Unit: Technical Assessment Unit

Public assessment report for biological products

Actemra 162mg/0.9ml

Administrative information:

Trade name of the medicinal product:	Actemra 162mg/0.9ml
INN (or common name) of the active substance(s):	Tocilizumab 162 mg/0.9ml
Manufacturer of the finished product	Vetter Pharma-Fertigung GmbH and Co. KG, Schützenstrasse 87 and 99-101, 88212 Ravensburg - Germany
Marketing Authorization holder	Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen - Germany
Applied Indication(s):	Actemra is indicated for: - Treatment of severe, active and progressive rheumatoid arthritis (RA), treatment of active systemic juvenile idiopathic arthritis (sJIA), in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA)
Pharmaceutical form(s) and strength(s):	- Solution for subcutaneous injection in prefilled syringe -The strength is 162mg/0.9ml
Route of administration	Subcutaneous (SC) injection
Approved Pack	Carton box containing 4 single use prefilled syringe of 0.9 ml solution with leaflet. -Syringe: 1 mL colorless (Type 1) Glass Barrel Syringe, stainless steel needle 26G ½ in Staked-In Needle (SIN). -Rigid needle shield: Elastomer seal with a polypropylene shell.

	-Plunger stopper: Gray Butyl rubber with a fluororesin coating. -Needle Safety Device: Two plastic sub-assemblies with a spring Polycarbonate with a metal spring -Plunger Rod: Lime green polypropylene
Registration track	**Reliance Level 1**
Type of registration (EMA/FDA – Local)	**EMA approved**

List of abbreviations:

cGMP	Current Good Manufacturing Practice
DP	Drug product
DS	Drug substance
GCA	**Giant cell arteritis**
I.V	Intravenous
IgG1	Immunoglobulin G1
IL-6R	**Interleukin-6 receptor**
KDa	Kilodalton
NSD	**needle safety device**
PFS	**Pre-filled syringe**
pJIA	**Polyarticular Juvenile Idiopathic Arthritis**
RNS	rigid needle shield
RA	Rheumatoid arthritis
SJIA	**Systemic Juvenile Idiopathic Arthritis**
TCZ	**Tocilizumab**

Table of contents

3. Non-clinical aspects…….....

4. Clinical aspect……..…

5. Benefit/risk conclusion……...

6. General Conclusion and Recommendations if any……..

Dossier initial submission and evaluation process:

-The file evaluated according to EDA regulation based on reliance pathway (Reliance level I), the company submitted the following:

-Complete CTD file.

-EMA unredacted Assessment

1. Introduction

-Actemra (tocilizumab) SC is supplied as a sterile, colorless to slightly yellowish, preservative-free liquid solution in a single-use 1 mL prefilled syringe (PFS) for subcutaneous (SC) injection, delivering 162 mg tocilizumab/0.9 mL.

-The primary container closure for Actemra SC includes a clear, pre-siliconized, pre-sterilized 1 mL glass barrel with a staked-in needle, which is sealed with a rigid needle shield (RNS) comprised of an elastomer seal with a polypropylene shell and a butyl rubber plunger stopper with a fluororesin coating. A needle safety device (NSD) is assembled with the PFS. It is not considered part of the primary container closure, as it does not directly contact the drug product and interacts only with the external surface of the syringe.

-Mechanism of action: Tocilizumab (TCZ) is a recombinant humanized anti-human interleukin-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass, which selectively binds to and inhibits the signaling of both the membrane bound and soluble forms of human IL-6R. Humanization was performed by grafting the complementary determining region (CDR) of a mouse anti-human IL-6R monoclonal antibody onto a human IgG1antibody framework. The TCZ molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and intermolecularly by disulfide linkages. Each light chain and heavy chain consist of 214 and 448 amino acids, respectively. The molecular mass of the protein moiety of the antibody is around 145 kDa. In addition to the protein moiety, N-linked glycostructures are attached to AsnH299 of the H chain. Thus, the molecular mass of the entire glycoprotein is around 149 kDa.

1. **Quality aspects:**
   - **Manufacturer(s):**

- **Drug Substance**

- The Active substance is manufactured at

-Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., BioProduction Operations Singapore, 8 Tuas, Bay Lane, 636986 - Singapore

-Genentech Inc. 1000 New Horizons Way, Vacaville, CA, 95688 – USA

- **Drug product**

- The Finished product is manufactured at Vetter Pharma-Fertigung GmbH and Co. KG, Schützenstrasse 87 and 99-101, 88212 Ravensburg - Germany

-Manufacturing of both DS and DP are performed in accordance with cGMP regulations.

- **Stability**

Drug substance:

- Approved Storage Conditions of the active substance: ≤-50°C.

-Approved shelf life for the active substance: 42 months.

Drug product:

-Approved Storage Conditions of the finished product:

Store in a refrigerator (2 – 8°C).
Do not freeze.
Don't shake
Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks at or below 30°C.
-Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

-Approved shelf life for the finished product: 36 months

2. **Non –Clinical aspect & Clinical aspect:**

- Collectively, the non-clinical data submitted bridges the previously characterized acute and chronic dosing animal safety program of Actemra using the IV route with the new intended route of SC administration. In addition, no new safety concerns, which can be addressed by animal studies using TCZ, have emerged from this change in the route of administration.

-Overall, the submitted data confirm the efficacy of SC tocilizumab compared with (IV) administration in treating rheumatoid arthritis, with sustained clinical improvements over time. The SC regimens was found to be non-inferior to the IV regimen.

-In conclusion the overall benefit/risk of Actemra SC is favorable in the treatment of active and progressive rheumatoid arthritis (RA), Giant cell arthritis (GCA), active systemic juvenile idiopathic arthritis (sJIA) and juvenile idiopathic polyarthritis (pJIA)

- **General Conclusion and Recommendations if any:**
  Based on the review of CTD modules and other supplementary documents, the product is approved.

  For more information, please visit EMA published assessment report link:

  https://www.ema.europa.eu/en/documents/assessment-report/roactemra-epar-public-assessment-report_en.pdf