Direct Healthcare Professional Communication

<Date>

RoActemra (tocilizumab) - Temporary Supply Shortage for 162 mg solution for subcutaneous injection (pre-filled syringe and pre-filled pen) and RoActemra 20 mg/mL concentrate for solution for infusion (IV) & recommendations to manage potential risk of disease flare in patients

Dear Healthcare Professional,

Roche Registration GmbH in agreement with the European Medicines Agency and the <National Authority> would like to inform you of the following:

Summary

- RoActemra (tocilizumab) is expected to be temporarily in supply shortage in **<Country>** as follows:
    - RoActemra162 mg solution for subcutaneous injection (pre-filled syringe and pre-filled pen) is expected to be temporarily in supply shortage as of **<Date>**. Re-supply is expected by **<Date>** <*modify as appropriate*>.
    - RoActemra 20 mg/mL concentrate for solution for infusion (IV) is expected to be temporarily in supply shortage as of **<Date>**. Re-supply is expected by **<Date>** <*modify as appropriate*>.
- Stopping treatment with RoActemra in case of shortage could lead to a flare-up (increased disease activity/worsening symptoms) in the following approved indications for IV and/or SC formulations: Rheumatoid Arthritis (RA) (adults), Giant Cell Arteritis (GCA) (adults), Polyarticular Juvenile Idiopathic Arthritis (pJIA) (2 years and older), Systemic Juvenile Idiopathic Arthritis (sJIA) (1 year and older).
- You should therefore re-assess the patient's current overall disease condition, treatment regimen, and the potential risk of flare (if RoActemra doses are missed for the duration of the shortage of approximately [to be completed at national level] weeks). In the case of RoActemra SC, please also consider the number of unused RoActemra pre-filled syringes/pens in the possession of the individual patient.

- *<modify as needed in agreement with local authority>* Alternative treatment options are available for patients at risk of a flare-up (please also refer to appropriate treatment guidelines <*modify as needed*>):

    - for RA, pJIA and sJIA

        -If SC is out of supply, start tocilizumab IV ~ 2 weeks after the last tocilizumab SC injection and re-introduce tocilizumab SC after shortage resolved (the next SC dose can be given at the scheduled IV dose). For RA, sarilumab SC is also authorized; consider whether transitioning the patient to this medicinal product may be appropriate.

        -If IV is out of supply, start tocilizumab SC at the next scheduled IV dose. Once the shortage is resolved, IV tocilizumab can be reintroduced ~ 2 weeks after the last SC injection.

        -If neither SC nor IV tocilizumab is available or at the healthcare professional`s discretion: consider adding/increasing the dose of conventional/biological/targeted oral DMARDs and/or glucocorticoids.

    - for GCA: as tocilizumab IV is not approved for GCA, if SC is out of supply, alternative treatment options may include re-initiating or increasing the dose of other treatments (e.g. corticosteroids).

    - for CAR-T cell-induced cytokine-release syndrome (CRS): as only tocilizumab IV is approved for CRS, if IV is out of supply please refer to CRS treatment guidance for other potential alternatives.

In some circumstances, patients may have to attend their hospital/clinic for administration of alternate treatment.

Background information and potential impact of stopping treatment

RoActemra (tocilizumab) is indicated for:

- Rheumatoid Arthritis (RA) in adult patients (SC and IV)
- Giant Cell Arteritis (GCA) in adult patients, SC only
- Polyarticular Juvenile Idiopathic Arthritis (pJIA)
    - in patients 2 years of age and older (pre-filled syringe and IV)
    - in patients 12 years of age and older (pre-filled pen)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
    - in patients 1 years of age and older (pre-filled syringe)
    - in patients 2 years of age and older (IV)
    - in patients 12 years of age and older (pre-filled pen)
- CAR-T induced Cytokine Release Syndrome (CRS) in adult patients and paediatric patients 2 years of age and older (IV only)

The purpose of this communication is to inform you about a temporary supply shortage for *<modify as needed for local shortage of IV/SC>* RoActemra 162 mg solution for subcutaneous

injection (RoActemra SC, pre-filled syringe and pre-filled pen presentations) and RoActemra 20 mg/mL concentrate for solution for infusion (RoActemra IV), and to provide options to be considered to mitigate any potential risk of flare to the patients during this supply shortage.

This supply shortage has not arisen due to any safety concern. The demand for RoActemra has been increasing at an unprecedented rate globally.

Roche has carefully considered various options for how to best manage this gap between supply and demand. For RoActemra SC there will be a controlled and staggered distribution strategy that aims to ensure no country is in shortage of RoActemra SC for more than 3 to 6 weeks. For RoActemra IV, the situation is being proactively managed on a continual basis. It is aimed to minimise impact on any individual patient. However, different countries will be impacted at different times, depending on the current inventory, and it cannot be ruled out that some countries may experience a shortage of RoActemra SC and RoActemra IV at the same time. The expected start and end dates for the supply shortage in your country are communicated both below and in the Summary section above.

A risk of "flare-up" (increased disease activity/worsening symptoms) cannot be excluded if patients miss one or more scheduled doses of RoActemra due to this temporary shortage. Alternative treatment options are available for patients at risk of flare-up as described in the Summary section above.

Roche is urgently working to increase manufacturing capacity and supply by extending the production network, and through active collaboration with external partners to maximise the production of RoActemra wherever possible with the goal of increasing the available supply globally.

Based on the current data, we expect to be in supply shortage < for Country> as follows:

- **A shortage of RoActemra SC is expected as of <Date>. Re-supply is expected by <Date>.**
- **A shortage of RoActemra IV is expected as of <Date>. Re-supply is expected by <Date>.**

Call for reporting

Health care professionals should report any adverse events suspected to be associated with the use of RoActemra (tocilizumab) to: <Insert local contact information>.

To be modified dependent on country: <Details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

Should you have any questions regarding the use of RoActemra (tocilizumab), please feel free to contact Roche at: [Insert local contact information].

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product/active substance	RoActemra (tocilizumab) 162 mg solution for subcutaneous (SC) injection (pre-filled syringe and pre-filled pen) RoActemra 20 mg/mL concentrate for solution for infusion (IV)
Marketing authorisation holder	Roche Registration GmbH
Safety concern and purpose of the communication	To inform relevant Healthcare providers (HCPs) in affected countries of the shortage of RoActemra SC and RoActemra IV, in their country and any actions to take/recommendations for mitigating the potential risk of flare to patients from treatment interruption.
DHPC recipients	Rheumatologists, paediatric rheumatologists, intensive care/emergency physicians, respiratory and infectious disease specialists, hematologists, hospital pharmacists (additionally, HCPs assessed locally as being involved in patient management)
Member States where the DHPC will be distributed	Information on countries where supply interruption of RoActemra SC/IV is expected is based on regularly updated estimates regarding supply. See Annex 1 for countries to date with anticipated shortages of RoActemra SC. See Annex 2 for countries to date with a current or anticipated shortage within the next 4 weeks of RoActemra IV. All other member states may also be impacted at a later date but accurate estimates of supply beyond the next 4 weeks cannot be made at present, due to the rapidly evolving nature of the demand and supply situation and the multiple factors affecting this. A further update on the supply situation for all member states will be provided on week commencing 25th August 2021. Each affiliate will be provided with local/national supply forecasts as soon as possible to inform discussions with local authorities on DHPC implementation.

DHPC COMMUNICATION PLAN	
Proposed tool(s)/programme for the evaluation of the DHPC effectiveness	Effectiveness of the DHPC process will be evaluated using distribution and receipt metrics to assess whether the DHPC letters were delivered to the target audience and whether they were actually received by them. The potential risk of disease flare in patients is not related to actual exposure to RoActemra but is instead solely a potential consequence of a supply shortage. Therefore, outcome indicators relating to evaluating adverse drug reactions are not considered to be appropriate for measuring effectiveness of this DHCP.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP/CMDh	**26 August 2021**
Submission of translated DHPCs to the national competent authorities for review	**27 August 2021**
Agreement of translations by national competent authorities	**02 September 2021**
Dissemination of DHPC	**03 September 2021 or later dependant on individual situation in affected country**

Annex 1

RoActemra Subcutaneous Treatment (Pre-filled syringe and/or Pre-filled pen)[1]

EU/EEA countries: Supply interruption during the second-half of 2021

Country	Projected start of supply interruption in week of	Projected end of supply interruption in week of[2]
Greece	26. Jul	23. Aug
Slovakia	26. Jul	23. Aug
Ireland	26. Jul	23. Aug
France	02. Aug	23. Aug
Bulgaria	02. Aug	23. Aug
Austria	02. Aug	30. Aug
Romania	02. Aug	30. Aug
Czech Republic	02. Aug	13. Sep
Norway	02. Aug	30. Aug
Latvia	09. Aug	30. Aug
The Netherlands	09. Aug	06. Sep
Italy	09. Aug	06. Sep
Portugal	02. Aug	30. Aug
Lithuania	09. Aug	06. Sep
Belgium	09. Aug	06. Sep
Slovenia	16. Aug	20. Sep
Finland	23. Aug	13. Sep
Estonia	23. Aug	04. Oct
Sweden	06. Sep	13. Sep
Croatia	20. Sep	01. Nov

[1] The shortage durations anticipated reflect shortage of **both** the pre-filled pen **and** pre-filled syringe SC presentations (which are interchangeable) in the country.

[2] The timelines are based on standard lead times

Annex 2

RoActemra IV Treatment (80mg, 200mg, 400mg)[1]

EU/EEA countries: Supply interruption within the next 4 weeks[2]

Country	Projected start of supply interruption in week of[3]	Projected end of supply interruption in week of
Portugal	6.Sept - 13.Sept	End of supply interruption depending on global demand evolution and approval of Samsung as new DS manufacturing site
Slovakia	6.Sept - 20.Sept	
France	13.Sept - 25.Oct	
Estonia	13.Sept - 27.Dec	

[1] The shortage start dates anticipated reflect shortage of all IV strengths (which are interchangeable) in the country.

[2] Rolling update to reflect the next 4 weeks of supply

[3] Range of anticipated shortage start depending on off-label use of Actemra IV for COVID in the respective country