swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: BeiGene Switzerland GmbH
Marketing authorisation no.: 68960
Decision and decision date: approved on 11 April 2024

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

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
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
AUCss	Area under the plasma concentration-time curve at steady state
CDC	Complement-dependent cytotoxicity
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
C_{min}	Minimum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
OC	Oesophageal cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
Fc	Fragment crystallisable
FDA	Food and Drug Administration (USA)
GC	Gastric cancer
GI	Gastrointestinal tract
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICC	Investigator's choice chemotherapy
ICI	Immune checkpoint inhibitors
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAB	Monoclonal antibody
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NAB	Neutralising Antibody

NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
NSCLC	non-small cell lung cancer
OECD	Organisation for Economic Cooperation and Development
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PBMCs	Peripheral blood mononuclear cells
Pop PK	Population pharmacokinetic
PS	Performance status
PSP	Pediatric study plan (US FDA)
PT	Preferred term
Q2W	Once every second week
Q3W	Once every third week
RMP	Risk management plan
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SCC	Squamous cell carcinoma
ss	Steady state
SSMO	Swiss Society for Medical Oncology
SwissPAR	Swiss Public Assessment Report
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)
Vc	Central volume of distribution
vCPS	Visually-estimated combined positivity score
Vd	Volume of distribution

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for tislelizumab in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Tevimbra, as monotherapy, is indicated for the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic oesophageal squamous cell carcinoma after prior systemic therapy."

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 August 2022
Formal control completed	6 September 2022
List of Questions (LoQ)	27 January 2023
Response to LoQ	27 April 2023
2nd List of Questions (LOQ)	18 July 2023
Response to 2nd LOQ	15 August 2023
Preliminary decision	16 November 2023
Response to preliminary decision	15 January 2024
Labelling corrections	12 March 2024
Response to labelling corrections	15 March 2024
Final decision	11 April 2024
Decision	approval

3 Medical context

Globally, oesophageal cancer is the seventh most common cancer. Approximately 600,000 new cases were reported in 2020 worldwide, and almost 550,000 deaths were estimated to be attributable to oesophageal cancer in 2020. 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. In Switzerland, there were 685 new cases of oesophageal cancer (all types) in 2020, making it the 20th most common cancer type with a five-year prevalence of 9.99/100,000.

There are two major histological subtypes of oesophageal cancer: squamous cell carcinoma (SCC) and adenocarcinoma. Worldwide, oesophageal SCC is by far the more common subtype, accounting for almost 90% of cases. In Europe, North America, and Australia on the other hand, adenocarcinomas comprise around 40-50% of all oesophageal cancers, with a trend towards a higher share of adenoid histology in recent years.

The histological subtype (SCC vs. adenocarcinoma) is highly relevant for treatment decisions. Curative treatment options for localised oesophageal SCC are surgical resection and definitive platinum-based radio-chemotherapy. Historically, surgical resection produced low long-term survival rates of only about 20%. This led to the development of multimodal therapies, including perioperative chemotherapy and radio-chemotherapy, which improved survival significantly Therapy algorithms are complex and depend on various tumour- and patient-related factors.

PD-1 inhibitors are anticancer drugs that act as immune checkpoint inhibitors (ICI). In the metastatic first-line oesophageal SCC setting, PD1 checkpoint inhibitors in combination with a platinum-based therapy are used in relation to PD-L1 expression (≥1%) leading to an increased median survival of 13-15 months as compared to less than 12 months with chemotherapy alone, respectively.

For the second line after chemoimmunotherapy, taxanes or irinotecan are options, as is the repetition of first-line treatment. The Onkopedia guidelines, which are supported by the Swiss Society for Medical Oncology (SSMO), recommend taxanes in the treatment algorithm for second line, and irinotecan is mentioned as an alternative option.

4 Quality aspects

4.1 Drug substance

Tislelizumab is a humanised monoclonal antibody of the IgG4 subclass. It binds to the T-cell surface receptor programmed cell death protein 1 (PD-1), prevents interaction of PD-1 with its ligands PD-L1 and PD-L2, and blocks PD-1–mediated inhibitory signalling. The Fc region has been engineered to eliminate binding to all Fc gamma receptors and to C1q.
The tislelizumab drug substance is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) grown in suspension, in serum-free media, and in a series of sequential passages. Tislelizumab is secreted into the culture medium and separated from cell debris by filtration. The purification process of the harvest comprises several chromatographic and filtration steps, as well as virus inactivation and virus retention filtration.
The manufacturing process is validated with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.
Changes were implemented during the development of the tislelizumab drug substance manufacturing process, including changes to manufacturing site, scale, and process. Comparability was shown at every major stage of development to assure product quality, and comparability of clinical and commercial drug substance batches was also demonstrated.
The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for drug substance release and stability include relevant tests and acceptance criteria, e.g. for appearance, identity, pH, protein concentration, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, stability data, and are in conformance with current compendial or regulatory guidelines. All specific analytical methods are described in sufficient detail and are fully validated.
Batch analysis data for development, clinical, and process performance qualification batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The drug substance is stored frozen. The established shelf life of the drug substance is justified by the results of ICH-compliant stability studies.

4.2 Drug product

Tislelizumab drug product is a clear to slightly opalescent, colourless to slightly yellowish solution and is supplied in a vial as a sterile solution containing 100 mg of tislelizumab. The drug product is intended for intravenous injection. It is for single use only and is preservative-free. The formulation is an aqueous solution buffered at pH 6.5 and containing a citrate histidine buffer, trehalose, and polysorbate 80. All excipients comply with the European Pharmacopoeia.
The manufacturing process of the finished drug product consists of thawing of the drug substance, bioburden reduction filtration and pooling, sterile filtration, filling and stoppering, capping and visual inspection. Process validation studies were executed at commercial scale using three validation batches.
The specifications for the drug product were set based on compendial requirements, experience from clinical trials, statistical data analysis of batch release and stability data, and on robustness studies performed during development. They include relevant tests and limits, e.g. for appearance, colour of solution, pH, osmolality, purity and impurities tests, identity, cell-based potency assay, protein concentration, extractable volume, sterility and bacterial endotoxins. All non-compendial methods are validated in accordance with ICH guidelines.
Batch analysis data for development, clinical, and process performance qualification batches were provided. All batch release data complied with the drug product specifications, which were valid at the time of batch release.

The primary container closure system of the finished product consists of a clear and colourless type I borosilicate glass vial with a chlorobutyl rubber stopper secured with aluminium seals. All components coming into contact with the finished product comply with Ph. Eur. requirements.
The drug product is stored at 2 – 8°C protected from light. No significant changes were observed within the proposed storage conditions. A shelf life of 36 months has been accepted.
The manufacturing process of drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical aspects

The nonclinical study programme for tislelizumab was based on ICH guidelines S6(R1) and S9, which is considered appropriate for the requested indication. The studies for the nonclinical development were conducted in China, including tissue cross-reactivity studies and the pivotal study for safety assessment (13-week toxicity study in cynomolgus monkeys), which were declared as non-OECD-GLP-compliant following an inspection by EU monitoring authorities. To mitigate the lack of GLP compliance of the nonclinical safety studies, the applicant initiated an additional 13-week toxicity study in monkeys in an OECD-GLP-compliant test facility. Although this study had not been requested by Swissmedic, evaluation of the report was considered necessary for the final nonclinical risk assessment, which should be based on the totality of data.

5.1 Pharmacology

Studies *in vitro* demonstrated that tislelizumab binds to human PD-1 with high affinity (K_d 0.11-0.15 nM). The binding affinity to cynomolgus monkey PD-1 was similar (K_d 0.14 nM), whereas tislelizumab did not bind to mouse PD-1.
In flow cytometry studies with a human lymphoma T-cell line expressing PD-1 (HuT78/PD-1 cells), tislelizumab competitively inhibited the binding of PD-L1 and PD-L2 up to 100% (IC_{50} values for both ligands ~0.5 nM). Similar results were also obtained in studies using HuT78 cells expressing monkey PD-1 (IC_{50} for inhibition of PD-L1 binding: 1.93 nM).
In co-culture studies with PD-L1-expressing cells, tislelizumab activated HuT78/PD-1 cells (EC_{50} 0.7-1.5 nM) and peripheral blood mononuclear cells (PBMCs) in a dose-dependent manner. These studies support the primary mode of action of tislelizumab (T-cell stimulation via inhibition of PD-1 signalling).
Tislelizumab (10 mg/kg once weekly, intraperitoneal administration) demonstrated significant anti-tumour activity in three xenograft allogenic cancer models (A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 NSCLC), in which human tumour cells and human PBMCs (healthy donors) were co-injected subcutaneously into immunocompromised mice. Tislelizumab also significantly inhibited tumour growth in human PD-1 transgenic mice bearing B16/F10 melanoma cells overexpressing murine granulocyte-macrophage colony-stimulating factor.
Tislelizumab (IgG4) has a modification in the Fc region to avoid the potential killing of tumour-infiltrating T-cells by macrophages through antibody-dependent cellular phagocytosis (ADCP). This is supported by studies published in Zhang et al. (2018)[1]. Tislelizumab also showed no, or only low, binding to Fcγ receptors and C1q in binding assays, and did not induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) *in vitro*.
No stand-alone safety pharmacology studies were conducted. In accordance with ICH S9, potential effects of tislelizumab on vital organ functions were assessed in the general toxicity studies in cynomolgus monkeys. There were no findings indicative of any cardiovascular, respiratory, or central nervous system toxicity.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of tislelizumab in cynomolgus monkeys was characterised after single and repeated administration via the intravenous (IV) route. After single dosing with 3-30 mg/kg, mean terminal half-life ($t_{1/2}$) was 88 to 223 hours (4-9 days), volume of distribution (Vd) was 22 to 87 mL/kg, and clearance (CL) was 0.18 to 0.34 mL/h/kg. The systemic exposure (C_{max} and AUC) increased dose-proportionally. The PK parameters from the single- and repeated-dose toxicity studies were similar. In male monkeys, accumulation and higher exposure than in female animals were observed after repeated (13 weeks) IV administration of 30 or 60 mg/kg every 2nd week (Q2W).
Tislelizumab was immunogenic in monkeys. In some animals, the presence of ADAs was associated with reduced systemic exposure. This had no impact on the validity of the toxicity studies, since most

[1] Zhang T, Song X, Xu L *et al*. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunology, Immunotherapy (2018) 67:1079–1090.

high-dose animals were sufficiently exposed. In one 13-week study, immunogenicity reactions related to ADA formation were observed (see *Toxicology*).
In vivo distribution, metabolism, and excretion studies were not conducted, in accordance with ICH S6(R1).

5.3 Toxicology

Pivotal toxicity studies were conducted in cynomolgus monkeys, which is a pharmacologically relevant species. It is to note that no specific binding of tislelizumab was detected in normal cynomolgus monkey and human tissues in tissue cross-reactivity studies. This is in line with the expected low target (PD-1) expression in healthy animals, which were used for the toxicity studies. However, the tissue cross-reactivity studies have some limitations, including lack of GLP-compliance and adequate positive control. Based on additional non-GLP examinations, the off-target binding potential of tislelizumab is considered low.
The test item formulation and method of administration (IV) in the toxicity studies were the same as proposed for clinical use. The dosing frequency in the repeated-dose studies in monkeys (Q2W) was higher than the clinical treatment regimen (Q3W); this accounts for the difference in $t_{1/2}$ (human $t_{1/2}$: 23.8 days). Based on ICH S9, the duration of the repeated-dose toxicity studies (3 months) is considered sufficient to support marketing authorisation.
No adverse effects were observed in mice or cynomolgus monkeys after administration of single doses up to 100 mg/kg. In both 13-week studies in cynomolgus monkeys, the NOAEL was at 30 mg/kg/Q2W, associated with an exposure (AUC) about 4- to 8-fold the clinical exposure at 200 mg Q3W. Treatment at 60 mg/kg/Q2W (high-dose level in the second 13-week study) was associated with adverse effects, including mortality, in females. The effects were attributed to immunogenicity reactions based on the presence of ADAs, clinical pathology data, and microscopic findings in kidneys and vessels of multiple tissues that were suggestive of immune complex disease. The clinical relevance of ADA-related reactions in monkeys is considered low. Adverse liver findings (including necrosis of hepatocytes and increased liver enzyme values) were observed in the moribund female at the 60 mg/kg/Q2W dose. Immune-mediated liver findings are an identified risk of treatment with tislelizumab.
No studies on genotoxicity or carcinogenicity were conducted with tislelizumab, in accordance with ICH S6(R1) and ICH S9.
No studies on reproductive and developmental toxicity were conducted with tislelizumab, based on ICH S9. There were no tislelizumab-related findings in the reproductive organs in the general repeated-dose toxicity studies in cynomolgus monkeys. However, most of the animals in these studies were not sexually mature, which precludes an assessment of potential effects on fertility. The applicant submitted a literature-based assessment on embryofetal toxicity. Since the PD-1/PD-L1 pathway plays a role in maintenance of immune tolerance to the fetus, pharmacologically mediated blockage of this interaction can disrupt the immune tolerance and result in fetal loss. Furthermore, since tislelizumab is an IgG4 antibody, it is likely that it crosses the placenta and is excreted in milk. Therefore, tislelizumab should not be used by pregnant or breastfeeding women; this is addressed in the information for healthcare professionals.
Local tolerance was evaluated in the general toxicity studies. There were no tislelizumab-related signs of reactions at the IV injection sites.
The 13-week toxicity studies in monkeys included specific endpoints for immunotoxicity (immunophenotyping and measurement of cytokines). No direct test item-related effects on these parameters or on standard haematology parameters and lymphoid organs (weight, histopathology) were observed. In addition, several studies were conducted for specific immunotoxicity endpoints. Tislelizumab did not elicit cytokine release *in vitro* in human whole blood-based or PBMC-based assays. Based on *in vitro* studies with PBMCs from healthy human donors, tislelizumab has a potential to enhance T-cell-mediated immunological recall response. *In vivo* in human PD-1 transgenic mice, tislelizumab had no effect on the IgG production following primary and secondary (recall) treatment with a T-cell dependent antigen.

The summary of the nonclinical data and the assessment of their relevance for clinical use in the RMP is considered adequate.
The risk for the environment by the medical use of tislelizumab is considered negligible.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support approval of tislelizumab in the proposed indication. The pharmacology studies showed that tislelizumab is an efficient inhibitor of PD-1 signalling. The toxicity studies in a relevant animal species did not reveal safety concerns for clinical use. Assessment of potential effects on reproductive organs/fertility is not possible based on the animal data. Due to its mechanism of action, tislelizumab may enhance T-cell mediated immune response and cause fetal harm and abortion. This is mentioned in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Biopharmaceutical Development
The same formulation of tislelizumab was employed during the clinical development, but there were two production processes with scale-ups. Material produced with the proposed commercial production process was administered in the pivotal Phase 3 study for oesophageal SCC (Study 302). The tislelizumab exposures after administration of drug material produced with the final manufacturing process at the 500 L and the 2000 L scales were similar.

Dose Proportionality
The studies included in the pop PK analysis covered a dose range between 0.5 mg/kg and 10 mg/kg and the proposed flat dose of 200 mg. A linear model described these data reasonably well. Consequently, the tislelizumab serum concentrations increased proportionally to the administered doses in this range. As tislelizumab binds to a cellular target, target-mediated disposition would be expected. However, the data indicate that saturation was reached.

Pharmacokinetics after multiple Dosing
The estimated time to reach 90% of the steady state after 200 mg Q3W was approximately 84 days (12 weeks). The accumulation ratios were 2.14, 1.62, and 2.49 for AUCss, Cmax,ss and Cmin,ss, respectively.

Distribution
The estimated tislelizumab central volume of distribution (Vc) in a typical subject was 3.05 L.

Metabolism
No studies regarding the metabolism of tislelizumab have been conducted considering the biological nature of the molecule.

Elimination
The estimated tislelizumab clearance in a typical subject was 0.153 L/day. The estimated half-life was 23.8 days.

Special Populations

The pharmacokinetics of tislelizumab in patients with advanced tumours was investigated in a pop PK analysis.

The dataset included 2596 patients, of whom 373 (14.4%) were patients with oesophageal cancer and 1141 (44.3%) were patients with non-small cell lung cancer (NSCLC). The majority (76.7%) of the patients were Asians, and most of them (78.7%) received tislelizumab as monotherapy after pre-treatment. Only 3.4% of the patients received tislelizumab as first-line therapy. The dataset included 432 (16.6%) ADA-positive patients.

The overall age and weight range of the patients was 18 to 90 years and 31.9 to 130 kg, respectively. The majority (67.4%) of the patients was < 65 years old, 28.4% were between 65 and 75 years old, and 4.2% were ≥ 75 years old.

The dataset included 47.1%, 40.3 % and 12.3% of patients with normal renal function, mild and moderate renal impairment, respectively, and 5 (0.193%) patients with severe renal impairment. With regard to hepatic function, it was normal in 84.2% of the patients. There were 15.3% of patients with

mild hepatic impairment. The dataset included 12 (0.463%) and 2 (0.0772%) patients with moderate and severe hepatic impairment, respectively.

Among others, body weight, age, sex, ADA status and tumour type (gastric cancer (GC) and classical Hodgkin lymphoma (cHL) versus others) were investigated for the impact on tislelizumab PK.

The final tislelizumab pop PK model was a linear 3-compartment model with first-order elimination. Time-dependence of CL was evaluated, but did not improve the fit. The model included the following covariate relationships:

- Body weight, serum albumin, baseline tumour size, ADA and tumour type on CL
- Body weight, sex and age on Vc

The model overpredicted the tislelizumab concentrations ≥ 84 h post-dose in the overall dataset, but described the data reasonably well at the earlier sampling times.

In the subgroups, it clearly underpredicted the tislelizumab concentrations in patients with oesophageal cancer, despite comparable clearance compared to the overall patient population.

Regarding the impact of each covariate individually, the changes in tislelizumab exposures were small. The largest change was a 31.4% increase of Cmin,ss due to tumour type. Usually, body weight is the most influential covariate of MAB PK. For tislelizumab, it was tumour type for AUCss and Cmin,ss, followed by body weight for Cmax,ss.

The impact of covariates on tislelizumab steady-state exposures was further investigated by simulations of the patients in the dataset. These simulations also included covariates, which were not formally investigated in the covariate analysis or did not reach statistical significance.

Body Weight

As expected for the proposed flat dosing regimen of 200 mg Q3W, the tislelizumab exposures decreased with increasing body weight. Compared to the geometric mean exposures of the overall population, the largest changes were observed for Cmin,ss. It was 14.5% higher in the patients in the first weight quartile and 17.3% lower in the patients in the fourth weight quartile.

In addition, the tislelizumab exposures after 200 mg Q3W and 3 mg/kg Q3W were compared. As expected, the largest differences occurred in the first and fourth weight quartiles. In the first weight quartile, the tislelizumab exposures were up to 14.5% higher compared to the geometric mean of the overall population after 200 mg Q3W and up to 11.7% lower after 3 mg/kg Q3W. In the fourth weight quartile, the tislelizumab exposures were up to 17.3% lower after the flat dose and up to 11.6% higher after a weight-based dose.

In summary, the impact of body weight on tislelizumab exposures was small, and the proposed flat dosing regimen is acceptable from a pharmacokinetic point of view.

The results for the other covariates are summarised below.

Covariate	**Comment**
Age	Minimal impact on tislelizumab exposures
Sex	Exposures up to 19% higher in women, but most likely due to differences in body weight
Race	Exposures up to 21% higher in Asians compared to Caucasians, but most likely due to differences in body weight

Immunogenicity	Exposures up to 41.3% lower in neutralising antibody (NAB)-positive compared to ADA/NAB-negative patients. Small number of NAB positives (0.8% of the patients)
Renal function	Up to 50.5% higher exposures in patients with severe renal impairment, but only 5 (0.2%) patients, who were older and had a lower body weight than the patients with better renal function
Hepatic function	Up to 15.4% lower exposures in patients with moderate hepatic impairment
Tumour type	Up to 34.8% higher exposures in cHL, and up to 13.6% lower exposures in GC. Minimal changes in NSCLC and oesophageal cancer (OC) but, as already said, the model did not cover the OC data very well
Combination therapy	Up to 8.8% higher exposures after combination therapy compared to tislelizumab monotherapy in the overall population, up to 16.6% in NSCLC patients, up to 47.6% in nonSq NSCLC patients (n=16, 1.05%)
Line of therapy	Up to 6.4% decrease for third-line therapy compared to the overall mean exposures

In summary, in most cases, the magnitude of the covariate effects was comparable to the inter-individual variability of the tislelizumab PK parameters. However, NAB might be associated with a lower efficacy.

Interactions

No *in vitro* or clinical interaction studies were conducted for tislelizumab as it is not metabolised by CYPs. Its mechanism of action is not expected to affect the activity of CYPs or transporters.

6.2 Dose finding and dose recommendation

The applicant submitted 2 studies that contain elements of dose finding and dose confirmation. The first-in-human study BGB-A317-001 was a Phase IA/IB global study to identify the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of tislelizumab and to evaluate efficacy and further investigate safety in select tumour types. Study BGB-A317-102 was a Phase I/II study testing the fixed dose of 200 mg i.v. every 3 weeks for different tumour entities in Chinese patients only.

The applicant concluded from both studies that a fixed dose of 200 mg intravenously every 3 weeks shows clinical activity in patients with advanced malignant tumours with a manageable safety profile Taken together, the dose finding is acceptable from a regulatory point of view.

6.3 Efficacy

The applicant submits one pivotal study BGB-A317-302 to support the marketing authorisation application for a new active substance (NAS).

The BGB-A317-302 study is a randomised, controlled, open-label, global phase 3 study comparing the efficacy of the anti-PD 1 antibody tislelizumab (BGB-A317) as monotherapy versus chemotherapy as second-line treatment in patients with advanced unresectable/metastatic oesophageal SCC. In total, 513 patients were randomised to receive either tislelizumab 200 mg by intravenous infusion every 3 weeks as monotherapy or investigator's choice chemotherapy (ICC; paclitaxel or docetaxel or irinotecan) according to local and/or country-specific guidelines as second-line therapy. The control arm is acceptable as relevant clinical guidelines include the ICC substances as second-line therapy. It is reasonable to include several ICC options because second-line therapy is variable and depends on

the substances used in first line. Overall survival (OS) in the ITT population was the primary endpoint. The open-label design is acceptable as OS is a hard endpoint that is not influenced by investigator or patient bias. Stratification factors were region (Asia [excluding Japan] versus Japan versus United States [US]/European Union [EU]), ECOG performance status (PS) score (0 versus 1), and ICC option (paclitaxel versus docetaxel versus irinotecan). These stratification factors are reasonable from a regulatory point of view.
The key secondary endpoint was OS in patients with a baseline PD-L1 visually-estimated combined positivity score (vCPS) ≥ 10%. VCPS was determined by measuring the total percentage of the tumour area covered by PD-L1-positive tumour and immune cells. This endpoint was included in the statistical plan in amendment 4.0 (dated 20 July 2020). PD-L1 vCPS analysis was started after this amendment.
For details regarding study design and dosing please refer to the attached information for healthcare professionals.

Results were presented with a clinical data cut-off (DCO) of 01 Dec 2020.
Baseline demographic characteristics were balanced between the two treatment arms. The median age in the ITT analysis set was 62.0 years. The majority of patients were Asian (79.7%). About a fifth of the patients was White or Caucasian (18.9%). Most patients were enrolled in the geographical region Asia (78.9%). In Europe/North America 21.1% of patients were enrolled. With oesophageal SCC incidence being highest in Asia, this distribution is acceptable.

Disease characteristics were imbalanced. In the ICC arm there were more dedifferentiated (G2/3) tumours compared to the tislelizumab arm (G2: 37.9% [ICC] vs 33.6% [tislelizumab], G3: 22.7% [ICC] vs 19.1% [tislelizumab]). In both groups almost a third of samples were not assessed regarding differentiation. Regarding PD-L1 status, patients were categorised into two groups with vCPS ≥ 10% or <10%. The proportion of PD-L1 vCPS ≥ 10% was higher in the tislelizumab arm compared to the ICC arm (34.8% vs 26.6%). The proportion of vCPS <10% was lower in the tislelizumab arm (45.3% vs 54.7%). In both arms, assessment of PD-L1 expression was missing for about a fifth of patients (19.9% vs 18.8%). The PD-L1 expression imbalance between the treatment arms was more pronounced in the Europe/North America region (vCPS ≥ 10% in the tislelizumab arm: 40.0% vs ICC arm: 18.9%).

With median follow-up period of 20.8 months in the tislelizumab arm and 21.1 months in the ICC arm (by reverse Kaplan-Meier methodology) there was a statistically significant and clinically meaningful difference in overall survival, with a hazard ratio (HR) of 0.70 (95% CI: 0.57 to 0.85) in favour of tislelizumab with a 1-sided p-value of 0.0001 from a stratified log-rank test. The median OS was 8.6 months (95% CI: 7.5 to 10.4 months) in the tislelizumab arm and 6.3 months (95% CI: 5.3 to 7.0 months) in the ICC arm. No interim analysis was performed, and the primary efficacy endpoint of OS in the ITT Analysis Set was tested just once at a 1-sided alpha of 0.025. The conducted sensitivity analyses and PDL1 vCPS subgroup analyses tested as a secondary endpoint supported the superiority of tislelizumab regarding the primary endpoint of OS.

The region subgroup Europe/North America (n=55 in the tislelizumab arm vs. n= 53 in the ICC arm) had a lower OS HR (0.55) than Asia (0.73), which might reflect the PD-L1 vCPS status imbalance between the subgroups. The OS HR of the race subgroup Asian and other was 0.72 compared to 0.53 for the subgroup White (n=53 in the tislelizumab arm and n=44 in the ICC arm).

Overall, the White and/or European/North American patients are considered most representative of the Swiss population. As this is a small subgroup, the reliability of the efficacy results is limited, which represents an uncertainty.

6.4 Safety

At the DCO of December 2020, the share of patients with at least one treatment-emergent adverse event (TEAE) was comparable in both treatment arms (tislelizumab: 95.7%, ICC: 98.3%).

The proportion of TEAEs ≥ Grade 3 was higher in the ICC arm (67.9%) than in the tislelizumab arm (46.3%). Most frequent TEAEs ≥ Grade 3 in the tislelizumab arm compared to the ICC arm were pneumonia (4.7% vs 7.1%), dysphagia (6.3% vs 2.9%), anaemia (5.9% vs 10.8%), dyspnoea (2.4% vs 1.3%), oesophageal obstruction (1.6% vs 0.4%), oesophageal stenosis (1.6% vs 0.4%) and upper GI haemorrhage (1.6% vs 1.7%), respectively.

The rate of serious TEAEs was similar in both treatment arms (tislelizumab: 41.2%; ICC 43.8%). Most frequent serious TEAEs in the tislelizumab arm compared to the ICC arm were dysphagia (4.7% vs 1.7%), pneumonia (7.1% vs 7.1%), pneumonitis (2.0% vs 0.8%) and oesophageal obstruction (2.0% vs 0.4%).

The proportion of TEAEs leading to death was numerically higher in the tislelizumab arm (tislelizumab: 13.7%, ICC: 11.7%). The primary cause of death was the disease under study in both arms. The only TEAE leading to death from a single preferred term (PT) recorded for more than one patient in the tislelizumab arm was pneumonia (3 patients, 1.2%; ICC arm: 1 patient, 0.4%).

In total, 21.2% of patients had at least one immune-mediated TEAE (tislelizumab arm only). Immune-mediated TEAEs were treated with corticosteroids in 13.7% of cases and led to treatment discontinuation in 3.1% of cases. Most frequent immune-mediated TEAEs were hypothyroidism (9%) and pneumonitis (7.1%). Most frequent immune-mediated TEAEs ≥ Grade 3 were pneumonitis (1.2%), hepatitis (0.8%) and myositis/rhabdomyolysis (0.8%).

In summary, the safety profile of tislelizumab in study BGB-A317-302 is well known and is in line with other checkpoint inhibitors of the same drug class. Also, the submitted pooled safety data for the substance did not contain unexpected critical safety signals. The toxicity of tislelizumab is manageable in the hands of experienced oncologists.

6.5 Final clinical benefit risk assessment

Tislelizumab exhibited linear pharmacokinetics across the investigated dose range of 0.5 mg/kg to 10 mg/kg, indicating that saturation of any target-mediated drug disposition was reached. Consequently, tislelizumab showed the typical pharmacokinetics of an IgG4 antibody with a small volume of distribution and a half-life of 24 days.
The final pop PK model predicted the overall data reasonably well, but it underpredicted the tislelizumab concentrations in patients with oesophageal cancer.
The pop PK analysis included a thorough investigation of covariate effects with special emphasis on body weight. The range of the continuous covariates in the dataset was sufficiently wide to detect any effects on tislelizumab exposures. It included a sufficient number of patients with mild or moderate renal impairment, but only 5 patients with severe renal impairment. It included a sufficient number of patients with mild hepatic impairment, but only a few patients with moderate or severe hepatic impairment. The majority of the patients in the dataset was Asian and male. However, after accounting for body weight in the model, no additional effects on tislelizumab PK due to race were detected.

The effects of all covariates, including body weight, on tislelizumab PK were small. Consequently, the changes in exposure in patients with high or low body weights after administration of the fixed dose of 200 mg Q3W were small and acceptable from a pharmacokinetic point of view

The use of tislelizumab in 2L oesophageal SCC patients resulted in a statistically significant and clinically meaningful overall survival benefit in comparison to the control arm with standard ICC. The safety profile is acceptable in the hands of experienced oncologists and in line with other PD(L)-1-targeting checkpoint inhibitors. In consideration of the above, and in view of the high medical need, the benefit-risk assessment of tislelizumab in 2L oesophageal SCC patients is considered positive for patients who did not receive ICI therapy in previous lines of therapy.

7 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.

8 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 variant humanised immunoglobulin G4 (IgG4) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Indications/Uses

Tevimbra is indicated as monotherapy for the second-line treatment of adult patients with advanced or metastatic oesophageal squamous cell carcinoma 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.

Usual dosage

The usual dose of Tevimbra is 200 mg administered every 3 weeks as an intravenous (i.v.) infusion. The first infusion should be administered over 60 minutes. If this is well tolerated, the subsequent infusions should be administered over a period of 30 minutes.

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

Immune-related ADR	Severity[1]	Tevimbra treatment modification
		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] 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

Immune-related ADR	Severity[1]	Tevimbra treatment modification
		prophylaxis of subsequent infusion reactions. Reduce infusion rate by 50%.
	Grade 2	Interrupt infusion. 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 are 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

Safety and efficacy in patients under 18 years of age have not been established.

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 should 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 and Guillain-Barré syndrome (see “Adverse effects” section).
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.

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 as a single agent. 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 physiological doses of systemic corticosteroids (prednisone 10 mg/day or equivalent dose of another corticosteroid), as they may impair pharmacodynamic activity and hence efficacy. 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.
With tislelizumab, no animal reproduction studies 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”).

Adverse 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, 37.3% were exposed for longer than 6 months and 20.4% 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 (0.1%) 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.

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 (N = 1,972)

Adverse drug reactions	All grades (%)	Grades 3-4 (%)
Blood and lymphatic system disorders[24]		
Lymphocytes decreased	Very common (38.5)	Common
Haemoglobin decreased	Very common (37.5)	Common
Leukocytes decreased	Very common (14.0)	Uncommon
Platelets decreased	Very common (13.0)	Uncommon
Neutrophils decreased	Very common (10.3)	Common
Haemoglobin increased	Common	Uncommon
Lymphocytes increased	Common	-
Endocrine disorders		

Adverse drug reactions	All grades (%)	Grades 3-4 (%)
Hypothyroidism[1]	Very common (11.8)	Rare
Hyperthyroidism[2]	Common	Rare
Thyroiditis[3]	Common	-
Adrenal insufficiency[4]	Uncommon	Uncommon
Hypophysitis[5]	Uncommon	-
Metabolism and nutrition disorders		
Hyperglycaemia[6]	Common	Common
Diabetes mellitus[7]	Uncommon	Uncommon
Sodium decreased[24]	Very common (31.3)	Common
Potassium decreased[24]	Very common (13.8)	Common
Potassium increased[24]	Common	Uncommon
Sodium increased[24]	Common	Uncommon
Nervous system disorders		
Guillain-Barré syndrome	-	-
Eye disorders		
Uveitis[8]	Uncommon	-
Cardiac disorders		
Myocarditis[9]	Uncommon	Uncommon
Pericarditis	Rare	-
Respiratory, thoracic and mediastinal disorders		
Cough	Very common (15.1)	Uncommon
Dyspnoea	Common*	Common
Pneumonitis[10]	Common*	Common
Gastrointestinal disorders		
Diarrhoea[11]	Very common (11.2)	Common
Stomatitis[12]	Common	Uncommon
Pancreatitis[13]	Uncommon	Uncommon
Colitis[14]	Uncommon	Uncommon
Hepatobiliary disorders		
Albumin decreased[24]	Very common (32.8)	Uncommon
Aspartate aminotransferase increased[24]	Very common (31.5)	Common
Alkaline phosphatase increased[24]	Very common (30.7)	Common
Alanine aminotransferase increased[24]	Very common (28.7)	Common
Bilirubin increased[24]	Very common (17.4)	Common
Hepatitis[15]	Common*	Common
Blood alkaline phosphatase increased	Common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[16]	Very common (16.3)	Common
Pruritus	Very common (10.6)	-
Severe skin reactions[17]	Uncommon	Rare
Stevens-Johnson Syndrome[25]	Unknown	Unknown
Toxic epidermal necrolysis[25]	Unknown	Unknown
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Uncommon
Myalgia	Common	-
Myositis[18]	Uncommon	Uncommon
Arthritis[19]	Uncommon	Uncommon
Renal and urinary disorders		
Nephritis[20]	Uncommon	Rare
General disorders and administration site conditions		
Fatigue[21]	Very common (24.6)	Common
Creatine kinase increased[24]	Very common (18.5)	Common
Creatinine increased[24]	Very common (13.6)	Uncommon
Injury, poisoning and procedural complications		
Infusion-related reactions[23]	Common	Uncommon

[1]Hypothyroidism includes preferred terms (PTs) of hypothyroidism, thyroxine free decreased, tri-iodothyronine free

Adverse drug reactions	All grades (%)	Grades 3-4 (%)

decreased, tri-iodothyronine decreased, anti-thyroid antibody increased, primary hypothyroidism and thyroxine decreased.

[2]Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.

[3]Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.

[4]Adrenal insufficiency includes PTs of adrenal insufficiency and secondary adrenocortical insufficiency.

[5]Hypophysitis includes PTs of hypopituitarism and lymphocytic hypophysitis.

[6]Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.

[7]Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, and latent autoimmune diabetes in adults.

[8]Uveitis includes PTs of uveitis and iritis.

[9]Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.

[10]Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.

[11]Diarrhoea includes PTs of diarrhoea and frequent bowel movements.

[12]Stomatitis includes PTs of stomatitis, mouth ulceration and aphthous ulcer.

[13]Pancreatitis includes PTs of amylase increased, lipase increased, pancreatitis, autoimmune pancreatitis and pancreatitis acute.

[14]Colitis includes PTs of colitis, immune-mediated enterocolitis and autoimmune colitis.

[15]Hepatitis includes PTs of hepatitis, hepatitis function abnormal, immune-mediated hepatitis and liver injury and autoimmune hepatitis.

[16]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.

[17]Severe skin reaction includes erythema multiforme.

[18]Myositis includes PTs of myositis, immune-mediated myositis and polymyalgia rheumatica.

[19]Arthritis includes PTs of arthritis, immune-mediated arthritis and polyarthritis.

[20]Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis and immune-mediated nephritis.

[21]Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.

[22]Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.

[23]Infusion-related reaction includes PTs of infusion-related reaction and infusion-related hypersensitivity reaction.

[24]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.

[*]including fatal outcomes.

[25]Post marketing event

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.

Immune-related pneumonitis

In patients treated with Tevimbra as monotherapy, immune-related pneumonitis occurred in 77 (3.9%) of 1,972 patients, including grade 1 (5 patients, 0.3%), grade 2 (34 patients, 1.7%), grade 3 (29 patients, 1.5%), grade 4 (5 patients, 0.3%) and grade 5 (4 patients, 0.2%) events.

The median time from first dose to onset of the event was 3.1 months (range: 1.0 day to 16.5 months), and the median duration from onset of the event to resolution was 5.8 months (range: 1+ days to 22.8+ months, + denotes a censored observation). Tevimbra was permanently discontinued in

36 patients (1.8%) and Tevimbra treatment was interrupted in 29 patients (1.5%). All 77 patients received systemic corticosteroids. Seventy (90.9%) of the 77 patients received high-dose systemic corticosteroids. Pneumonitis resolved in 37 (48.1%) of the 77 patients.

Immune-related hepatitis

In patients treated with Tevimbra as monotherapy, immune-related hepatitis occurred in 36 (1.8%) of 1,972 patients, including grade 1 (1 patient, 0.1%), grade 2 (12 patients, 0.6%), grade 3 (20 patients, 1.0%), grade 4 (1 patient, 0.1%) and grade 5 (2 patients, 0.1%) events.

The median time from first dose to onset of the event was 1.3 months (range: 8.0 days to 34.8 months), and the median duration from onset of the event to resolution was 1.2 months (range: 1.0 day to 37.9+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 9 patients (0.5%) and Tevimbra treatment was interrupted in 21 patients (1.1%).

Thirty-five (97.2%) of the 36 patients received systemic corticosteroids. Thirty (83.3%) of the 36 patients received high-dose systemic corticosteroids. One (2.8%) of the 36 patients received another immunosuppressive treatment. Hepatitis resolved in 20 (55.6%) of the 36 patients.

Immune-related adverse skin reactions

In patients treated with Tevimbra as monotherapy, immune-related adverse skin reactions occurred in 32 (1.6%) of 1,972 patients, including grade 1 (8 patients, 0.4%), grade 2 (12 patients, 0.6%), grade 3 (8 patients, 0.4%) and grade 4 (4 patients, 0.2%) events.

The median time from first dose to onset of the event was 1.9 months (range: 2.0 days to 19.8 months). The median duration from onset of the event to resolution was 6.7 months (range: 4.0 days to 34.0+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 5 patients (0.3%) and Tevimbra treatment was interrupted in 11 patients (0.6%).

Thirty-one (96.9%) of the 32 patients received systemic corticosteroids. Fifteen (46.9%) of the 32 patients received high-dose systemic corticosteroids. Two of 32 patients (6.3%) received another immunosuppressive treatment. Adverse skin reactions resolved in 17 (53.1%) of the 32 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 19 (1.0%) of 1,972 patients, including grade 2 (12 patients, 0.6%) and grade 3 (7 patients, 0.4%) events.

The median time from first dose to onset of the event was 3.1 months (range: 12 days to 14.4 months), and the median duration from onset of the event to resolution was 21.0 days (range: 1.0 day to 15.6+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 3 patients (0.2%) and Tevimbra treatment was interrupted in 12 patients (0.6%).

All 19 patients received systemic corticosteroids. Fourteen (73.7%) of the 19 patients received high-dose systemic corticosteroids. Two (10.5%) of the 19 patients received another immunosuppressive treatment. Colitis resolved in 15 (78.9%) of the 19 patients.

Immune-related myositis/rhabdomyolysis

In patients treated with Tevimbra as monotherapy, immune-related myositis/rhabdomyolysis occurred in 14 (0.7%) of 1,972 patients, including grade 1 (3 patients, 0.2%), grade 2 (5 patients, 0.3%), grade 3 (5 patients, 0.3%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 1.8 months (range: 15.0 days to 17.6 months), and the median duration from onset of the event to resolution was 2.1 months (range: 5.0 days to 11.2+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 3 patients (0.2%) and Tevimbra treatment was interrupted in 10 patients (0.5%).

All 14 patients received systemic corticosteroids. 10 (71.4%) of the 14 patients received high-dose systemic corticosteroids. None of the patients received immunosuppressive treatment. Myositis/rhabdomyolysis resolved in 8 (57.1%) of the 14 patients.

Immune-related endocrinopathies

Thyroid disorders

Hypothyroidism

In patients treated with Tevimbra as monotherapy, immune-related hypothyroidism occurred in 133 (6.7%) of 1,972 patients, including grade 1 (25 patients, 1.3%), grade 2 (107 patients, 5.4%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 3.6 months (range: 0 days to 16.6 months). The median duration from onset of the event to resolution was not evaluable from the available data (range: 12.0 days to 46.1+ months. + denotes a censored observation). Tevimbra was not permanently discontinued in any patient, and Tevimbra treatment was interrupted in 6 patients (0.3%). Two (1.5%) of the 133 patients received systemic corticosteroids. No patient received high-dose systemic corticosteroids. All 133 patients received hormone replacement therapy. Hypothyroidism resolved in 37 (27.8%) of the 133 patients.

Hyperthyroidism

In patients treated with Tevimbra as monotherapy, hyperthyroidism occurred in 12 (0.6%) of 1,972 patients, including grade 1 (2 patients, 0.1%), grade 2 (9 patients, 0.5%) and grade 3 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 1.3 months (range: 19.0 days to 14.5 months). The median duration from onset of the event to resolution was 1.6 months (range: 22.0 days

to 4.0+ months. + denotes a censored observation). Tevimbra was permanently discontinued in 1 patient (0.1%) and Tevimbra treatment was interrupted in 1 patient (0.1%).
One (8.3%) of the 12 patients received systemic corticosteroids (not high dose). All 12 patients received hormone replacement therapy. Hyperthyroidism resolved in 11 (91.7%) of the 12 patients.

Thyroiditis

In patients treated with Tevimbra as monotherapy, immune-related thyroiditis occurred in 13 (0.7%) of 1,972 patients, including grade 1 (3 patients, 0.2%) 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 not evaluable (range: 22.0 days to 18.6+ months. + denotes a censored observation). Tevimbra was not permanently discontinued in any patient, and Tevimbra treatment was interrupted in 2 patients (0.1%). One (7.7%) of the 13 patients received systemic corticosteroids. Twelve (92.3%) of the 13 patients received hormone replacement therapy. One (7.7%) of the 13 patients received high-dose systemic corticosteroids. Twelve (92.3%) of the 13 patients received hormone replacement therapy. Thyroiditis resolved in 3 (23.1%) of the 13 patients.

Adrenal insufficiency

In patients treated with Tevimbra as monotherapy, immune-related adrenal insufficiency occurred in 6 (0.3%) of 1,972 patients, including grade 2 (4 patients, 0.2%), grade 3 (1 patient, 0.1%) and grade 4 (1 patient, 0.1%) events.
The median time from first dose to onset of the event was 3.4 months (range: 1.3 months to 11.6 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 5 patients (0.3%). All 6 patients received systemic corticosteroids. Two (33.3%) of the 6 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 1 (16.7%) of the 6 patients.

Hypophysitis

In patients treated with Tevimbra as monotherapy, hypopituitarism (grade 2) occurred in 1 (0.1%) of 1,972 patients receiving Tevimbra.

Type 1 diabetes mellitus

In patients treated with Tevimbra as monotherapy, type 1 diabetes mellitus occurred in 8 patients (0.4%), including grade 1 (1 patient, 0.1%), grade 3 (6 patients, 0.3%) and grade 4 (1 patient, 0.1%) events.

The median time from first dose to onset of the event was 2.5 months (range: 29 days to 13.8 months). The median duration from onset of the event to resolution was not reached (range: 2 days to 20.2+ months, + denotes a censored observation with ongoing events at the time of the analysis). Tevimbra was permanently discontinued in three (0.2%) of the patients and Tevimbra treatment was interrupted in 2 (0.1%) patients. Type 1 diabetes mellitus resolved in one (12.5%) of 8 patients. The median duration for all resolved events was not evaluable (range: 2 days to 20.2+ months). All patients received hormone 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 10 (0.5%) of 1,972 patients, including grade 2 (4 patients, 0.2%), grade 3 (3 patients, 0.2%), grade 4 (2 patients, 0.1%) and grade 5 (1 patient, 0.1%) events.
The median time from first dose to onset of the event was 1.2 months (range: 3 days to 5.8 months). The median duration from onset of the event to resolution was 1.9 months (range: 3+ days to 16.2+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 4 patients (0.2%) and Tevimbra treatment was interrupted in 4 patients (0.2%).
Nine (90%) of 10 patients received systemic corticosteroids. Seven (70%) of the 10 patients received high-dose systemic corticosteroids. One (10%) of the 10 patients received immunosuppressive treatment. Immune-related nephritis and renal dysfunction resolved in 5 (50.0%) of the 10 patients.

Immune-related myocarditis

In patients treated with Tevimbra as monotherapy, immune-related myocarditis occurred in 7 (0.4%) of 1,972 patients, including grade 1 (1 patient, 0.1%), grade 2 (2 patients, 0.1%), 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 7.6+ months, + denotes a censored observation). Tevimbra was permanently discontinued in 5 patients (0.3%) and Tevimbra treatment was interrupted in 3 patients (0.2%).
All 7 patients received high-dose systemic corticosteroids at a median initial dose of 80 mg/day (range: 20.0 to 200.0 mg/day) for a median duration of 15 days (range: 1.0 day to 2.4+ months). One (14.3%) of the 7 patients received immunosuppressive treatment. Myocarditis resolved in 4 (57.1%) of the 7 patients.

Infusion-related reactions

In patients treated with Tevimbra as monotherapy, infusion-related reactions occurred in 83 (4.2%) of 1,972 patients, including grade 3 reactions (5 patients, 0.3%). Twenty-six (31.3%) of the 83 patients were treated with corticosteroids.

Tevimbra was permanently discontinued in 5 (0.3%) patients and Tevimbra treatment was interrupted in 21 patients (1.1%).

Immunogenicity

Of the 1,916 patients treated at the recommended dose of 200 mg every 3 weeks, 350 patients (18.3%) tested positive for treatment-emergent ADA (anti-drug antibody), and neutralising antibodies (NAbs) were detected in 18 patients (0.9%). 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, efficacy or safety. A higher incidence of grade 3 TEAEs or higher (62.6%) was observed for ADA-positive patients in the tislelizumab arms in Study BGB-A317-302 compared to ADA-negative patients (39.2%).

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 the 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

Oesophageal squamous cell carcinoma (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 tumour 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 score ≥10% of tumour cells expressing PD-L1. 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

BeiGene Switzerland GmbH
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Information last revised

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