swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Tevimbra

International non-proprietary name:	tislelizumab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	100 mg / 10 ml
Route(s) of administration:	intravenous use
Marketing authorisation holder:	BeOne Medicines I GmbH
Marketing authorisation no.:	68960
Decision and decision date:	approved on 3 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental risk assessment
ESCC	Esophageal squamous cell carcinoma
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
HRQoL	Health-related quality of life
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICIs	Immune checkpoint inhibitors
Ig	Immunoglobulin
imAE	Immune-related adverse event
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
P+C	Placebo in combination with chemotherapy
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report

T+C	Tislelizumab in combination with standard chemotherapy
TAP	Tumour area positivity
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC).

2.2.2 Approved indication

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%

2.2.3 Requested dosage

Summary of the requested standard dosage:

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	17 May 2024
Formal objection	14 June 2024
Response to formal objection	20 June 2024
Formal control completed	16 July 2024
List of Questions (LoQ)	11 November 2024
Response to LoQ	10 January 2025
Preliminary decision	21 March 2025
Response to preliminary decision	2 May 2025
Labelling corrections and/or other aspects	5 June 2025
Response to labelling corrections and/or other aspects	13 June 2025

Final decision	3 July 2025
Decision	approval

3 Medical context

Globally, esophageal cancer is the seventh most common cancer. Roughly, 600,000 new cases have been reported in 2020 worldwide, and almost 550,000 deaths were estimated to be attributable to esophageal cancer in 2020.[1] The majority of cases occur in Eastern Asia and Eastern and Southern Africa, whereas in Western Europe and North America it is a less common type of cancer.[1,2] In Switzerland, there were 685 new cases of esophageal cancer (all types) in 2020, making it the 20th most common cancer type with a five-year prevalence of 9.99/100,000.[3]

Esophageal squamous cell carcinomas (ESCC) that are advanced or metastasised generally have a poor prognosis. Before the introduction of new therapy regimens, overall survival was below 1 year for patients with metastasised ESCC. The use of immune checkpoint inhibitors (ICIs) with chemotherapy has recently improved survival for this patient group.[1,4]

4 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the new indication applied for.

5 Clinical aspects

5.1 Clinical pharmacology

The clinical pharmacology profile of tislelizumab had already been characterised in various studies conducted in patients with ESCC as a second-line monotherapy. In the present application, the pharmacokinetics of tislelizumab were studied in combination with platinum-based therapy as first-line treatment. Exposure similar to that observed in patients in the pivotal second-line study was achieved. The pharmacokinetic model was not updated due to lack of data. Immunogenicity showed a similar profile (treatment-induced anti-drug antibodies and neutralising antibodies were approximately 20% and less than 1.0%, respectively). Analysis of the response to exposure showed no relationship between exposure and efficacy or safety.

5.2 Dose finding and dose recommendation

The Applicant did not submit any dose-finding studies.

Tislelizumab 200 mg was administered via intravenous infusion once every 3 weeks, which is also the approved dosage for the indication of second-line treatment of esophageal cancer in Switzerland.

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[1] Obermannova R et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2022.

[2] Abnet C. et al. Epidemiology of Esophageal Squamous Cell Cancer. Gastroenterology 2018.
WHO International Agency for Research on Cancer. Switzerland.

[3] WHO International Agency for Research on Cancer. Switzerland.
https://gco.iarc.fr/today/data/factsheets/populations/756-switzerland-fact-sheets.pdf. Accessed 15 Nov 2022

[4] Stahl M et al. Onkopedia Leitlinie Ösophaguskarzinom. 2023
NCCN Guidelines Version 4.2024 Esophageal and Esophagogastric Junction Cancers, 2022

5.3 Efficacy

The efficacy assessment was primarily based on the results from one pivotal study, BGB-A317-306, a randomised, placebo-controlled, double-blind, global Phase 3 study, to compare the efficacy and safety of tislelizumab in combination with standard chemotherapy (T+C, n = 326) to placebo in combination with chemotherapy (P+C, n = 323) when given as the first-line treatment in patients with locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC).

For further details of study design, administration, and study population please refer to the attached Information for healthcare professionals in section 8.

The primary endpoint (data cut-off: 28 February 2022) overall survival (OS) in the intention-to-treat (ITT) analysis set was met with a statistically significant and clinically meaningful improvement in favour of the experimental arm (HR 0.66, median OS 17.2 (95% CI 15.8, 20.1) vs 10.6 (95% CI 9.3, 12.19)) months.

A sequential testing hierarchy was used for the key secondary endpoints progression-free survival by the investigator in the ITT analysis set, objective response rate (ORR) by the investigator in the ITT analysis set, OS in the programmed death ligand 1 (PD-L1) TAP score ≥ 10% subgroup, and health-related quality of life (HRQoL) in the ITT analysis set. Treatment with tislelizumab plus chemotherapy also resulted in a statistically significant difference over placebo plus chemotherapy in these key secondary endpoints except for HRQoL.

Additional subgroup analyses for OS based on PD-L1 expression TAP score showed that the OS results in the ITT set were driven by the PD-L1 ≥ 5% population (HR 0.57 (95% CI: 0.44, 0.75), median OS 19.6 vs 10.0 months), and no clinically meaningful OS benefit was observed in the population whose tumours expressed a PD-L1 score < 5%.

5.4 Safety

Overall, toxicity was higher with tislelizumab combined with chemotherapy compared to placebo + chemotherapy, with an increased rate of serious adverse events (SAEs; 48.1% vs. 39.6%),AEs leading to discontinuation (31.8% vs. 22.4%), and, as expected, immune-related adverse events (imAEs; 35.2% vs. 18.7%). The rates are considered to be acceptable and in line (preferred terms) with the known safety profile of the respective drugs and the underlying disease.
Please refer to the attached Information for healthcare professionals in section 8 of this report for more details on safety.

5.5 Final clinical benefit risk assessment

Considering the clinically relevant OS benefit with tislelizumab in combination with standard chemotherapy over placebo in combination with standard chemotherapy in the population with a PD-L1 score ≥ 5% and the manageable toxicity, the final benefit-risk assessment is positive for an approval without special condition for patients with a PD-L1 expression ≥ *5%.*

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tevimbra was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Adverse effects” section for advice on the reporting of adverse reactions.

Tevimbra 100 mg / 10 ml concentrate for solution for infusion

Composition

Active substances

Tislelizumab.

Excipients

Sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20 and water for injection.
Each vial contains 16 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile concentrate).
Clear to slightly opalescent, colourless to slightly yellowish solution.
The solution has a pH of approximately 6.5 and an osmolality of approximately 270 to 330 mOsm/kg.
Each ml of concentrate for solution for infusion contains 10 mg of tislelizumab. Each vial contains 10 ml with 100 mg of tislelizumab.
Tislelizumab is an Fc-engineered humanised immunoglobulin G4 (IgG4) variant monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Indications/Uses

Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 (HER-2)-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.

Esophageal squamous cell carcinoma (ESCC)

Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumours express PD-L1 with a tumour area positivity (TAP) score ⩾ 5%

Tevimbra is indicated as monotherapy for the second-line treatment of adult patients with advanced or metastatic ESCC who have progressed on or after platinum-based systemic therapy, who have not received prior immune checkpoint inhibitor therapy.

Dosage/Administration

Tevimbra should be administered under the supervision of a physician experienced in cancer treatment.

PD-L1 testing

If specified in the indication, patient selection for treatment with Tevimbra based on the tumour expression of PD-L1 should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

Usual dosage

Tevimbra monotherapy

Second-line treatment of ESCC

The usual dose of Tevimbra is 200 mg administered every 3 weeks as an intravenous (i.v.) infusion.

Tevimbra combination therapy

First-line treatment of G/GEJ adenocarcinoma and ESCC

The recommended dose of Tevimbra is 200 mg administered by i.v. infusion every 3 weeks, in combination with chemotherapy.

When Tevimbra and chemotherapy are administered on the same day, Tevimbra should be administered before chemotherapy. The Product Information 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.
For combination treatments, reference is made to the prescribing information of the accompanying therapies; for detailed information on dosages in the studies, see "Clinical efficacy".

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Duration of treatment

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

Dose adjustment following undesirable effects/interactions

No dose reductions are recommended when using Tevimbra. Depending on the severity of the adverse drug reaction (ADR), treatment with Tevimbra must be either suspended or permanently discontinued.

The table below shows the recommended treatment modifications for managing immune-related adverse effects.

Detailed guidelines for the management of immune-related adverse effects are described in the "Warnings and precautions" section.

Recommended treatment modifications for Tevimbra

Immune-related ADR	**Severity[1]**	**Tevimbra treatment modification**
Pneumonitis	Grade 2	Suspend treatment[2,3]
	Recurrent grade 2; grade 3 or 4	Permanently discontinue treatment[3]
Hepatitis	ALT or AST >3-8 × ULN or total bilirubin >1.5-3 × ULN	Suspend treatment[2,3]
	ALT or AST >8 × ULN or total bilirubin >3 × ULN	Permanently discontinue treatment[3]
Rash	Grade 3	Suspend treatment[2,3]
	Grade 4	Permanently discontinue treatment[3]
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Suspend treatment[2,3] If a SCAR (SJS or TEN) is suspected, treatment must not be restarted until SJS/TEN has been ruled out in consultation with an appropriate specialist.
	Confirmed SCARs, including SJS or TEN	Permanently discontinue treatment[3]
Colitis	Grade 2 or 3	Suspend treatment[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue treatment[3]
Myositis/Rhabdomyolysis	Grade 2 or 3	Suspend treatment[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue treatment[3]
Hypothyroidism	Grade 2, 3 or 4	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hyperthyroidism	Grade 3 or 4	Suspend treatment[2,3] For grade 3 or 4 hyperthyroidism that has improved to grade ≤2 and is controlled with antithyroid drugs, continued treatment with Tevimbra, where indicated, may be considered after corticosteroid taper if required. Otherwise, treatment should be discontinued.[3]
Adrenal insufficiency	Grade 2	Consider suspending treatment until control is achieved with hormone replacement therapy (HRT).
	Grade 3 or 4	Suspend treatment[2,3]

Immune-related ADR	Severity[1]	Tevimbra treatment modification
		For grade 3 or 4 adrenal insufficiency that has improved to grade ≤2 and is controlled with HRT, continued treatment with Tevimbra, where indicated, may be considered after corticosteroid taper if required. Otherwise, treatment should be discontinued.[3]
Hypophysitis	Grade 2	Consider suspending treatment until control is achieved with hormone replacement therapy (HRT).
	Grade 3 or 4	Suspend treatment[2,3] For grade 3 or 4 hypophysitis that has improved to grade ≤2 and is controlled with HRT, continued treatment with Tevimbra, where indicated, may be considered after corticosteroid taper if required. Otherwise, treatment should be discontinued.[3]
Type 1 diabetes	Type 1 diabetes with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or with ketoacidosis	Suspend treatment[2,3] For grade 3 or 4 type 1 diabetes that has improved to grade ≤2 and is controlled with HRT, continued treatment with Tevimbra, where indicated, may be considered after corticosteroid taper if required. Otherwise, treatment should be discontinued.[3]
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5-3 × baseline or between 1.5-3 × ULN)	Suspend treatment[2,3]
	Grade 3 (creatinine >3 × baseline or >3-6 × ULN) Grade 4 (creatinine >6 × ULN)	Permanently discontinue treatment[3]
Myocarditis	Grade 2, 3 or 4	Permanently discontinue treatment[3]
Neurological toxicities	Grade 2	Suspend treatment[2,3]
	Grade 3 or 4	Permanently discontinue treatment[3]
Pancreatitis	Grade 3 pancreatitis or grade 3 or 4 increase in serum amylase or lipase levels (to >2 × ULN)	Suspend treatment[2,3]
	Grade 4	Permanently discontinue treatment[3]
Other immune-related ADRs	Grade 3	Suspend treatment[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue treatment[3]
Other ADRs		
Infusion-related reactions	Grade 1	Consider using premedication for prophylaxis of subsequent infusion reactions. Reduce infusion rate by 50%.
	Grade 2	Interrupt infusion.

Immune-related ADR	Severity[1]	Tevimbra treatment modification
		Resume infusion if resolved or decreased to grade 1, and reduce infusion rate by 50%.
	Grade 3 or 4	Permanently discontinue treatment[3]

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 4.03 (NCI-CTCAE v4). Hypophysitis grade is in accordance with NCI CTCAE v5.0.
[2] In patients with complete or partial resolution (grade 0 to 1), restart treatment after corticosteroid taper over at least 1 month. Permanently discontinue if complete or partial improvement does not occur within 12 weeks of initiating corticosteroid administration, or if prednisone cannot be reduced to 10 mg per day or less (or to the equivalent dose of another corticosteroid) within 12 weeks of initiating corticosteroid administration.
[3] An initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by reduction to 10 mg/day or less (or equivalent dose of another corticosteroid) over at least 1 month is recommended, except for pneumonitis, where an initial dose of 2-4 mg/kg/day is recommended.

Patients with hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment of Tevimbra is necessary in patients with mild hepatic impairment. Data from patients with severe or moderate hepatic impairment is too limited to draw conclusions for this population (see “Properties/Effects” section). A higher incidence of SAEs, including fatal SAEs, was observed in patients with mild/moderate hepatic impairment.

Patients with renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment of Tevimbra is necessary in patients with mild or moderate renal impairment. Data from patients with severe renal impairment is too limited to draw conclusions for this population (see “Properties/Actions” section).

Elderly patients

No dose adjustment of Tevimbra is required in elderly patients aged 65 years and over (see “Pharmacokinetics” section).

Children and adolescents

Tevimbra is not approved for the use in patients under 18 years .

Mode of administration

Tevimbra is for intravenous use only. The diluted solution must be administered by infusion via an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter.
The first Tevimbra infusion should be administered over 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes.
Tevimbra must not be administered as an intravenous push or single bolus injection.

For instructions on the dilution of the medicinal product before administration, see “Other information, Instructions for handling” section.

Contraindications

Hypersensitivity to the active substance or any of the excipients.

Warnings and precautions

Immune-related adverse drug reactions

Tevimbra is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed cell death receptor-1 (PD-1) or the PD-ligand 1 (PD-L1) and thus block the PD-1/PD-L1 pathway, thereby reversing inhibition of the immune response. This potentially leads to loss of peripheral tolerance and the occurrence of adverse effects. The important immune-related adverse effects listed under “Warnings and precautions” may not include all possible severe and fatal immune-related adverse effects. Immune-related adverse effects, including severe and fatal cases, have been reported in patients treated with immune checkpoint inhibitors including Tevimbra. Most immune-related adverse effects occurring during treatment with Tevimbra were reversible and could be managed by suspending treatment with Tevimbra, administering corticosteroids and/or with supportive measures. In patients whose immune-related adverse effects cannot be controlled by corticosteroid therapy, administration of other systemic immunosuppressants should be considered. Immune-related adverse effects have also been reported after the last dose of Tevimbra. Immune-related adverse effects can also occur simultaneously in several organ systems. For suspected immune-related adverse effects, adequate evaluation to confirm aetiology or exclude alternative aetiologies, including infection, should be ensured.

Immune-related pneumonitis

Cases of immune-related pneumonitis have been reported in patients treated with Tevimbra, including some with fatal outcome. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated by radiography, and infectious or disease-related causes should be excluded. Patients with immune-related pneumonitis should be managed according to the treatment modifications recommended under section “Dosage/Administration” and according to local treatment guidelines.

Immune-related hepatitis

Cases of immune-related hepatitis have been reported in patients treated with Tevimbra, including some with fatal outcome. Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function tests (LFT) should be performed at the start of treatment and at regular intervals during treatment. Patients with immune-related hepatitis should be managed

according to the treatment modifications recommended under section “Dosage/Administration” and according to local treatment guidelines.

Immune-related skin reactions

Cases of immune-related skin rash or dermatitis have been reported in patients receiving Tevimbra. Patients should be monitored for signs and symptoms of suspected skin reactions, and other causes should be excluded. Depending on the severity of adverse reactions, treatment with Tevimbra should be suspended or permanently discontinued according to the recommendations in the “Dosage/Administration” section and local treatment guidelines.

Cases of severe cutaneous adverse reactions (SCARs) including erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN), some of them with fatal outcome have been reported in patients receiving Tevimbra. Patients should be monitored for signs or symptoms of SCARs (e.g. a prodromal stage with fever, flu-like symptoms, mucosal lesions or progressive rash) and other causes should be excluded. For a suspected SCAR, treatment with Tevimbra should be suspended, and the patient should be referred to a specialized facility for assessment and treatment. If a SCAR, is confirmed, Tevimbra should be permanently discontinued (see “Dosage/Administration” section).

Immune-related colitis

Immune-related colitis has been reported in patients treated with Tevimbra. This is frequently associated with diarrhoea. Patients should be monitored for signs and symptoms of colitis. Infectious and disease related causes should be excluded. Patients with immune-related colitis should be managed according to the treatment modifications recommended under section “Dosage/Administration” and according to local treatment guidelines.

Immune-related endocrinopathies

Immune-related endocrinopathies including thyroid disorders, adrenal insufficiency and hypophysitis, which may require supportive care, have been reported during treatment with Tevimbra.
Patients with an immune-related endocrinopathy should be managed according to the treatment modifications recommended under section “Dosage/Administration” and according to local treatment guidelines.

Thyroid disorders

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients treated with Tevimbra. Thyroiditis can occur with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Patients should be monitored for changes in thyroid function (at the start

of treatment, at regular intervals during treatment and based on clinical assessment) and for clinical signs and symptoms of thyroid disorders. Hypothyroidism may be manageable with replacement therapy without interrupting treatment and without using corticosteroids. Hyperthyroidism may be treated symptomatically.

Adrenal insufficiency
Adrenal insufficiency has been reported in patients treated with Tevimbra. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and hormone replacement should be administered as clinically indicated.

Hypophysitis/hypopituitarism
Hypophysitis/hypopituitarism has been reported in patients treated with Tevimbra. Hypophysitis can cause hypopituitarism. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and hormone replacement should be administered as clinically indicated.

Type 1 diabetes mellitus
Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with Tevimbra. Patients should be monitored for signs and symptoms of hyperglycaemia or other signs and symptoms of diabetes mellitus. Insulin should be administered as clinically indicated for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (grade ≥3), treatment with Tevimbra should be suspended and anti-hyperglycaemic treatment should be administered (see “Dosage/Administration” section). Treatment with Tevimbra should be resumed when metabolic control is achieved.

Immune-related nephritis with renal dysfunction
Immune-related nephritis with renal dysfunction has been reported in patients treated with Tevimbra. Patients should be monitored for changes in renal function (increase in serum creatinine), and other causes of renal dysfunction should be excluded. Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications recommended in the “Dosage/Administration” section and according to local treatment guidelines.

Other immune-related adverse effects
Other clinically important immune-related adverse effects have been reported in patients treated with Tevimbra: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, Guillain-Barré syndrome and coeliac disease (see “Adverse effects” section).

Cases of pancreatic exocrine insufficiency have been reported during treatment with other immune checkpoint inhibitors, which may occur also during the treatment with tislelizumab.
Patients with other immune-related adverse effects should be managed according to the treatment modifications recommended under section “Dosage/Administration” and according to local treatment guidelines.

Patients with pre-existing autoimmune disease
Patients with pre-existing autoimmune disease (AID) were excluded from clinical studies with tislelizumab. Data from observational studies with immune checkpoint inhibitors indicate an increased risk of immune-mediated undesirable effects in patients with AID compared to patients without pre-existing AID. In addition, relapses of the underlying AID occurred frequently, but were mostly mild and well manageable.

Adverse effects in transplant patients
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with Tevimbra may increase the risk of rejection in solid organ transplant recipients. The benefits of treatment with Tevimbra should be weighed against the risk of possible organ rejection in these patients.

Infusion-related reactions
Severe infusion reactions (grade ≥3) have been reported in patients receiving Tevimbra. Patients should be monitored for signs and symptoms of infusion reactions.
Infusion reactions should be managed as recommended under “Dosage/Administration”.

Sodium content
This medicinal product contains 32 mg of sodium per 20 ml dose, corresponding to 1.6% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

Tevimbra is a humanised monoclonal antibody that is cleared from the circulation by catabolism. No formal pharmacokinetic interaction studies have been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug-metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not expected to affect the pharmacokinetics of Tevimbra.
The use of systemic corticosteroids and other immunosuppressants before starting treatment with Tevimbra should be avoided, except for low doses of systemic corticosteroids (prednisone 10 mg/day or equivalent dose of another corticosteroid), as they may impair pharmacodynamic activity and efficacy of tislelizumab. However, systemic corticosteroids and other immunosuppressants can be

used to treat immune-related adverse effects after starting treatment with Tevimbra (see “Warnings and precautions” section).

Pregnancy/Breast-feeding

Women of childbearing potential

Women of childbearing potential should be instructed to use effective contraception (methods that result in a pregnancy rate of less than 1%) during treatment with Tevimbra and for at least 4 months after the last administration of Tevimbra.

Pregnancy

There is no available data on the use of Tevimbra in pregnant women. Based on its mechanism of action, Tevimbra may harm the foetus.
No animal reproduction studies of tislelizumab have been conducted. However, in murine models of pregnancy, blockade of PD-1/PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in increased foetal loss.
Human IgG4 (immunoglobulins) are known to cross the placental barrier. Therefore, since tislelizumab is an IgG4 variant, it can be transmitted from the mother to the developing foetus.
Tevimbra must not be used during pregnancy unless the clinical condition of the woman requires treatment with tislelizumab.

Breast-feeding

There is no information regarding the presence of tislelizumab in human milk or its effects on the breast-fed child or on milk production. Due to the possible excretion of antibodies in breast milk, a risk to newborns/infants cannot be ruled out. A decision must be made whether to discontinue breast-feeding during treatment and for at least 4 months after the last dose of tislelizumab or to forgo treatment with Tevimbra, taking into account both the benefit of breast-feeding to the child and the benefit of treatment to the woman.

Fertility

There is no data on the effects of Tevimbra on human fertility. For data from animal studies, see “Preclinical data” section.

Effects on ability to drive and use machines

Tevimbra has a minor influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of tislelizumab (see “Adverse effects”).

Undesirable effects

Summary of the safety profile

The safety profile of Tevimbra as monotherapy is based on the pooled data set (N = 1,972) of two randomised, open-label, active-controlled studies and five open-label, single-arm studies in which 307 patients with ESCC, 639 patients with NSCLC and 1,026 patients with various other malignancies were treated with ⩾1 dose of tislelizumab.

Tevimbra was administered at a dose of 200 mg intravenously once every 3 weeks except in one of the studies, where patients received a variety of dosing regimens, including 200 mg once every 3 weeks.
Of the 1,972 patients, 37.8% were exposed for longer than 6 months and 21.8% for longer than 12 months.
The most common adverse effect (with a frequency of ≥20% with Tevimbra as monotherapy) was fatigue.
The most common grade 3/4 adverse effects (with a frequency of ≥2% with Tevimbra as monotherapy) were aspartate aminotransferase increased and fatigue.
Fatal adverse effects were pneumonitis (0.1%), hepatitis (0.05%), hepatic function abnormal (0.05%) and dyspnoea (0.05%).
For patients with ESCC from study BGB-A317-302, higher incidences of dysphagia 28 (11%) versus 20 (8.3%), esophageal obstruction 6 (2.4%) versus 1 (0.4%) and esophageal stenosis 4 (1.6%) versus 2 (0.8%) were reported in the tislelizumab arm compared to the ICC arm, respectively. The frequency of fatal TEAEs in the respiratory, thoracic, and mediastinal disorders SOC was higher in the tislelizumab arm with 5 (2.0%) events reported versus 1 (0.4%) event in the ICC arm. The 5 fatal tislelizumab events were bronchiectasis, hemoptysis, pulmonary arterial hypertension, pulmonary embolism, and pulmonary haemorrhage.

The safety profile of Tevimbra in combination with chemotherapy is based on the pooled data set (N=1,336) of two randomized, open-label, active-controlled studies, one open-label multi-cohort study and two randomized, double-blind, placebo-controlled studies with various malignancies.
Among the 1,336 patients, 56.4% were exposed to Tevimbra for 6 months and longer, and 29.3% were exposed to Tevimbra for 12 months and longer.
The most common adverse effects (reported at a frequency >20%, with Tevimbra in combination with chemotherapy were nausea, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, diarrhoea, and rash.
The most common Grade 3/4 adverse effects (reported at a frequency >2%, with Tevimbra in combination with chemotherapy) were fatigue, hypokalaemia, rash, alanine aminotransferase increased, aspartate aminotransferase increased and diarrhoea.

Fatal adverse effects were reported in 0.7% of patients and include pneumonitis (0.22%), myocarditis (0.22%), and dyspnoea (0.15%).

List of adverse effects

Adverse effects are ranked by MedDRA system organ class and frequency using the following convention:

“very common” (≥1/10)

“common” (≥1/100 to <1/10),

“uncommon” (≥1/1,000 to <1/100)

“rare” (≥1/10,000 to <1/1,000)

“very rare” (<1/10,000)

“not known” (cannot be estimated from the available data)

Adverse drug reactions with Tevimbra as monotherapy (n = 1,972) and in combination with chemotherapy (n=1336)

	Tislelizumab monotherapy n = 1 972		**Tislelizumab + chemotherapy n = 1336**	
Adverse drug reactions	**All grades (%)**	**Grades 3-4 (%)**	**All grades (%)**	**Grades 3-4 (%)**
Immune system disorders				
Sjogren’s syndrome	-	-	Uncommon	-
Immune thrombocytopenia[1]	-	-	Rare	Rare
Blood and lymphatic system disorders[24]				
Lymphocytes decreased	Very common (40.4)	Common	Very common (61.7)	Very common (14.5)
Haemoglobin decreased	Very common (39.2)	Common	Very common (81.3)	Very common (13.1)
Leukocytes decreased	Very common (14.6)	Uncommon	Very common (74.0)	Very common (18.8)
Platelets decreased	Very common (13.8)	Common	Very common (63.5)	Very common (13.6)
Neutrophils decreased	Very common (10.7)	Common	Very common (76.1)	Very common (40.2)
Haemoglobin increased	Common	Uncommon	Common	-
Lymphocytes increased	Common	Uncommon	Common	Rare
Endocrine disorders				
Hypothyroidism[2]	Very common (12.7)	Rare	Very common (14.2)	Rare
Hyperthyroidism[3]	Common	Rare	Common	-
Thyroiditis[4]	Common	-	Uncommon	Rare
Adrenal insufficiency[5]	Uncommon	Uncommon	Uncommon	Uncommon
Hypophysitis[6]	Uncommon	-	Uncommon	Rare
Metabolism and nutrition disorders				
Hyperglycaemia[7]	Common	Common	Common	Uncommon
Diabetes mellitus[8]	Uncommon	Uncommon	Common	Uncommon
Sodium decreased[9]	Very common (33.5)	Common	Very common (55.8)	Very common (11.6)
Hypokalaemia[10]	Common (	Common	Very common (17.3)	Common
Potassium increased[9]	Very common (10.9)	Uncommon	Very common (16.6)	Common
Sodium increased[9]	Common	Rare	Common	Uncommon
Nervous system disorders				
Guillain-Barré syndrome	-	-	Rare	Rare
Encephalitis[11]	-	-	Rare	Rare
Myasthenia gravis	-	-	Rare	Rare
Eye disorders				
Uveitis[12]	Uncommon	-	Uncommon	Rare
Cardiac disorders				
Myocarditis[13]	Uncommon	Uncommon	Common	Uncommon

	Tislelizumab monotherapy n = 1 972		Tislelizumab + chemotherapy n = 1336	
Adverse drug reactions	**All grades (%)**	**Grades 3-4 (%)**	**All grades (%)**	**Grades 3-4 (%)**
Pericarditis	Rare	-	Rare	Rare
Respiratory, thoracic and mediastinal disorders				
Cough	Very common (15.7)	Uncommon	Very common (11.6)	Uncommon
Dyspnoea	Common*	Common	Common	Uncommon
Pneumonitis[14]	Common*	Common	Common	Common
Gastrointestinal disorders				
Diarrhoea[15]	Very common (11.7)	Uncommon	Very common (22.6)	Common
Stomatitis[16]	Common	Uncommon	Very common (11.2)	Common
Pancreatitis[17]	Uncommon	Uncommon	Common	Common
Colitis[18]	Uncommon	Uncommon	Common	Uncommon
Coeliac disease	Rare	-	-	-
Nausea	Very common (13.3)	Uncommon	Very common (43.9)	Common
Hepatobiliary disorders				
Albumin decreased[9]	Very common (35.4)	Common	Very common (50.2)	Uncommon
Aspartate aminotransferase increased[9]	Very common (33.0)	Common	Very common (52.4)	Common
Alkaline phosphatase increased[9]	Very common (32.4)	Common	Very common (32.7)	Uncommon
Alanine aminotransferase increased[9]	Very common (30.0)	Common	Very common (44.3)	Common
Bilirubin increased[9]	Very common (17.8)	Common	Very common (30.0)	Common
Hepatitis[19]	Common*	Common	Common	Common
Blood alkaline phosphatase increased	Common	Uncommon	Common	Uncommon
Skin and subcutaneous tissue disorders				
Rash[20]	Very common (16.5)	Common	Very common (20.7)	Common
Pruritus	Very common (10.8)	-	Common	Uncommon
Severe skin reactions[21]	Uncommon	Rare	Rare	-
Vitiligo[22]	Uncommon	--	Rare	-
Stevens-Johnson Syndrome[1]	Unknown	Unknown	Unknown	Unknown
Toxic epidermal necrolysis[1]	Unknown	Unknown	Unknown	Unknown
Musculoskeletal and connective tissue disorders				
Arthralgia	Common	Uncommon	Common	Rare
Myalgia	Common	-	Common	Uncommon
Myositis[23]	Uncommon	Uncommon	Uncommon	Uncommon
Arthritis[24]	Uncommon	Uncommon	Common	Uncommon
Creatine kinase increased[9]	Very common (20.2)	Common	Very common (23.9)	Common
Renal and urinary disorders				
Nephritis[25]	Uncommon	Rare	Uncommon	Uncommon
Creatinine increased[9]	Very common (14.4)	Uncommon	Very common (20.6)	Common
General disorders and administration site conditions				
Fatigue[26]	Very common (25.4)	Common	Very common (42.8)	Common
Pyrexia	Very common (14.4)	Uncommon	Very common (19.0)	Uncommon
Injury, poisoning and procedural complications				
Infusion-related reactions[27]	Common	Uncommon	Common	Uncommon

[1] Post marketing event

[2]Hypothyroidism includes preferred terms (PTs) of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, anti-thyroid antibody increased, primary hypothyroidism, central hypothyroidism and thyroxine decreased.

	Tislelizumab monotherapy n = 1 972		Tislelizumab + chemotherapy n = 1336	
Adverse drug reactions	**All grades (%)**	**Grades 3-4 (%)**	**All grades (%)**	**Grades 3-4 (%)**

[3]Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.
[4]Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.
[5]Adrenal insufficiency includes PTs of adrenal insufficiency, glucocorticoid deficiency, immune-mediated adrenal insufficiency, and secondary adrenocortical insufficiency.
[6]Hypophysitis includes PTs of hypopituitarism and lymphocytic hypophysitis.
[7]Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.
[8]Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, and latent autoimmune diabetes in adults.
[9]The incidence in each test is based on the number of patients for whom both the baseline value and at least one post-baseline laboratory measurement were available: range: 1,891 to 1,911 patients.
[10]Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[11] Encephalitis includes PT of immune-mediated encephalitis
[12]Uveitis includes PTs of uveitis, iritis iridocyclitis and chorioretinitis.
[13]Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.
[14]Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.
[15]Diarrhoea includes PTs of diarrhoea and frequent bowel movements.
[16]Stomatitis includes PTs of stomatitis, mouth ulceration, oral mucosa erosion and aphthous ulcer.
[17]Pancreatitis includes PTs of amylase increased, lipase increased, pancreatitis, autoimmune pancreatitis and pancreatitis acute.
[18]Colitis includes PTs of colitis, immune-mediated enterocolitis and autoimmune colitis.
[19]Hepatitis includes PTs of hepatitis, hepatitis function abnormal, immune-mediated hepatitis, drug-induced liver injury, liver injury and autoimmune hepatitis.
[20]Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune-mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum, granulomatous dermatitis, nodular rash, pemphigoid and transient acantholytic dermatosis.
[21]Severe skin reaction includes erythema multiforme.
[22]Vitiligo includes PTs of vitiligo, skin hypopigmentation, skin depigmentation, and leukoderma.
[23]Myositis includes PTs of myositis, immune-mediated myositis, rhabdomyolysis, and polymyalgia rheumatica.
[24]Arthritis includes PTs of arthritis, immune-mediated arthritis and polyarthritis.
[25]Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis, tubulointerstitial nephritis, and immune-mediated nephritis.
[26]Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[27]Infusion-related reaction includes PTs of rash, infusion-related reaction, chills, rash erythematous, rhinitis allergic, urticaria, drug hypersensitivity, laryngeal oedema, rash macular, rash pruritic, swelling face, anaphylactic reaction, corneal oedema, dermatitis allergic, drug eruption, face oedema, gingival swelling, lip oedema, lip swelling, mouth swelling, pruritus allergic,

	Tislelizumab monotherapy n = 1 972		Tislelizumab + chemotherapy n = 1336	
Adverse drug reactions	**All grades (%)**	**Grades 3-4 (%)**	**All grades (%)**	**Grades 3-4 (%)**
tongue oedema and type I hypersensitivity. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock have been reported in the post-marketing setting..				
**including fatal outcomes.*				

Description of specific adverse effects and additional information

Immune-related adverse effects

The data below reflects information on adverse effects with Tevimbra as monotherapy in clinical studies. Details for the ADRs for Tevimbra when given in combination are presented if clinically relevant differences were noted in comparison to Tevimbra monotherapy.

Immune-related pneumonitis

In patients treated with Tevimbra as monotherapy, immune-related pneumonitis occurred in 96 (4.9%) of 1,972 patients, including grade 1 (20 patients, 1.0%), grade 2 (38 patients, 1.9%), grade 3 (31 patients, 1.6%), grade 4 (5 patients, 0.3%) and grade 5 (2 patients, 0.1%) events.
The median time from first dose to onset of the event was 3.0 months (range: 1.0 day to 26.2 months), and the median duration from onset of the event to resolution was 5.8 months (range: 1+ days to 33.9+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 38 patients (1.9%) and Tevimbra treatment was interrupted in 32 patients (1.6%). Seventy-four (77.1%) of the 96 patients received systemic corticosteroids. Sixty-five (87.8%) of the 74 patients received high-dose systemic corticosteroids. Pneumonitis resolved in 48 (50.0%) of the 96 patients.

Immune-related hepatitis

In patients treated with Tevimbra as monotherapy, immune-related hepatitis occurred in 24 (1.2%) of 1,972 patients, including grade 1 (2 patient, 0.1%), grade 2 (7 patients, 0.4%), grade 3 (10 patients, 0.5%), grade 4 (4 patient, 0.2%) and grade 5 (1 patients, 0.1%) events.
The median time from first dose to onset of the event was 1.3 months (range: 4 days to 34.8 months), and the median duration from onset of the event to resolution was 1.1 months (range: 6 days to 6.6 months). Tevimbra was permanently discontinued in 3 patients (0.2%) and Tevimbra treatment was interrupted in 13 patients (0.7%).
18 (75.0%) of the 24 patients received systemic corticosteroids. Thirteen (72.2%) of the 18 patients received high-dose systemic corticosteroids (defined as a dose ≥40 mg/day of prednisone or equivalent). Two (8.3%) of the 24 patients received another immunosuppressive treatment. Hepatitis resolved in 17 (70.8%) of the 24 patients.

Immune-related adverse skin reactions

In patients treated with Tevimbra as monotherapy, immune-related adverse skin reactions occurred in 301 (15.3%) of 1,972 patients, including grade 1 (213 patients, 10.8%), grade 2 (70 patients, 3.5%), grade 3 (17 patients, 0.9%) and grade 4 (1 patients, 0.1%) events.

The median time from first dose to onset of the event was 1.5 months (range: 1 day to 27.6 months). The median duration from onset of the event to resolution was 1.9 months (range: 1 day to 51.5+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 2 patients (0.1%) and Tevimbra treatment was interrupted in 18 patients (0.9%).
Thirty (10.0%) of the 301 patients received systemic corticosteroids. Thirteen (43.3%) of the 30 patients received high-dose systemic corticosteroids. One out of 301 patients (0.3%) received another immunosuppressive treatment. Adverse skin reactions resolved in 190 (63.1%) of the 301 patients. Cases of SJS and TEN have been reported from post-marketing experience, including some with fatal outcome (see section “Dosage/Administration” and “Warnings and Precautions”).

Immune-related colitis

In patients treated with Tevimbra as monotherapy, immune-related colitis occurred in 16 (0.8%) of 1,972 patients, including grade 1 (2 patients, 0.1%), grade 2 (8 patients, 0.4%) and grade 3 (6 patients, 0.3%) events.
The median time from first dose to onset of the event was 6.8 months (range: 12 days to 28.2 months), and the median duration from onset of the event to resolution was 23.0 days (range: 2 day to 6.5 months,). Tevimbra was permanently discontinued in 4 patients (0.2%) and Tevimbra treatment was interrupted in 5 patients (0.3%).
Twelve of the 16 patients (75%) received systemic corticosteroids. Eight (66.6%) of the 12 patients received high-dose systemic corticosteroids. Two (12.5%) of the 12 patients received another immunosuppressive treatment. Colitis resolved in 15 (93.8%) of the 16 patients.

Immune-related myositis/rhabdomyolysis

In patients treated with Tevimbra as monotherapy, immune-related myositis/rhabdomyolysis occurred in 15 (0.8%) of 1,972 patients, including grade 1 (6 patients, 0.3%), grade 2 (5 patients, 0.3%), grade 3 (4patients, 0.2%) and grade 4 (4 patients, 0.2%) events.
The median time from first dose to onset of the event was 1.6 months (range: 15.0 days to 22.3 months), and the median duration from onset of the event to resolution was 43.0 days (range: 5.0 days to 5.2 months, Tevimbra was permanently discontinued in 4 patients (0.2%) and Tevimbra treatment was interrupted in 8 patients (0.4%).
Eight (53.3%) of 15 patients received systemic corticosteroids. Five (62.5%) of the 8 patients received high-dose systemic corticosteroids. One patient received immunosuppressive treatment.
Myositis/rhabdomyolysis resolved in 11 (73.3%) of the 15 patients.

Immune-related endocrinopathies

Thyroid disorders

Hypothyroidism

In patients treated with Tevimbra as monotherapy, immune-related hypothyroidism occurred in 250 (12.7%) of 1,972 patients, including grade 1 (115 patients, 5.8%), grade 2 (134 patients, 6.8%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 3.4 months (range: 1 day to 29.0 months). The median duration from onset of the event to resolution was 15.2 months (range: 1+ day to 48.5+ months.; + denotes a censored observation). Tevimbra was not permanently discontinued in any patient, and Tevimbra treatment was interrupted in 7 patients (0.4%). Two (0.8%) of the 250 patients received systemic corticosteroids. No patient received high-dose systemic corticosteroids. 158 patients received hormone replacement therapy. Hypothyroidism resolved in 79 (31.6%) of the 250 patients.

Hyperthyroidism

In patients treated with Tevimbra as monotherapy, hyperthyroidism occurred in 95 (4.8%) of 1,972 patients, including grade 1 (77 patients, 3.9%), grade 2 (17 patients, 0.9%) and grade 3 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 2.1 months (range: 6 days to 25.5 months). The median duration from onset of the event to resolution was 1.8 months (range: 5 days to 48.4+ months. + denotes a censored observation). Tevimbra was permanently discontinued in 1 patient (0.1%) and Tevimbra treatment was interrupted in 4 patients (0.2%).

One (1.1%) of the 95 patients received systemic corticosteroids (not high dose). Fourteen (14.7%) of the 95 patients received hormone replacement therapy. Hyperthyroidism resolved in 72 (75.8%) of the 95 patients. The median duration for all resolved events was 1.4 months (range: 5 days to 22.1 months).

Thyroiditis

In patients treated with Tevimbra as monotherapy, immune-related thyroiditis occurred in 24 (1.2%) of 1,972 patients, including grade 1 (14 patients, 0.7%) and grade 2 (10 patients, 0.5%) events.

The median time from first dose to onset of the event was 2.0 months (range: 20 days to 20.6 months). The median duration from onset of the event to resolution was 5.6 months (range: 20 days to 43.9+ months. + denotes a censored observation). Tevimbra was not permanently discontinued in any patient, and Tevimbra treatment was interrupted in 3 patients (0.2%).

Two (8.3%) of the 24 patients received systemic corticosteroids. Thirteen (54.2%) of the 24 patients received hormone replacement therapy. None of the 24 patients received high-dose systemic

corticosteroids. Thirteen (54.2%) of the 24 patients received hormone replacement therapy. Thyroiditis resolved in 10 (41.7%) of the 24 patients.

Adrenal insufficiency

In patients treated with Tevimbra as monotherapy, immune-related adrenal insufficiency occurred in 8 (0.4%) of 1,972 patients, including grade 2 (5 patients, 0.3%), grade 3 (2 patients, 0.1%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 7.3 months (range: 1.3 months to 16.9 months). The median duration from onset of the event to resolution was not evaluable (range: 1 month to 27.9+ months. + denotes a censored observation). Tevimbra was not permanently discontinued in any patient, and Tevimbra treatment was interrupted in 7 patients (0.4%). All 8 patients received systemic corticosteroids. Three (37.5%) of the 8 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 2 (25.0%) of the 8 patients.

Hypophysitis

In patients treated with Tevimbra as monotherapy, hypopituitarism (grade 2) occurred in 4 (0.2%) of 1,972 patients receiving Tevimbra.

The median time from first dose to onset of the event was 5.5 months (range: 22 days to 9.0 months). The median duration from onset to resolution was not evaluable (range: 91+ days to 23.3+ months. + denotes a censored observation). Tevimbra was not permanently discontinued in any patient and Tevimbra treatment was interrupted in 1 patient (0.1%).

Three (75%) of the 4 patients received systemic corticosteroids. The median duration for steroid treatment was not evaluable (3.0 days to 23.1 months). One (33.3%) of the 3 patients received high-dose systemic corticosteroids. Hypopituitarism did not resolve in any of the 4 patients at the time of data cut-off.

Type 1 diabetes mellitus

In patients treated with Tevimbra as monotherapy, type 1 diabetes mellitus occurred in 18 patients (0.9%), including grade 1 (2 patient, 0.1%), grade 2 (8 patients, 0.4%), grade 3 (7 patients, 0.4%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 5.3 months (range: 8 days to 33.1 months). The median duration from onset of the event to resolution was 3.3 months (range: 2 days to 30.1+ months, + denotes a censored observation with ongoing events at the time of the analysis). Tevimbra was permanently discontinued in 3 (0.2%) of the patients and Tevimbra treatment was interrupted in 3 (0.2%) patients.

Type 1 diabetes mellitus resolved in 5 (27.8%) of 18 patients. The median duration for all resolved events was 27.5 days (range: 2 days to 3.6 months). Twelve (66.7%) patients received insulin therapy for type 1 diabetes mellitus.

Immune-related nephritis and renal dysfunction

In patients treated with Tevimbra as monotherapy, immune-related nephritis and renal dysfunction occurred in 6 (0.3%) of 1,972 patients, including grade 1 (2 patient, 0.1%), grade 2 (3 patients, 0.2%), grade 3 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 3.1 months (range: 15 days to 34.5 months). The median duration from onset of the event to resolution not evaluable (range: 9+ days to 19.4+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 1 patient (0.1%) and Tevimbra treatment was interrupted in 3 patients (0.2%).

Three (50.0%) out of 6 patients received high-dose systemic corticosteroids. Seven (70%) of the 10 patients received high-dose systemic corticosteroids. One (20.0%) of the 6 patients received immunosuppressive treatment. Immune-related nephritis and renal dysfunction resolved in 2 (33.3%) of the 6 patients.

Immune-related myocarditis

In patients treated with Tevimbra as monotherapy, immune-related myocarditis occurred in 13 (0.7%) of 1,972 patients, including grade 1 (5 patient, 0.3%), grade 2 (4 patients, 0.2%), grade 3 (3 patients, 0.2%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14.0 days to 6.1 months), and the median duration from onset of the event to resolution was 5.1 months (range: 4.0 days to 26.4+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 7 patients (0.4%) and Tevimbra treatment was interrupted in 6 patients (0.3%).

Eight (61.5%) of the 13 patients received systemic corticosteroids with a median initial dose of 75 mg/day (range: 20.0 to 200.0 mg/day) for a median duration of 26.0 days (range: 1.0 day to 2.4 months). Six (75%) of the 8 received high-dose corticosteroids (defined as a dose $\geqslant$40 mg/day of prednisone or equivalent). One (7.7%) of the 13 patients received immunosuppressive treatment. Myocarditis resolved in 7 (53.8%) of the 13 patients. The median duration for all resolved events was 3.0 months (range: 4.0 days to 15.6 months).

In patients treated with Tevimbra in combination with chemotherapy, grade 5 immune-related myocarditis occurred in 3 (0.3%) of 1336 patients.

Infusion-related reactions

In patients treated with Tevimbra as monotherapy, infusion-related reactions occurred in 99 (5.0%) of 1,972 patients, including grade 3 (2 patients, 0.1%) and grade 4 (1 patient, 0.1%). Twenty-six (26.3%) of the 99 patients were treated with corticosteroids.

Tevimbra was permanently discontinued in 4 (0.2%) patients and Tevimbra treatment was interrupted in 15 patients (0.8%).

Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post-marketing setting.

Immunogenicity

Of 2,386 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks, the incidence of treatment-emergent ADA was 16.3% among 1,424 evaluable patients in the monotherapy studies and 23.4% among 962 evaluable patients in the combination therapy studies. Neutralizing antibodies (Nabs) were detected in 24 (1.0%) patients. The incidence of neutralizing antibodies was 0.8% among the 1424 evaluable patients in the monotherapy studies and 1.4% among the 962 evaluable patients in the combination therapy studies. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance, however, the presence of treatment-emergent ADA against tislelizumab appears to have no clinically relevant impact on pharmacokinetics.. The impact on efficacy cannot be fully characterized.

Overall, higher incidences of ⩾ grade 3 TEAEs (72.2% vs. 60.1%), serious TEAEs (44.4% vs. 37.6%), and grade 5 TEAEs (7.3% vs. 5.9%) were observed in pooled ADA-positive patients in Tevimbra arm compared to pooled ADA-negative patients.

Elderly patients

No overall differences in safety were observed with tislelizumab as monotherapy or in combination with chemotherapy between patients aged < 65 years and patients aged between 65 and 74 years. Data for patients aged 75 years and above are too limited to draw conclusions.

In patients ≥ 65 years treated with Tevimbra in combination with chemotherapy, grade 5 TEAEs occurred in 8.4% of patients. In Study BGB-A317-306, a higher incidence of grade 5 TEAEs was observed in older patients (⩾ 65 years) receiving Tevimbra in combination with chemotherapy compared with those aged < 65 years (10.7% vs. 5.7%).

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals

are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

Overdose

There is no information on overdose with tislelizumab. No cases of overdose have been reported in clinical studies. In case of overdose, patients should be monitored for signs and symptoms of adverse effects, and appropriate symptomatic treatment instituted immediately.

Properties/Actions

ATC code

L01FF09

Mechanism of action

Binding of the PD-1 ligands PD-L1 and PD-L2 to the PD-1 receptor found on T cells leads to inhibition of T cell proliferation and cytokine production. Up-regulation of PD-1 ligands occurs in some tumours, and signalling via this pathway can contribute to inhibition of active T cell immune surveillance of tumours.
Tislelizumab is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1 with high specificity and affinity (KD = 0.15 nM). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling and enhancing the functional activity in T cells in *in vitro* cell-based assays. Tislelizumab does not bind to Fc gamma receptors (FcγRs) and *C1q*, and therefore does not induce antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) or complement-dependent cytotoxicity (CDC). In addition, tislelizumab demonstrated decreased tumour growth in several human cancer allogeneic xenograft models and a human PD-1 transgenic mouse model.

Pharmacodynamics

Clinical efficacy

First-line treatment of gastric or gastroesophageal junction (G/GEJ) adenocarcinoma in combination with platinum and fluoropyrimidine-based chemotherapy

BGB-A317-305 is a randomised, multicentre, double-blind, placebo-controlled phase III study comparing the efficacy and safety of Tevimbra plus platinum and fluoropyrimidine-based chemotherapy versus placebo plus platinum and fluoropyrimidine-based chemotherapy as first-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma.

The study included only patients with histologically confirmed adenocarcinoma and with no prior systemic therapy for advanced disease. Patients were enrolled regardless of their tumour PD-L1 expression level.
PD-L1 expression was evaluated using TAP (tumour area positivity) score, defined as the total percentage of the tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining at any intensity and tumour-associated immune cells with PD-L1 staining at any intensity, as visually estimated using the VENTANA PD-L1 (SP263) Assay.

The study excluded patients who had squamous cell or undifferentiated or other histological type G/GEJ cancer; patients who had known HER-2 positive tumours; patients who had active leptomeningeal disease or uncontrolled brain metastasis; patients with active autoimmune disease or history of autoimmune disease that may relapse, patients who have previously been treated with an anti-PD-(L)1, anti-PD-L2 antibody or with another drug that acts on the checkpoint or T-cell co-stimulation pathway.

Randomisation was stratified by geographical region (China [including Taiwan] versus Japan and South Korea versus rest of the world [ROW, including US and Europe]), PD-L1 expression (PD-L1 score ≥5% versus PD-L1 score <5%), presence of peritoneal metastasis (yes versus no) and ICC option (oxaliplatin plus capecitabine versus cisplatin plus 5-FU).

Patients were randomised (1:1) to receive tislelizumab 200 mg every 3 weeks or placebo in combination with platinum and fluoropyrimidine-based chemotherapy on a 21-day cycle. Tislelizumab (or placebo) was administered until disease progression or unacceptable toxicity.

Chemotherapy consisted of:
- oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1 000 mg/m^2 orally twice daily for 14 consecutive days, repeated every 3 weeks. Oxaliplatin was administered for up to 6 cycles and capecitabine was administered as maintenance therapy at investigator's discretion until disease progression or unacceptable toxicity.

or

- cisplatin 80 mg/m² IV on day 1, and 5-FU 800 mg/m^2/day by continuous IV infusion over 24 hours daily on days 1 to 5, repeated every 3 weeks. Cisplatin and 5-FU were given for up to 6 cycles.

Cross-over between treatment arms was not allowed.

The primary efficacy endpoint was overall survival (OS) in the PD-L1 Positive Analysis Set (PD-L1 score ≥5%). The most important secondary efficacy endpoint was PFS.
Tumour assessment was performed approximately every 6 weeks during the first 48 weeks and thereafter approximately every 9 weeks.

A total of 997 patients were randomised to either the tislelizumab + chemotherapy arm (n = 501) or the placebo + chemotherapy arm (n = 496). Of the 997 patients, 546 (54.8%) had PD-L1 score ≥5% (tislelizumab + chemotherapy: n = 274; placebo + chemotherapy: n = 272).

The baseline characteristics for the ITT population were: median age of 61 years (range: 23 to 86), 34.5% age 65 years or older; 69.4% male; 22.4% White and 75% Asian; 32.4% with ECOG PS of 0 and 67.6% with ECOG PS of 1. A total of 80.2% patients had primary tumour location of stomach; 98.7% of patients had metastatic disease at baseline; 37.9% and 43.5% patients had liver metastasis and peritoneal metastasis, respectively.

At prespecified interim analysis, with a minimum study follow-up of 7.9 months, BGB-A317-305 demonstrated a statistically significant improvement in OS for patients randomised to the tislelizumab + chemotherapy arm as compared to the placebo + chemotherapy arm in patients with PD-L1 score ≥5%.
The stratified HR was 0.74 (95% CI: 0.59 to 0.94; 1-sided p-value of 0.0056), with a median OS of 17.2 months in the tislelizumab + chemotherapy arm compared to 12.6 months in the placebo + chemotherapy arm.
The study also demonstrated a statistically significant improvement in PFS in patients with PD-L1 score ≥5%. The stratified HR was 0.67 (95% CI: 0.55 to 0.83; 1-sided p-value < 0.0001), with a median PFS of 7.2 months for tislelizumab plus chemotherapy compared to 5.9 months for placebo plus chemotherapy.
The final analysis efficacy results for patients with PD-L1 score ≥5% are shown below.

Efficacy results in BGB-A317-305 patients with PD-L1 score ≥ 5% (final analysis)

	Tislelizumab + chemotherapy (N = 274)	**Placebo + chemotherapy (N = 272)**
	Patients with PD-L1 score ≥ 5%	
Median study follow-up (months)[a]	32.5	32.2
OS		
Death, n (%)	192 (70.1)	219 (80.5)
Median[b] (months) (95% CI)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)
Hazard ratio[c] (95% CI)	0.71 (0.58, 0.86)	
PFS		
Disease progression or death, n (%)	189 (69.0)	216 (79.4)
Median[b] (months) (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)
Hazard ratio[c] (95% CI)	0.68 (0.56, 0.83)	

OS = overall survival; CI = confidence interval; PFS = progression-free survival.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians were estimated using Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Stratified by regions (east Asia versus US, Europe) and peritoneal metastasis.

Esophageal squamous cell carcinoma (ESCC)

First-line treatment of ESCC
RATIONALE-306 (Study BGB-A317-306)

The Study RATIONALE is a randomised, double-blind placebo-controlled, global phase III study to compare the efficacy of tislelizumab in combination with chemotherapy versus placebo in combination with chemotherapy in patients with unresectable, locally advanced recurrent or metastatic ESCC. The study enrolled patients who were not amenable to chemoradiation or surgery with curative intent. PD-L1 expression measured by TAP score was evaluated at a central laboratory using the Ventana PD-L1(SP263) assay that identified PD-L1 staining on both tumour and tumour-associated immune cells.

Patients who had received prior systemic therapy for advanced or metastatic disease or prior therapies targeting PD-L1 expression measured by TAP score or prior therapies targeting PD-1, PD-L1, or PD-L2 were excluded. A treatment-free interval of at least 6 months was required if the patient had received prior neoadjuvant/adjuvant therapy.

Patients with active leptomeningeal disease or uncontrolled brain metastases, active autoimmune disease, a disease requiring systemic corticosteroids or immunosuppressants, or evidence of a fistula or complete oesophageal obstruction that is not treatable were excluded from the study.

Randomisation was stratified by geographic region (Asia [excluding Japan] versus Japan versus rest of the world), prior definitive therapy (yes versus no) and chemotherapy at the investigator's discretion (ICC; platinum with fluoropyrimidine or platinum with paclitaxel).

Patients were randomised (in a 1:1 ratio) to either: tislelizumab 200 mg every 3 weeks or placebo each in combination with chemotherapy of the investigator's choice (ICC). The chemotherapy regimen consisted of:

- Platinum (cisplatin [60 to 80 mg/m^2 i.v. on day 1] or oxaliplatin [130 mg/m^2 i.v. on day 1]) and a fluoropyrimidine (5-FU [750 to 800 mg/m^2 i.v. on days 1 to 5] or capecitabine [1000 mg/m^2 twice daily p.o. on days 1 to 14]), or
- Platinum (cisplatin [60 to 80 mg/m^2 i.v. on day 1 or 2] or oxaliplatin [130 mg/m^2 i.v. on day 1 or 2]) and (paclitaxel 175 mg/m^2 i.v. on day 1)

--Cross-over between treatment arms or between fluoropyrimidine and paclitaxel during the study treatment period was not allowed.

Patients were treated with tislelizumab in combination with chemotherapy or placebo in combination with chemotherapy until disease progression, as assessed by the investigator per RECIST version 1.1 or unacceptable toxicity. After 24 months of treatment, the study therapy could be continued beyond the 2 years if, in the investigator's assessment, it was in the best interest of the patient regarding clinical benefit and potential risks.

The tumour assessments were conducted every 6 weeks for the first 48 weeks, and every 9 weeks thereafter.

The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. The most important secondary efficacy endpoints were progression-free survival (PFS) and OS in the PD-L1 positive (PD-L1 score ≥10%) subgroup.

A total of 649 patients were randomised to receive tislelizumab in combination with chemotherapy (n = 326) or placebo in combination with chemotherapy (n = 323). Of the 649,358 patients had PD-L1 score ≥5%,and 107 patients had PD-L1 status unknown.

The baseline characteristics for patients in the ITT population were: median age 64.0 years (range: 26 to 84), 48.1% age 65 years or older; 86.7% male; 23.9% White and 74.9% Asian. 86.4% had metastatic disease at study entry and 13.6% had locally advanced disease. 99.8% patients had histological confirmation of squamous cell carcinoma. Baseline ECOG performance status was 0 (32.8%) or 1 (67.2%).

BGB-A317-306 showed an improvement in OS for patients with PD-L1 score ≥ 5% randomised to the tislelizumab in combination with chemotherapy arm as compared to the placebo in combination with chemotherapy arm. As of the data cut-off date of interim analysis, the median follow-up times by reverse Kaplan-Meier methodology were 22.8 months in the tislelizumab in combination with chemotherapy arm and 23.3 months in the placebo in combination with chemotherapy arm for patients with PD-L1 score ≥ 5%. Efficacy results for patients with PD-L1 score ≥ 5% as of interim analysis are shown below.

Efficacy results in BGB-A317-306 patients with PD-L1 score ≥ 5%

Endpoint	Tislelizumab + chemotherapy (N = 172)	Placebo + chemotherapy (N = 186)
OS		
Deaths, n (%)	97 (56.4)	132 (71.0)
Median (months) (95% CI)	19.6 (16.1, 25.0)	10.0 (8.6, 11.9)
HR (95% CI)[a]	0.57 (0.44, 0.75)	
PFS		
Events, n (%)	108 (62.8)	148 (79.6)
Median (months) (95% CI)	8.2 (7.0, 9.8)	5.5 (4.3, 6.4)
HR (95% CI)[a]	0.52 (0.40, 0.68)	

OS = overall survival; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.
[a] Based on a stratified Cox regression model.

As of the study completion date (22 Aug 2024), the median follow-up by reverse Kaplan-Meier methodology was 49.9 months for tislelizumab in combination with chemotherapy and 48.2 months for placebo in combination with chemotherapy for patients with PD-L1 score ≥5%. The median OS was 19.1 months versus 10.0 months in tislelizumab or placebo in combination with chemotherapy arm respectively for patients with PD-L1 score ≥5%. The OS improvement of patients with PD-L1 score ≥ 5% subgroup was consistent with the interim analysis with a stratified HR 0.61 (95% CI: 0.48 to 0.78).

Second-line treatment of ESCC

The efficacy of Tevimbra was evaluated in RATIONALE-302 (NCT03430843), a multicentre, randomised, open-label, active-controlled, global phase III study comparing the efficacy of Tevimbra versus chemotherapy in patients with unresectable, recurrent, locally advanced or metastatic ESCC who progressed on or after prior systemic treatment.
Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, the archival/fresh tumour tissue specimens taken were retrospectively tested for PD-L1 expression status. PD-L1 expression was centrally assessed using the analytically validated VENTANA PD-L1 (SP263) assay with tumor area positivity (TAP) score which is defined as the total percentage of the tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining at any intensity and tumour-associated immune cells with PD-L1 staining at any intensity, as visually estimated . Patients with inactive or asymptomatic carrier status, chronic or active hepatitis B virus (HBV) status and patients with detectable hepatitis C virus (HCV) receiving antivirals at screening were also enrolled in the study.

The study excluded patients with active brain tumour invasion or leptomeningeal metastases, tumour invasion into organs located close to the oesophagus (e.g. aorta or respiratory tract), active autoimmune disease or history of autoimmune disease, any condition requiring systemic treatment with corticosteroids or other immunosuppressants and patients with known HIV infection. The study also excluded patients who had previously received anti-PD-1 or PD-L1 targeted therapies.
Patients were randomised (1:1) to receive either Tevimbra 200 mg every 3 weeks or the investigator's choice of chemotherapy (ICC), selected from the following, all given intravenously:

- paclitaxel 135 to 175 mg/m^2 on day 1, given every 3 weeks (also at doses of 80 to 100 mg/m^2 on a weekly schedule according to local and/or country-specific standard of care guidelines, also administered in Japan as 100 mg/m^2 on days 1, 8, 15, 22, 29 and 36, followed by one week off),
- docetaxel 75 mg/m^2 on day 1, given every 3 weeks (in Japan at a dose of 70 mg/m^2 on day 1, given every 21 days), or
- irinotecan 125 mg/m^2 on days 1 and 8, given every 3 weeks.

Crossover between the Tevimbra arm and ICC arm was not permitted. In the ICC arm, switching between the different chemotherapy options was not permitted.
Randomisation was stratified by geographic region (Asia [excluding Japan] vs Japan vs USA/EU), ECOG PS score (0 vs 1) and ICC option (paclitaxel vs docetaxel vs irinotecan). The choice of ICC was determined by the investigator before randomisation.
Patients were treated with Tevimbra or one of the ICC until disease progression or unacceptable toxicity.
The tumour assessments were conducted every 6 weeks for the first six months, and every 9 weeks thereafter. Treatment beyond first investigator-assessed disease progression was possible in patients receiving Tevimbra in the following cases if there was no rapid progression of the disease: existing investigator-assessed benefit, good tolerability, stable performance status, no delay of an imminent intervention (to prevent serious complications associated with disease progression such as brain metastases).
The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. The key secondary efficacy endpoint was OS in the PD-L1 positive analysis set (defined as PD-L1 score ≥10%).
A total of 512 patients were enrolled and randomised to Tevimbra (n = 256) or ICC (n = 256): paclitaxel (n = 85), docetaxel (n = 53) or irinotecan (n = 118). Of the 512 patients, 142 (27.7%) had a PD-L1 score ≥10%, 222 (43.4%) had a PD-L1 score <10% and 148 (28.9%) had unknown baseline PD-L1 status.
The baseline characteristics of the study population were: median age 62 years (range: 35 to 86 years), 37.9% age 65 years or older; 84% male; 19% White and 80% Asian; 25% with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 75% with ECOG PS of 1.

Ninety-five percent of the study population had metastatic disease at study entry. All patients had received at least one prior systemic anti-cancer therapy.
The RATIONALE 302 trial demonstrated a statistically significant improvement in OS for patients randomised to the Tevimbra arm compared to the ICC arm. The median follow-up times by the reverse Kaplan-Meier method were 20.8 months in the Tevimbra arm and 21.1 months in the ICC arm.

Efficacy results in the RATIONALE 302 study (ITT analysis set)

Endpoint	Tevimbra (N = 256)	Chemotherapy (N = 256)
OS		
Deaths n (%)	197 (77.0)	213 (83.2)
Median (months)[a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio (95% CI)[b]	0.70 (0.57, 0.85)	
p-value[c]	p = 0.0001	

List of abbreviations: OS = overall survival; CI = confidence interval.
[a] Estimated using Kaplan-Meier method.
[b] Based on Cox regression model including treatment as covariate stratified by baseline ECOG status and investigator's choice of chemotherapy.
[c] One-sided p-value based on a log-rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

Efficacy results in RATIONALE-302 by baseline PD-L1 status

	PD-L1 ≥10%		PD-L1 <10%	
Endpoint	**Tevimbra (N = 80)**	**Chemotherapy (N = 62)**	**Tevimbra (N = 100)**	**Chemotherapy (N = 122)**
OS				
Deaths, n (%)	54 (67.5)	53 (85.5)	83 (83.0)	106 (86.9)
Median (months)[a] (95% CI)	10.0 (8.5, 15.1)	5.1 (3.8, 8.2)	7.5 (5.5, 8.9)	5.8 (4.8, 6.9)
Hazard ratio (95% CI)[b]	0.49 (0.33, 0.74)		0.83 (0.62, 1.12)	
p-value[c]	0.0003		-	

List of abbreviations: OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response.
[a] Estimated using Kaplan-Meier method.
[b] Based on Cox regression model including treatment as covariate stratified by baseline ECOG status and investigator's choice of chemotherapy.
[c] One-sided p-value based on a log-rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

The one-sided p-value was estimated from the log-rank test stratified by ECOG status and ICC option.
Hazard ratio was based on Cox regression model including treatment as covariate stratified by ECOG status and ICC option.

OS benefit with Tevimbra over ICC was consistent across all subgroups, including age, gender, chemotherapy options chosen (paclitaxel, docetaxel and irinotecan), smoking status, ECOG performance status, region (Asia versus America/Europe), baseline PD-L1 status and ethnicity (Asian

versus White). No formal statistical testing was planned for these subgroup analyses and the significance of the subgroup analyses is therefore limited.

PD-L1 subgroups

Of the 512 patients, 142 (27.7%) had PD-L1 positive ESCC, defined as PD-L1 TAP score ≥10%. The remaining 222 (43.4%) had PD-L1 negative ESCC, defined as PD-L1 score <10% of tumour cells expressing PD-L1, and 148 (28.9%) had baseline PD-L1 status missing.

In a prespecified analysis of OS in the PD-L1 positive subgroup (PD-L1 score ≥10%), the stratified hazard ratio (HR) for OS was 0.49 (95% CI: 0.33 to 0.74), with a 1-sided stratified log-rank test p-value of 0.0003. The median survival was 10.0 months (95% CI: 8.5 to 15.1 months) and 5.1 months (95% CI: 3.8 to 8.2 months) for the Tevimbra arm and ICC arm, respectively.

In the PD-L1 negative subgroup (PD-L1 score <10%), the stratified HR for OS was 0.83 (95% CI: 0.62 to 1.12), with median overall survival of 7.5 months (95% CI: 5.5 to 8.9 months) and 5.8 months (95% CI: 4.8 to 6.9 months) for the Tevimbra arm and ICC arm, respectively.

Paediatrics

The safety and efficacy of Tevimbra have not been established in children and adolescents under 18 years of age. No data is available (see “Dosage/Administration” for information on use in children and adolescents).

Pharmacokinetics

The pharmacokinetics (PK) of tislelizumab were characterised using population PK analysis with concentration data from 2,596 patients with advanced malignancies who received tislelizumab doses of 0.5 to 10 mg/kg every 2 weeks, 2.0 and 5.0 mg/kg every 3 weeks, and 200 mg every 3 weeks. The time to reach 90% steady-state level is approximately 84 days (12 weeks) after administration of 200 mg once every 3 weeks (Q3W), and the steady-state accumulation ratio for tislelizumab pharmacokinetic exposure is approximately 2-fold.

Absorption

Tislelizumab is administered intravenously and is therefore immediately and completely bioavailable.

Distribution

A population pharmacokinetic analysis indicates that the steady-state volume of distribution is 6.42 l, which is typical of monoclonal antibodies with limited distribution.

Metabolism

Tislelizumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Based on population PK analysis, the clearance of tislelizumab was 0.153 l/day with an interindividual variability of 26.3%, and the geometric mean terminal half-life was approximately 23.8 days with a coefficient of variation (CV) of 31%. Time-varying clearance was not observed in tislelizumab PK.

Linearity/non-linearity

Linear and dose-proportional tislelizumab PK was observed with dosing regimens ranging from 0.5 mg/kg to 10 mg/kg once every 2 or 3 weeks (including administration of 200 mg once every 3 weeks), suggesting saturation of the target-mediated elimination pathway.

Kinetics in specific patient groups

The effects of various covariates on tislelizumab PK were assessed in population PK analyses. The following factors had no clinically relevant effect on the exposure of tislelizumab: age (range 18 to 90 years), weight (range 32 to 130 kg), gender, ethnicity (White, Asian and other), mild to moderate renal impairment (creatinine clearance [CL_{Cr}] ≥30 ml/min), mild hepatic impairment (total bilirubin ≤1.5 times ULN and any AST) and tumour burden.

Hepatic impairment

No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of tislelizumab, no clinically important differences in the clearance of tislelizumab were found in patients with mild hepatic impairment (bilirubin ≤ULN and AST >ULN or bilirubin >1.0 to 1.5 × ULN and any AST, n = 396), compared to patients with normal hepatic function (bilirubin ≤ULN and AST ≤ULN, n = 2,182) (see “Dosage/Administration” section). Based on the limited number of patients with moderate hepatic impairment (bilirubin >1.5 to 3 × ULN and any AST, n=12) or severe hepatic impairment (bilirubin >3 × ULN and any AST, n = 2), the effect of moderate or severe hepatic impairment on tislelizumab pharmacokinetics is unknown.
Hepatic impairment was defined by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria of hepatic dysfunction.

Renal impairment

No dedicated studies of tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild renal impairment (CL_{Cr}) 60 to 89 ml/min, n = 1,046), moderate renal impairment (CL_{Cr} 30 to 59 ml/min, n = 320) and patients with normal renal function (CL_{Cr} ≥90 ml/min, n = 1,223). Mild and moderate renal impairment had no effect on the exposure of Tevimbra (see “Dosage/Administration” section). Based on the limited number of patients with severe renal impairment (n = 5), the effect of severe renal impairment on tislelizumab pharmacokinetics is unknown.

Elderly patients

Of the 2,596 patients who received Tevimbra, 1,750 patients (67.4%) were aged <65 years and 846 (32.6%) patients were aged ≥65 years (737 patients between 65 and 75 years and 109 (4.2%) patients >75 years).
Of the 256 patients with ESCC who were treated with Tevimbra in the clinical study, 99 (38.7%) were aged 65 years and over.
Of the 983 patients with NSCLC who were treated with Tevimbra in the clinical study, 310 (31.5%) were aged 65 years and over.
Based on population PK and exposure-response analysis, no clinically relevant differences in PK or safety or efficacy of Tevimbra were observed in patients aged <65 years, patients aged 65 to 75 years and patients aged >75 years (see “Dosage/Administration” section).

Preclinical data

In toxicity studies with repeated intravenous administration of tislelizumab to monkeys (3, 10, 30 or 60 mg/kg every 2 weeks for 13 weeks (7 administrations)), no apparent treatment-related toxicity and no histopathological changes were observed at doses up to 30 mg/kg every 2 weeks, which is 4 to 8 times the human exposure at the clinical dose of 200 mg. The 60 mg/kg dose was not tolerated by female monkeys due to immunogenicity.
No developmental, reproductive toxicity or fertility studies have been conducted with tislelizumab in animals. In the general toxicity studies, many of the monkeys were not sexually mature, so no clear conclusions can be drawn regarding the effects on the reproductive organs.

No studies have been conducted to investigate the carcinogenic or genotoxic potential of tislelizumab.

Other information

Incompatibilities

As no compatibility studies have been performed, this medicinal product must not be mixed with other medicinal products except sodium chloride, which is used to prepare the diluted solution.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Shelf life after opening

The diluted infusion preparation contains no preservative. It is recommended to prepare the solution immediately after taking it out of the refrigerator. For microbiological reasons, the ready-to-use preparation should be used immediately after dilution. If this is not possible, duration and conditions of storage are the responsibility of the user and should not normally exceed 24 hours at 2-8°C. The 24 hours include storage of the diluted solution under refrigeration (2 to ~8°C) for no more than 20 hours,

the time required for the return to room temperature (25°C and below) and the time to complete the infusion within 4 hours.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

The diluted solution for infusion must be prepared by a healthcare professional using aseptic techniques. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of solution for infusion

- Two Tevimbra vials are required for each dose. Remove the vials from the refrigerator, taking care not to shake them.
- Each vial must be visually inspected for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellowish solution. Do not use a vial if the solution is cloudy or if discolouration or visible particles are observed.
- Swirl the vials gently without shaking them. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) and transfer into an intravenous infusion bag containing 9 mg/ml (0.9%) sodium chloride to prepare a diluted solution with a final concentration of 1 to 5 mg/ml. Mix the diluted solution by swirling gently to avoid foaming or excessive shearing of the solution.

Mode of administration

- Administer the diluted tislelizumab solution by intravenous infusion via an intravenous infusion line containing 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 cm^2.
- The first infusion should be administered over 60 minutes. If this is 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 diluted solution must not be frozen.
- The infusion line must be flushed at the end of the infusion.

Tevimbra is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Swissmedic number

68960

Pack sizes

Vial containing 100 mg /10 ml of tislelizumab concentrate for solution for infusion (sterile concentrate). [A]

Marketing authorisation holder

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