LIBTAYO®
(cemiplimab)

Important Safety Information to Minimise Complications From Any Immune-Related Adverse Reactions

A Guide for Healthcare Professionals (HCPs)

REGENERON

MEDISON

This guide:

- Is for HCPs who prescribe LIBTAYO
- Must be read before prescribing and administering LIBTAYO
- Is provided to inform HCPs of the risks associated with the use of LIBTAYO and the management of adverse reactions such as immune- related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies, immune-related skin adverse reactions, immune-related nephritis, other possible immune-related adverse reactions, and infusion-related reactions
- Introduces the Patient Alert Card and Patient Guide

Abbreviated important information

LIBTAYO can increase the risk of immune-related adverse reactions, such as pneumonitis, colitis, hepatitis, endocrinopathies, skin adverse reactions, nephritis, and others

Severe and fatal immune-related adverse reactions have been observed with LIBTAYO. These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with LIBTAYO; however, immune-related adverse reactions can occur after discontinuation of LIBTAYO

Immune-related adverse reactions should be managed with LIBTAYO treatment modifications, corticosteroids, and hormone replacement therapy (for cases where clinically indicated). For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related adverse reaction and to exclude other possible causes. Depending upon the severity of the adverse reaction, LIBTAYO should be withheld or permanently discontinued

LIBTAYO can cause severe or life-threatening infusion-related reactions. Patients should be monitored for signs and symptoms of infusion-related reactions and managed with LIBTAYO treatment modifications and corticosteroids

Early recognition and appropriate management of suspected adverse reactions are needed to minimise the chances of life-threatening complications. Refer to the full LIBTAYO SmPC for complete guidance on the identification and management of suspected adverse reactions

The Patient Alert Card and Patient Guide must be given to each patient before initiating treatment with LIBTAYO. HCPs should instruct patients to whom they prescribed LIBTAYO to carry the Patient Alert Card with them at all times and to show it to every HCP at each medical visit. HCPs should instruct patients to immediately report to their HCP any symptoms of immune-related adverse reactions

Treatment modifications for immune-related adverse reactions

Adverse reaction	Severity*	Dose modification	Additional intervention
Pneumonitis	Grade 2	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with AST or ALT >3 and ≤5 × ULN or total bilirubin >1.5 and ≤3 × ULN	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥3 with AST or ALT >5 × ULN or total bilirubin >3 × ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

*Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

Grade of adverse reaction per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL†; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Hepatitis (hepatobiliary disorders—other)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately Life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

*Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADLs refer to bathing, dressing and undressing, self-feeding, using the toilet, taking medications, and not being bedridden. ADL=activities of daily living.

Treatment modifications for immune-related adverse reactions (continued)

Adverse reaction	Severity*	Dose modification	Additional intervention
Hypothyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate thyroid hormone replacement as clinically indicated
		Resume LIBTAYO when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate symptomatic management
		Resume LIBTAYO when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume LIBTAYO if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency	Grade 2 to 4	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume LIBTAYO if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 diabetes mellitus	Grade 3 or 4 (hyperglycaemia)	Withhold LIBTAYO	Initiate treatment with antihyperglycaemics as clinically indicated
		Resume LIBTAYO when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	

*Toxicity should be graded with the current version of NCI CTCAE.

Grade of adverse reaction per NCI CTCAE v5 (continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL†; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diabetes mellitus (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

*Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADLs refer to bathing, dressing and undressing, self-feeding, using the toilet, taking medications, and not being bedridden. ADL=activities of daily living; ULN=upper limit of normal.

Treatment modifications for immune-related adverse reactions (continued)

Adverse reaction	Severity*	Dose modification	Additional intervention
Skin adverse reactions	Grade 2 lasting longer than 1 week, Grade 3, or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-related skin reaction or other immune-related adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold LIBTAYO	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction or other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis with renal dysfunction	Grade 2 Creatinine increased	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 creatinine increased	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

*Toxicity should be graded with the current version of NCI CTCAE.

Grade of adverse reaction per NCI CTCAE v5 (continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash maculopapular	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL*; rash covering >30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL†		
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10%-30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10%-30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self-care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Stevens-Johnson syndrome			Skin sloughing covering <10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10%-30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	Death
Toxic epidermal necrolysis				Skin sloughing covering ≥30% BSA with associated symptoms (eg, erythema, purpura, or epidermal detachment)	Death
Nephritis (renal and urinary disorders—other)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

*Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADLs refer to bathing, dressing and undressing, self-feeding, using the toilet, taking medications, and not being bedridden.
ADL=activities of daily living; BSA=body surface area; ICU=intensive care unit.

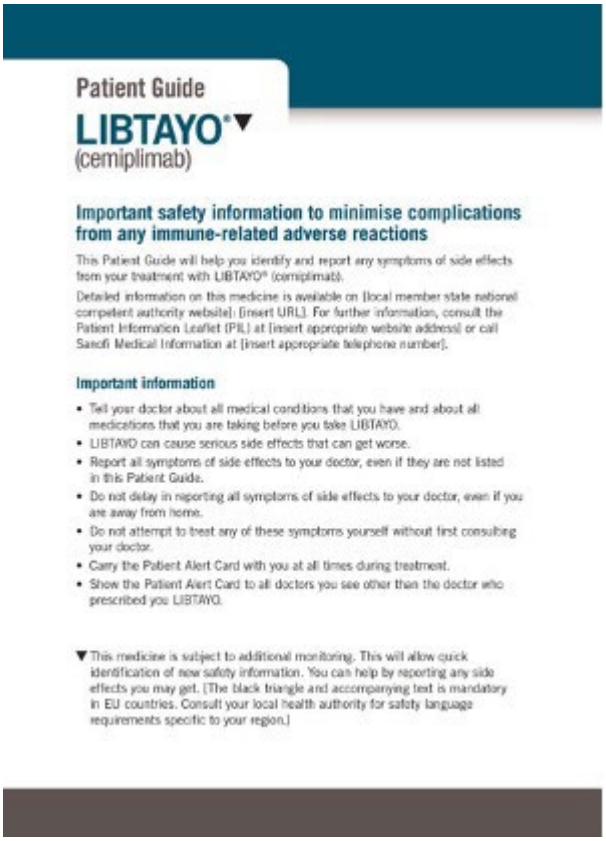
Treatment modifications for immune-related adverse reactions (continued)

<table>
<tr><th>Adverse reaction</th><th>Severity*</th><th>Dose modification</th><th>Additional intervention</th></tr>
<tr><td rowspan="3">Other immune-related adverse reactions (including but not limited to paraneoplastic encephalomyelitis, meningitis, myositis, solid organ transplant rejection, graft-vs-host disease, Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral, myocarditis, pericarditis, immune thrombocytopenic purpura, vasculitis, arthralgia, arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, keratitis, stomatitis, thyroiditis)</td><td rowspan="2">Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above</td><td>Withhold LIBTAYO</td><td>Initiate symptomatic management</td></tr>
<tr><td colspan="2">Resume LIBTAYO if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent</td></tr>
<tr><td>• Grade 4 adverse reaction (excluding endocrinopathies)
• Recurrent Grade 3 immune-related adverse reaction
• Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 weeks or longer (excluding endocrinopathies)
• Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks</td><td>Permanently discontinue</td><td>Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td rowspan="2">Infusion-related reaction</td><td>Grade 1 or 2</td><td>Interrupt or slow rate of infusion</td><td rowspan="2">Initiate symptomatic management</td></tr>
<tr><td>Grade 3 or 4</td><td>Permanently discontinue</td></tr>
</table>

*Toxicity should be graded with the current version of NCI CTCAE.
PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1.

Patient Alert Card and Patient Guide

It is important that HCPs provide the Patient Alert Card and Patient Guide to the patient and review their contents with the patient before initiating treatment with LIBTAYO. All prescribers of LIBTAYO should be familiar with the educational materials and inform the patients about the Patient Alert Card explaining what to do should they experience any symptom of immune-related adverse reactions and infusion-related reactions. HCPs should discuss the risks of LIBTAYO therapy with their patients, including the symptoms of immune-related adverse reactions and the need to report them immediately to their HCP.



Patient Guide

LIBTAYO® ▼
(cemiplimab)

Important safety information to minimise complications from any immune-related adverse reactions

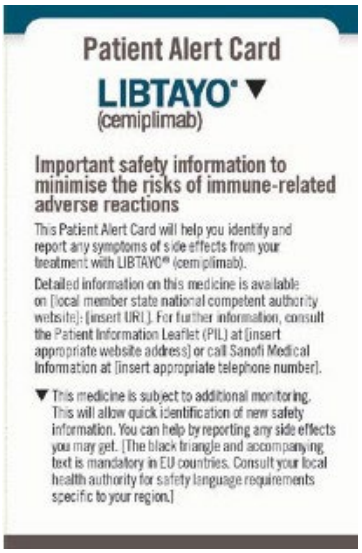
This Patient Guide will help you identify and report any symptoms of side effects from your treatment with LIBTAYO® (cemiplimab).

Detailed information on this medicine is available on [local member state national competent authority website]: [insert URL]. For further information, consult the Patient Information Leaflet (PIL) at [insert appropriate website address] or call Sanofi Medical Information at [insert appropriate telephone number].

Important information

- Tell your doctor about all medical conditions that you have and about all medications that you are taking before you take LIBTAYO.
- LIBTAYO can cause serious side effects that can get worse.
- Report all symptoms of side effects to your doctor, even if they are not listed in this Patient Guide.
- Do not delay in reporting all symptoms of side effects to your doctor, even if you are away from home.
- Do not attempt to treat any of these symptoms yourself without first consulting your doctor.
- Carry the Patient Alert Card with you at all times during treatment.
- Show the Patient Alert Card to all doctors you see other than the doctor who prescribed you LIBTAYO.

▼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. [The black triangle and accompanying text is mandatory in EU countries. Consult your local health authority for safety language requirements specific to your region.]



Patient Alert Card

LIBTAYO® ▼
(cemiplimab)

Important safety information to minimise the risks of immune-related adverse reactions

This Patient Alert Card will help you identify and report any symptoms of side effects from your treatment with LIBTAYO® (cemiplimab).

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▼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. [The black triangle and accompanying text is mandatory in EU countries. Consult your local health authority for safety language requirements specific to your region.]

HCPs should remind patients at first, and subsequent, visits to:

- Contact their HCP immediately to report symptoms of immune-related adverse reactions and infusion-related reactions
- Not treat symptoms of adverse reactions themselves Carry the Patient Alert Card with them at all times
- Ask their HCP if they have any questions about treatment

Reporting adverse events

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.

Adverse events can be reported to the Ministry of Health using the online form for adverse event reporting which can be found on the Ministry of Health website: www.health.gov.il or by using the following link: https://sideeffects.health.gov.il/

Adverse events can be also reported to Medison Pharma Ltd.
according to following contact details:
Email: PVIsrael@Medisonpharma.com Fax: 03-9234218

This guide was approved according to the guidelines ofthe Ministry of Health in February 2024.