Advice for administration of third primary dose COVID-19 vaccine for individuals on immunosuppressive or immunomodulating therapy

Disclaimer:

The information contained in this document is based on information on individual medicines from their Summary of Product Characteristics (SmPC), which can be accessed via https://www.medicines.org.uk/emc.[1] It should be used in conjunction with the latest specialist advice available for these medicines, and the latest advice in Chapter 14a COVID-19 of the Green Book.[2]

Care has been taken in the preparation of this document and it is believed to be an accurate reflection of the medical literature at the time of preparation. However, any person using this document is expected to interpret the information using their independent personal, medical and/or clinical judgment in the context of the individual clinical circumstances or to seek out expert advice from a specialist clinician.

Purpose:

The purpose of this document is:

- to provide clinical medicines information support to health care professionals when identifying patients who are eligible for a third primary dose of COVID-19 vaccine in accordance with the advice published by the Joint Committee on Vaccination and Immunisation (JCVI) on 1 September 2021.[3]
- to provide a list of medicines that corresponds with the groups of medicines specifically mentioned in the JVCI advice: *JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a 6-month period), T-cell co-stimulation modulators, monoclonal tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL-23 inhibitors.*
- to advise on the appropriate timing of a third primary dose of COVID-19 vaccine taking in to consideration the half-life of the medicine and expected nadir of immunosuppression as advised by JCVI, where this information is provided in the published evidence.

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Scope:

This document covers the groups of medicines named in the JCVI advice on 1 September 2021, **it is not exhaustive**. It does NOT include advice for individuals who are receiving immunosuppressive chemotherapy (including antineoplastic monoclonal antibodies) or radiotherapy for any indication. Please refer to the UK Chemotherapy Board guidance on COVID-19 vaccine for patients receiving Systemic Anti-Cancer Therapy (SACT).[4] This document also does not include advice for those who are receiving moderate or high-dose corticosteroids or non-biological oral immune modulating drugs such as methotrexate, azathioprine, 6-mercaptopurine, or mycophenolate.

For individuals on combination therapy of more than one immunosuppressant or immunomodulating medicine, advice taking into consideration the immunosuppressive effect of the additional agents should be obtained from the specialist involved in their care on a case-by-case basis.

The information provided refers only to the inactivated COVID-19 vaccines, which are authorised for use in the UK, namely Comirnaty® (Pfizer-BioNTech), Spikevax® (Moderna) and Vaxzevria® (AstraZeneca).

Introduction:

The JCVI advise that a third primary dose of COVID-19 vaccine be offered to individuals aged 12 years and over with severe immunosuppression at the time of their first or second COVID-19 vaccine doses in the primary schedules. The full advice can be accessed here.[3]

The JCVI advise that individuals on immunosuppressive or immunomodulating therapy **at the time of vaccination** include:

- those who were receiving or had received immunosuppressive therapy for a solid organ transplant in the previous 6 months
- those who were receiving or had received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a 6-month period), T-cell co-stimulation modulators, monoclonal tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL-23 inhibitors (note: this list is not exhaustive)

In general, vaccines administered during periods of minimum immunosuppression (where this is possible) are more likely to generate an effective immune response than if vaccinated when immunosuppression is greater. The JCVI advise that the third primary dose of COVID-19 vaccine should ideally be given **at least 8 weeks** after the second dose, with special attention paid to current or planned immunosuppressive therapies guided by the following principles:

- where possible, the third primary dose of vaccine should be delayed until 2 weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent
- if not possible, consideration should be given to vaccination during a treatment 'holiday' or at a nadir of immunosuppression between doses of treatment

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What advice is currently available?

The Green Book highlights that no groups of potentially immunosuppressed patients should be excluded from receiving primary doses of a COVID-19 vaccine based on their treatment or disease alone. It is, however, noted that some immunosuppressed patients may have a suboptimal response to the vaccine and should therefore continue to avoid exposure to risk of infection unless they are advised otherwise by their doctor.[2]

There is already a wealth of information available to support decisions on using COVID-19 vaccines, as follows:

- Immunisation against Infectious Disease "Green Book" latest information on COVID-19 vaccination [2]
- Specialist Pharmacy Service. Using COVID-19 vaccines in patients taking immunosuppressive medicines [5]
- MS Society consensus statement on MS treatments and COVID-19 vaccines [6]
- British Association of Dermatologists advice for Dermatology HCPs during COVID-19 pandemic [7]
- British Society for Rheumatology COVID-19 guidance [8]
- British Society of Gastroenterology COVID-19 guidance and advice [9]
- UK Chemotherapy Board guidance on COVID-19 vaccine for patients receiving Systemic Anti-Cancer Therapy (SACT) [4]
- NHS Blood and Transplant Organ Donation and Transplantation COVID-19 vaccine information [10]

As there is limited evidence on response to the COVID-19 vaccines in immunosuppressed individuals, there is also very little evidence upon which to base advice on the optimal timing of delivery. **Appendix 1** provides a list of medicines with suggested advice on the timing of the third primary dose of COVID-19 vaccination from published evidence or advice from specialist organisations with administering inactivated vaccines and immunosuppressants.

If you require further advice on interpreting this information, please contact your local Medicines Information and Advice Service in the first instance. Contact details for services in each Health Board can be accessed here.

Limitations and considerations for those using this information

The table of medicines in appendix 1 highlights when there are no timing concerns relating to administering a third primary dose of COVID-19 vaccine noted in the published evidence. The specialist pharmacy advice provides a guide where data are limited, and gives practical suggestions on when to administer the vaccine in relation to a patient's immunosuppressive therapy.

The Medicines and Healthcare products Regulatory Agency (MHRA) requests that all suspected side effects to COVID-19 vaccines are reported via the dedicated coronavirus Yellow Card site.[11]

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APPENDIX 1 – suggested advice for timing of vaccination while being treated with the immunotherapies listed in the JCVI advice – last updated 09 September 2021

This table provides best practice advice which has been extrapolated from the limited data available. Where specific advice is available in the published evidence this has been highlighted. A link to the BNF monograph for each medicine has been provided so that the dosing schedule can be checked before using the table.[12]

For some medicines, where there are no specific recommendations about timing, the practical approach is to administer the vaccine at the midpoint between scheduled treatment doses to avoid confusing side effects of the vaccine with those of the patient's treatment. For example:

- If immunotherapy treatment is a weekly dose on a Saturday, then schedule vaccination for the following Tuesday/Wednesday
- If immunotherapy treatment is every 2 weeks, then schedule vaccination for the following Saturday (7 days after immunotherapy)
- If immunotherapy treatment is every 3 weeks or less frequently, then schedule vaccination for anytime but leave a 7-day gap before the next treatment

Immunotherapy	Specialist pharmacy advice for timing of the vaccine dose to optimise response and reduce side effects
Abatacept	No specific timing issues found. Suggest scheduling vaccination for anytime but leave a 7-day gap before the next treatment
Adalimumab	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Alemtuzumab	Alemtuzumab may reduce the vaccine response so it is recommended that vaccination should be delayed for 3 months after an alemtuzumab infusion. A second course of alemtuzumab can be safely delayed by a few months to support scheduling of COVID-19 vaccination. Discuss with MS team whether it is preferable to delay treatment so that vaccination can take place. If patient chooses to get vaccinated first it is advisable to wait 2-4 weeks after the third dose before starting treatment.[6]
Anakinra	Schedule vaccination at any time
Baricitinib	Schedule vaccination at any time
Basiliximab	Ideally receive vaccination before treatment starts and wait 2 weeks after vaccination before transplantation surgery. Confirm with specialist clinician.[10]
Belimumab	No specific timing issues found. Suggest scheduling vaccination anytime but leave a 7-day gap before the next treatment
Benralizumab	No specific timing issues found. Suggest scheduling vaccination for anytime but leave a 7-day gap before the next treatment
Brodalumab	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Certolizumab pegol	SmPC states that patients can receive concurrent vaccinations.[1] Suggest scheduling vaccination midpoint between the last and next dose

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Immunotherapy	Specialist pharmacy advice for timing of the vaccine dose to optimise response and reduce side effects
Denosumab	The Royal Osteoporosis Society advise that there are no recommendations around having vaccination at different times to denosumab. If offered they can be given on the same day. Ideally, to avoid adverse effects, schedule vaccination and denosumab a week apart. Do not delay denosumab treatment.[13]
Dupilumab	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Eculizumab	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Etanercept	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Filgotinib	Schedule vaccination at any time
Golimumab	Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Guselkumab	Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Infliximab	Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Ixekizumab	Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Mepolizumab	Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Natalizumab	No reason to expect efficacy of the vaccine will be reduced by natalizumab.[6] Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Ocrelizumab	It may be beneficial to delay a first course of ocrelizumab to receive the third dose of COVID-19 vaccine, but little benefit in delaying second or third course of ocrelizumab in the hope of increasing vaccine effectiveness.[6] The MS Society advise waiting at least 12 weeks after ocrelizumab infusion before having the COVID-19 vaccination. Discuss with MS team whether it is preferable to delay treatment to allow vaccination. If patient chooses to get vaccinated first, it is advisable to wait 2-4 weeks after the third dose before starting treatment.[6]
Ofatumumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Omalizumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Ravulizumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Reslizumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Risankizumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment

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Immunotherapy	Specialist pharmacy advice for timing of the vaccine dose to optimise response and reduce side effects
Rituximab	The British Society of Rheumatology recommends:[8] • scheduling COVID-19 vaccines 2 weeks or more before rituximab treatment. • rituximab treatment should not be delayed in patients with acute severe organ-threatening multi-system disease who need urgent treatment to control their disease • if a patient is offered a date for COVID-19 vaccination, vaccinate and delay rituximab by 2 weeks if clinically appropriate • if patient on rituximab is B-cell depleted, do not delay COVID-19 vaccination until B-cells recover but vaccinate as soon as possible • for patients already on rituximab, a shared decision between clinician and patient should be made on whether to defer COVID-19 vaccination for 4-8 weeks, depending on the prevalence of COVID-19 Rituximab use for oncology indications is outside the scope of this document - Please refer to the UK Chemotherapy Board guidance.[4]
Ruxolitinb	Schedule vaccination at any time
Sarilumab	No specific timing issues found. Suggest scheduling vaccination midpoint between the last and next dose
Secukinumab	No specific timing issues found. Ideally give half way between each treatment if on an initial dosing regimen. For maintenance schedule vaccination 2 weeks before next treatment
Tocilizumab	No specific timing issues found. For patients receiving intravenous tocilizumab, suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment. For patients receiving weekly subcutaneous tocilizumab suggest scheduling vaccination midpoint between the last and next dose
Ustekinumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment
Vedolizumab	No specific timing issues found. Suggest scheduling vaccination at any time but leave a 7-day gap before the next treatment

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