Public Assessment Report
ETAPIDI

INFORMASI PRODUK

Nama obat	:	ETAPIDI
Bentuk sediaan	:	Larutan konsentrat untuk infus
Zat aktif	:	Tislelizumab 100 mg
Kemasan	:	Dus, 1 vial @ 10 ml
Pendaftar	:	Etana Biotechnologies Indonesia
Produsen	:	BeOne Guangzhou Biologics Manufacturing Co., Ltd., Guangzhou, China
Kategori Registrasi	:	Registrasi produk biologi yang sudah terdaftar dengan indikasi dan posologi baru
Indikasi yang diajukan (yang diajukan bercetak tebal)	:	*a. Non-Small Cell Lung Cancer (NSCLC)* *Tislelizumab in combination with Paclitaxel plus Carboplatin or Paclitaxel for Injection (Albumin Bound) plus Carboplatin as first-line treatment in adult patients with unresectable, locally advanced or metastatic squamous NSCLC.* *Tislelizumab in combination with pemetrexed and platinum chemotherapy as the first-line treatment in adult patients with unresectable, locally advanced or metastatic non-squamous NSCLC whose tumors have PD-L1 expression on >50% of tumor cells, with EGFR genomic tumor aberrations negative and ALK genomic tumor negative.* *Tislelizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) of either squamous or non-squamous histology with EGFR genomic tumor aberrations negative and ALK genomic tumor negative, that has progressed after prior platinum-based chemotherapy.* *b. Esophageal Squamous Cell Carcinoma (ESCC).* *Tislelizumab is indicated for the treatment of adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following to first-line standard chemotherapy.* ***c. Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma*** ***Tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.***
Posologi yang diajukan	:	*Tislelizumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer.* *Patients with first line non squamous NSCLC should be evaluated for treatment based on the tumor cell expression of PD-L1 (see section 14. PHARMACODYNAMICS).* *Posology* *<u>Tislelizumab monotherapy</u>* *The recommended dose of Tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks.* *<u>Tislelizumab combination therapy</u>* *The recommended dose of Tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy.* *When Tislelizumab and chemotherapy are administered on the same day, Tislelizumab should be administered before chemotherapy. The Summary of Product Characteristics (SmPC) for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as pre-medication for the prevention of chemotherapy-related adverse reactions.* *<u>Duration of treatment</u>* *Patients should be treated with Tislelizumab until disease progression or unacceptable toxicity.* *<u>Dose delay or discontinuation (see also section 7. WARNINGS AND PRECAUTIONS)</u>* *No dose reductions of Tislelizumab as monotherapy or in combination therapy are recommended. Tislelizumab should be withheld or discontinued based on safety and tolerability as described in Table 1.*

Detailed guidelines for the management of immune related- adverse reactions are described in section 7.

WARNINGS AND PRECAUTION

Table 1: Recommended treatment modification for Tislelizumab

Immune-related adverse reaction	*Severity[1]*	*Treatment modification*
Pneumonitis	*Grade 2*	*Withhold[2,3]*
	Recurrent grade 2; grade 3 or 4	*Permanently discontinue[3]*
Hepatitis	*ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN*	*Withhold[2,3]*
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	*Permanently discontinue[3]*
Rash	*Grade 3*	*Withhold[2,3]*
	Grade 4	*Permanently discontinue[3]*
Severe cutaneous adverse reactions (SCARs)	*Suspected SCARs, including SJS or TEN*	*Withhold[2,3]* *For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).*
	Confirmed SCARs, including SJS or TEN	*Permanently discontinue*
Colitis	*Grade 2 or 3*	*Withold[2,3]*
	Recurrent grade 3; grade 4	*Permanently discontinue[3]*
Myositis/ rhabdomyolysis	*Grade 2 or 3*	*Withhold[2,3]*
	Recurrent grade 3; grade 4	*Permanently discontinue[3]*
Hypothyroidism	*Grade 2, 3, or 4*	*Hypothyroidism may be managed with replacement therapy without treatment interruption.*
Hyperthyroidism	*Grade 3 or 4*	*Withhold[2]* *For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.*
Adrenal insufficiency	*Grade 2*	*Consider withholding treatment until controlled by HRT.*
	Grade 3 or 4	*Withhold[3]* *For grade 3 or 4 that has improved to grade ≤2 and is*

		controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Hypophysitis	*Grade 2*	*Consider withholding treatment until controlled by HRT.*
	Grade 3 or 4	*Withhold*[2,3] *For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.*[3]
Type 1 diabetes mellitus	*Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis*	*Withhold* *For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tislelizumab may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.*
Nephritis with renal dysfunction	*Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)*	*Withhold*[2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	*Permanently discontinue*[3]
Myocarditis	*Grade 2, 3 or 4*	*Permanently discontinue*[3]
Neurological toxicities	*Grade 2*	*Withhold*[2,3]
	Grade 3 or 4	*Permanently discontinue*[3]
Pancreatitis	*Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)*	*Withhold*[2,3]
	Grade 4	*Permanently discontinue*[3]
Other immune-related adverse reactions	*Grade 3*	*Withhold*[2,3]
	Recurrent grade 3; grade 4	*Permanently discontinue*[3]
Other adverse drug reactions		
Infusion-related reactions	*Grade 1*	*Consider pre-medication for prophylaxis of subsequent infusion reactions.* *Slow the rate of infusion by 50%*

	Grade 2	*Interrupt infusion.* *Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%*
	Grade 3 or 4	*Permanently discontinue.*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens Johnson syndrome, TEN = Toxic epidermal necrolysis, ULN = upper limit of normal

1 *Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.*

2 *Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤ 10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.*

3 *Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤ 10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.*

Special Populations

a. *Pediatric population*
   The safety and efficacy of Tislelizumab in patients aged below 18 years have not been established. No data are available.
b. *Elderly*
   No dose adjustment is needed for patients aged ≥ 65 years (see section 11. ADVERSE REACTIONS).
c. *Renal impairment*
   No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population (see section 15. PHARMACOKINETICS).
d. *Hepatic impairment*
   No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing recommendations for this population (see section 15. PHARMACOKINETICS).

Method of Administration

Tislelizumab is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection.

The first infusion should be administered over a period of 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes. The infusion should be given via an intravenous line containing a sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron in-line or add-on filter.

Other medicinal products must not be mixed or co-administered through the same infusion line.

Preparation of solution for infusion

- *Two Tislelizumab vials are required for each dose.*
- *Remove the vials from the refrigerator, taking care not to shake them.*
- *Inspect each vial visually for particulate matter and discoloration prior to administration. The concentrate is a clear to slightly opalescent, colorless to slightly yellowish solution. Do not use a vial if the solution is cloudy, or if visible particles or discoloration are observed.*

- *Invert the vials gently without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) into a syringe and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/ml. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.*

Administration

- *Administer the diluted Tislelizumab solution by infusion through an intravenous administration line with a sterile, non-pyrogenic, low-protein-binding 0.2 micron or 0.22 micron in-line or add-on filter with a surface area of approximately 10 cm².*
- *The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.*
- *Other medicinal products should not be co-administered through the same infusion line.*
- *Tislelizumab must not be administered as an intravenous push or single bolus injection.*
- *The intravenous line must be flushed at the end of the infusion.*
- *Discard any unused portion left in the vial.*
- *Tislelizumab vials are for single use only*

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PENGANTAR

ETAPIDI adalah produk biologi baru yang berisi tislelizumab. Tislelizumab adalah antibodi varian IgG4 yang berasal dari klon hibridoma murin. Antibodi ini dihasilkan menggunakan teknik hibridoma standar dari tikus BALB/c yang diimunisasi dengan PD-1 domain ekstraseluler (ECD).

Pendaftar mengajukan penambahan indikasi adenokarsinoma lambung atau *gastroesophageal junction* (G/GEJ). Kanker lambung, termasuk adenokarsinoma lambung atau *gastroesophageal junction* (G/GEJ), merupakan salah satu jenis kanker yang berkontribusi besar terhadap beban kanker secara global, berada di peringkat kelima tertinggi untuk insidensi dan menjadi salah satu penyebab utama kematian akibat kanker di dunia dengan lebih dari 1 juta kasus baru dan hampir 800 ribu kematian setiap tahunnya menurut statistik epidemiologi internasional terbaru. Tumor-tumor ini seringkali terdiagnosis pada stadium lanjut atau metastatik akibat gejala awal yang tidak spesifik, sehingga prognosisnya secara umum buruk jika hanya diobati dengan kemoterapi standar. PD-1/PD-L1 inhibitor yang digabung dengan kemoterapi telah menunjukkan perbaikan signifikan dalam survival dan respons klinis dibanding kemoterapi konvensional pada pasien dengan karsinoma adenokarsinoma G/GEJ yang lanjut dan HER2 negatif, menjadikan imunoterapi sebagai standar baru yang terbukti secara klinis untuk lini pertama pengobatan pada kondisi tersebut. Di Indonesia, dimana beban kanker secara umum terus meningkat, diagnosis sering terlambat, dan pilihan *targeted therapy* masih terbatas. Terapi inovatif seperti tislelizumab dapat memberikan pilihan pengobatan untuk meningkatkan *overall survival* dan kualitas hidup pasien dengan adenokarsinoma lambung atau G/GEJ yang memiliki ekspresi biomarker yang relevan.

ASPEK MUTU

Tidak ada evaluasi aspek mutu

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Tidak ada evaluasi data non-klinik

Studi Klinik

Studi Klinik yang diserahkan yaitu sebagai berikut:

1. **Studi fase III BGB-A317-305**

   Studi 305 merupakan uji klinis Fase 3 yang acak (1:1), *double-blind*, dan plasebo terkontrol, n=997, yang mengevaluasi tislelizumab dikombinasikan dengan platinum dan fluoropirimidin dibandingkan dengan plasebo dikombinasikan dengan platinum dan fluoropirimidin sebagai terapi lini pertama pada pasien dengan adenokarsinoma lambung atau *gastroesophageal junction* (G/GEJ) lokal lanjut yang tidak dapat direseksi atau metastasis. Uji klinis Fase 3 multinasional ini merekrut total 997 pasien dengan adenokarsinoma lambung atau gastroesophageal junction (GEJ) lokal lanjut yang tidak dapat direseksi atau metastasis dari 13 negara/wilayah di Asia Timur dan wilayah lainnya (*Rest of World*, ROW). Seluruh pasien diacak ke salah satu lengan (arm) terapi dan dimasukkan dalam *Intent-to-Treat* (ITT) *Analysis Set*. Dari jumlah tersebut, 546 pasien (54,8%) dengan skor PD-L1 ≥ 5% termasuk dalam PD-L1 *Positive Analysis Set*. Karakteristik dasar pasien dilaporkan seimbang antara kedua lengan pengobatan dalam ITT *Analysis Set*.

Hasil evaluasi terhadap studi studi di atas

- Efikasi:

  Studi RATIONALE-305 (N=997) dilakukan pada pasien kanker lambung atau gastroesophageal junction (G/GEJ) stadium lanjut lokal yang tidak dapat direseksi atau metastatik, dengan adenokarsinoma terkonfirmasi secara histologis dan mengeksklusi pasien dengan HER2-positif. Studi ini membandingkan Tislelizumab dikombinasikan dengan platinum dan fluoropirimidin vs plasebo dikombinasikan dengan platinum dan fluoropirimidin, hasil studi menunjukkan:

  - Pada ITT Analysis Set, Overall Survival (OS) Tislelizumab + kemoterapi lebih baik dibanding plasebo+kemoterapi, dengan median OS 15,0 bulan vs 12,9 bulan; *Stratified hazard ratio* sebesar 0,78 (95% CI 0,68–0,90) dan *unstratified hazard ratio* sebesar 0,79 (95% CI 0,69–0,90).
  - Analisis subgrup final berdasarkan PD-L1 score menggunakan assay VENTANA SP263 dengan algoritme *Tumour Area Positivity* (TAP), menunjukkan bahwa pada subjek dengan status PD-L1 >= 1%, memberikan hasil efikasi yang lebih baik dibandingkan subjek dengan PD-L1 < 1%:
    - Pada populasi PD-L1 TAP >=1% (sekitar 89% pasien), median OS lebih panjang signifikan pada kombinasi Tislelizumab + kemoterapi dibanding kemoterapi saja (HR 0,78; median 15,0 vs 12,8 bulan). Hasil serupa ditunjukkan oleh parameter perbaikan PFS (HR 0,78; median 6,9 vs 5,9 bulan), ORR (47,7% vs 41,1%), dan DoR (8,6 vs 7,2 bulan).
    - Pada populasi PD-L1 TAP <1%, median OS lebih panjang pada kombinasi Tislelizumab + kemoterapi dibandingkan kemoterapi saja, yaitu 15,4 vs 13,8 bulan, tetapi tidak bermakna secara statistik, dengan HR 0,98 (95% CI 0,64–1,50).

- Keamanan:
  Profil keamanan Tislelizumab konsisten dengan kelas PD-1 inhibitor. Risiko utama adalah *immune-mediated adverse reactions* (IMAR), yang dapat mengenai paru (pneumonitis), hati (hepatitis), usus (kolitis), kulit (ruam berat/SJS/TEN), endokrin (hipo/hipertiroidisme, insufisiensi adrenal, diabetes tipe 1, hipofisitis), ginjal (nefritis), serta jantung dan otot (miokarditis, perikarditis, miositis). Kejadian serius/fatal dilaporkan seperti pneumonitis, kolitis, atau emboli paru.

EVALUASI
Penilaian Manfaat – Risiko

Tislelizumab adalah antibodi monoklonal humanized IgG4 varian yang secara selektif menargetkan reseptor programmed cell death-1 (PD-1) pada permukaan limfosit T. Blokade jalur PD-1/PD-L1/PD-L2 oleh tislelizumab menghasilkan aktivasi kembali sel T, ditandai dengan peningkatan proliferasi, sekresi sitokin (seperti IL-2 dan IFN γ), serta perbaikan fungsi imun anti-tumor.

Etapidi terdaftar dengan bentuk sediaan larutan konsentrat untuk infus. Zat tambahan yang digunakan adalah *trisodium citrate dihydrate, citric acid monohydrate, l-histidine monohydrochloride monohydrate, l-histidine, trehalose dihydrate, polysorbate 20,* dan *water for injection*. Etapidi dikemas dalam vial dengan besar kemasan Dus, 1 vial @ 10 ml. Obat ini harus disimpan dalam lemari pendingin (2-8ºC) dan stabil selama 36 bulan.

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, Etapidi memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut:

1. Aspek yang menguntungkan
   a. Tislelizumab plus kemoterapi menunjukkan *overall survival* lebih baik dibanding plasebo plus kemoterapi, dengan median OS 15,0 vs 12,9 bulan, HR terstratifikasi 0,78 [95% CI: 0,68–0,90]) dan perbaikan 2,1 bulan pada median OS.
   b. Analisis subgrup pasien dengan PD-L1 ≥1% (89% pasien), kombinasi tislelizumab + kemoterapi menunjukkan median OS 15,0 vs 12,8 bulan dengan HR 0,78 (95% CI 0,67-0,90), konsisten menunjukkan manfaat survival. Tren menunjukkan semakin tinggi ekspresi PD-L1, semakin besar manfaat klinis, dengan keuntungan numerik terbesar pada PD-L1 ≥10% (median OS 22,5 vs 12,3 bulan; HR 0,57).
   c. Profil keamanan tislelizumab konsisten dengan kelas PD-1 inhibitor.

2. Aspek yang tidak menguntungkan
   a. Efek samping yang dimediasi imun lebih sering terjadi pada tislelizumab dibandingkan kelompok yang mendapat plasebo.
   b. RMP mengidentifikasi *immune mediated adverse reactions* sebagai *important identified risk* dan *reproductive & developmental toxicity* sebagai *important potential risk*.

3. Ketidak pastian dan keterbatasan (NA)

Kesimpulan evaluasi manfaat – risiko:
Secara keseluruhan Etapidi menunjukkan kemanfaatan dalam pengobatan *gastric or gastroesophageal junction (G/GEJ) adenocarcinoma*. Kejadian efek samping yang terjadi sesuai dengan profil keselamatan yang sudah dikenal dari obat studi dan rejimen kemoterapi dan tidak ada *issue* keamanan. Dengan demikian, dipertimbangkan manfaat Etapidi lebih besar dari risikonya.

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi Etapidi diterima dengan **perbaikan indikasi** menjadi sebagai berikut:

Indication

a. Non-Small Cell Lung Cancer (NSCLC)

Tislelizumab in combination with Paclitaxel plus Carboplatin or Paclitaxel for Injection (Albumin Bound) plus Carboplatin as first-line treatment in adult patients with unresectable, locally advanced or metastatic squamous NSCLC.

Tislelizumab in combination with pemetrexed and platinum chemotherapy as the first-line treatment in adult patients with unresectable, locally advanced or metastatic non-squamous NSCLC whose tumors have PD-L1 expression on >=50% of tumor cells, with EGFR genomic tumor aberrations negative and ALK genomic tumor negative.

Tislelizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) of either squamous or non-squamous histology with EGFR genomic tumor aberrations negative and ALK genomic tumor negative, that has progressed after prior platinum-based chemotherapy.

b. Esophageal Squamous Cell Carcinoma (ESCC)

Tislelizumab is indicated for the treatment of adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following to first-line standard chemotherapy.

c. Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma

Tislelizumab in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with HER-2 negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with a PD-L1 expression >1%

Posology :

Tislelizumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Posology

Tislelizumab monotherapy

The recommended dose of Tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks.

Tislelizumab combination therapy

The recommended dose of Tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy.

When Tislelizumab and chemotherapy are administered on the same day, Tislelizumab should be administered before chemotherapy. The Summary of Product Characteristics (SmPC) for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as pre-medication for the prevention of chemotherapy-related adverse reactions.

Duration of treatment

Patients should be treated with Tislelizumab until disease progression or unacceptable toxicity.

Patient selection

Prior to the use of tislelizumab for the treatment of first-line non-squamous NSCLC or first-line G/GEJ adenocarcinoma, tumour PD-L1 status must be established. Testing used in clinical practice should be adequately comparable to the testing used in pivotal trials (Ventana PD-L1 (SP263) assay)

Dose delay or discontinuation (see also section 7. WARNINGS AND PRECAUTIONS)

No dose reductions of Tislelizumab as monotherapy or in combination therapy are recommended. Tislelizumab should be withheld or discontinued based on safety and tolerability as described in Table 1.

Detailed guidelines for the management of immune related? adverse reactions are described in section 7. WARNINGS AND PRECAUTION

Table 1: Recommended treatment modification for Tislelizumab

Immune-related adverse reaction	***Severity[1]***	***Treatment modification***
Pneumonitis	*Grade 2*	*Withhold [2,3]*
	Recurrent grade 2; grade 3 or 4	*Permanently discontinue [3]*
Hepatitis	*ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN*	*Withhold [2,3]*
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	*Permanently discontinue [3]*
Rash	*Grade 3*	*Withhold [2,3]*
	Grade 4	*Permanently discontinue [3]*
Severe cutaneous adverse reactions (SCARs)	*Suspected SCARs, including SJS or TEN*	*Withhold [2,3]* *For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).*
	Confirmed SCARs, including SJS or TEN	*Permanently discontinue*
Colitis	*Grade 2 or 3*	*Withhold [2,3]*
	Recurrent grade 3; grade 4	*Permanently discontinue [3]*
Myositis/ rhabdomyolysis	*Grade 2 or 3*	*Withhold [2,3]*
	Recurrent grade 3; grade 4	*Permanently discontinue [3]*
Hypothyroidism	*Grade 2, 3, or 4*	*Hypothyroidism may be managed with replacement therapy without treatment interruption.*

Hyperthyroidism	*Grade 3 or 4*	*Withhold* [2] *For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.*
Adrenal insufficiency	*Grade 2*	*Consider withholding treatment until controlled by HRT.*
	Grade 3 or 4	*Withhold* [3] *For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.*[3]
Hypophysitis	*Grade 2*	*Consider withholding treatment until controlled by HRT.*
	Grade 3 or 4	*Withhold* [2,3] *For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tislelizumab may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.*[3]
Type 1 diabetes mellitus	*Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis*	*Withhold* *For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tislelizumab may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.*
Nephritis with renal dysfunction	*Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)*	*Withhold* [2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	*Permanently discontinue* [3]

Myocarditis	*Grade 2, 3 or 4*	*Permanently discontinue* [3]
Neurological toxicities	*Grade 2*	*Withhold* [2,3]
	Grade 3 or 4	*Permanently discontinue* [3]
Pancreatitis	*Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)*	*Withhold* [2,3]
	Grade 4	*Permanently discontinue* [3]
Other immune-related adverse reactions	*Grade 3*	*Withhold* [2,3]
	Recurrent grade 3; grade 4	*Permanently discontinue* [3]
Other adverse drug reactions		
Infusion-related reactions	*Grade 1*	*Consider pre-medication for prophylaxis of subsequent infusion reactions.* *Slow the rate of infusion by 50%*
	Grade 2	*Interrupt infusion.* *Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%*
	Grade 3 or 4	*Permanently discontinue.*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens Johnson syndrome, TEN = Toxic epidermal necrolysis, ULN = upper limit of normal

[1] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.

[2] Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤ 10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤ 10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.

Special Populations

a. Pediatric population

The safety and efficacy of Tislelizumab in patients aged below 18 years have not been established. No data are available.

b. Elderly

No dose adjustment is needed for patients aged >=65 years (see section 11. ADVERSE REACTIONS).

c. Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population (see section 15. PHARMACOKINETICS).

d. Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing recommendations for this population (see section 15. PHARMACOKINETICS).

Method of Administration

Tislelizumab is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection.

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Other medicinal products must not be mixed or co-administered through the same infusion line.