TYENNE. TYENNE treatment must not be initiated in patients with active or suspected infections. Administration of TYENNE should be interrupted if the patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of TYENNE 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 the patient to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving TYENNE as signs and symptoms of acute inflammation may be lessened, delaying the diagnosis. 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. Timely and appropriate measures should be implemented to address serious infections.

Inform patients and parents/guardians that TYENNE may lower the patient's resistance to infections. Instruct the patient 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.

As recommended for other biologic treatments, all patients should be screened for latent tuberculosis (TB) prior to starting TYENNE therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating TYENNE. 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 and parents/guardians of 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 TYENNE.

In COVID-19 patients, TYENNE should not be administered if they have any other concurrent severe active infection. Healthcare professionals should exercise caution when considering the use of TYENNE 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.

2. Complication of diverticulitis (including gastrointestinal perforation)

Inform patients and parents/guardians of patients that some patients who have been treated with tocilizumab 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.

TYENNE 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 MAS 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.[1-4]

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.

3.1 IL-6 inhibition and MAS

Some of the laboratory features associated with TYENNE 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 TYENNE administration). Ferritin levels frequently decrease with TYENNE 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 TYENNE administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

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

References:

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.

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

Decreases in neutrophil and platelet counts have occurred following treatment with TYENNE 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 TYENNE to date.

In patients not previously treated with TYENNE, initiation is not recommended in patients with an ANC below 2 x 10^9 /L. Caution should be exercised when considering initiation of TYENNE treatment in patients with a low platelet count (i.e. platelet count below 100 x 103 /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.

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 TYENNE treatment (see 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 TYENNE. 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 TYENNE (see section 4.8 of the SmPC). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of TYENNE. Cases of liver failure resulting in liver transplantation have been reported.

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 TYENNE 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.

Monitoring:

- **In RA, GCA, pJIA and sJIA patients,** ALT/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, TYENNE treatment should be interrupted.
- For recommended modifications including TYENNE discontinuation, based on transaminases levels see section 4.2 of the SmPC.
- For ALT or AST elevations >3 to 5 x ULN, confirmed by repeat testing, TYENNE treatment should be interrupted

Please see sections 4.2 Posology and Method of Administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable Effects of the SmPC for further information.

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 TYENNE treatment is not recommended. In COVID-19 patients, ALT/AST should be monitored according to current standard clinical practices.

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

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 TYENNE. 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 TYENNE 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. 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 TYENNE is currently unknown. Please see section 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 TYENNE.

Infusion Reactions

RA

In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 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 8/4,009 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 tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab. Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab (see section 4.4 of the SmPC for further details).

pJIA

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 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 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 RA and sJIA patients.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

sJIA

In sJIA, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion.

In the 12 week controlled phase, 4% of patients from the tocilizumab 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 12 week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but were not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (<1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial.

Injection Reactions

RA

During the 6-month controlled period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous TYENNE and the subcutaneous placebo (intravenous group) weekly injections, respectively. These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

pJIA

A total of 28.8% (15/52) pJIA patients experienced ISRs to TYENNE SC. These ISRs occurred in 44% of patients ≥30 kg compared to 14.8% of patients below 30 kg. The most common ISRs were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

sJIA

In the SC Study (WA28118), a total of 41.2% (21/51) sJIA patients experienced ISRs to TYENNE SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

GCA

In the TYENNE subcutaneous weekly group, a total of 6% (6/100) patients reported an adverse reaction occurring at the site of a subcutaneous injection. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

10. Dose interruption in sJIA and pJIA (applicable to the IV formulation & subcutaneous pre-filled syringe)

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

Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC >1	Maintain dose.
ANC 0.5 to 1	Interrupt TYENNE dosing. When ANC increases to >1 x 10^9 /L resume TYENNE.
ANC <0.5	Discontinue TYENNE. The decision to discontinue TYENNE 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/L)	Action
50 to 100	Modify the dose of the concomitant MTX if appropriate. Interrupt TYENNE dosing. When platelet count is >100 x 10^3 /μL resume TYENNE
<50	Discontinue TYENNE. The decision to discontinue TYENNE 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 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 TYENNE. 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 treatment with TYENNE. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

The safety and efficacy of TYENNE subcutaneous formulation in children with conditions other than sJIA or pJIA have not been established.

11. Dose and Administration

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

Paediatric patients

- The safety and efficacy of TYENNE 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 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..

Paediatric patients

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

Patients should report any device issues to their pharmacy to arrange for a replacement and the return of the device. Devices should be returned, and not disposed of in a sharps bin if faulty. Any adverse events associated with a device fault should be reported.

12. General Recommendations

Before you administer TYENNE, 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 are feeling unwell
- Has herpes zoster or any other skin infection with open sores
- Has had any allergic reactions to previous medications, including TYENNE
- Has diabetes or other underlying conditions that may predispose him or her to infection
- Has or has had tuberculosis (TB), or has been in close contact with someone who has had TB – RA, GCA, sJIA and pJIA patients should be screened for latent TB infection prior to starting TYENNE therapy. Patients with latent TB should be treated with standard anti mycobacterial therapy before initiating TYENNE
- Is taking other biological drugs to treat RA, sJIA, pJIA or GCA, or receiving atorvastatin or simvastatin, calcium channel blockers, dexamethasone or methylprednisolone, 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 or raised cholesterol levels or moderate to severe kidney function problems
- Has persistent headaches

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

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

13. Call for reporting

Reporting suspected adverse 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 in box below).

For full information on all possible adverse reactions please see the Summary of Product Characteristics (SmPC) or the Package Leaflet, which can be found at the EMA website (www.ema.europa.eu) or www.medicines.ie.

Reporting of side effects - ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information.

You can help by reporting any side effects you may get.

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the Package Leaflet. You can also report side effects directly via United Kingdom: Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Ireland: HPRA Pharmacovigilance Website: www.hpra.ie You should also report side effects to Fresenius Kabi by emailing pharmacovigilance.gb@fresenius-kabi.com or calling +44 (0) 1928 533 575

By reporting side effects you can help provide more

information on the safety of this medicine.

As TYENNE is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

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