A.35	Tislelizumab for locally advanced or metastatic urothelial carcinoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Urothelial carcinoma (UC) describes a range of tumors that arise from the urothelial endothelium, which includes bladder, renal pelvis, ureter, and urethra. UC can be located in the lower (bladder and urethra) or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder cancer is the second most common malignancy in urologic cancer patients and the ninth most common malignancy worldwide. The incidence rate is 5.3 per 100,000 persons/years leading to an estimated 165,000 cancer-related deaths per year. Urothelial carcinoma (UC) accounts approximately for 90% of bladder cancer in Europe and North America (Ferlay 2015; Global Burden of Disease Cancer Collaboration 2017).
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	The Application regards the inclusion in the Model List of tislelizumab under the category of immunomodulators. Tislelizumab was approved by the Chinese medicine authority NMPA for the treatment of patients with high PD-L1 expression with locally advanced or metastatic UC who have failed platinum containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months. Although not clearly stated in the Application, this Reviewer assumes that the Applicant proposal for inclusion regards this indication. Cisplatin-based systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic UC. MVAC-polychemotherapy, consisting of methotrexate, vinblastine, adriamycin and cisplatin, has been the mainstay of treatment of advanced and metastatic bladder cancer. Overall survival (OS) was reported to be up to 15 months (von der Maase 2005). However, patients who are unable to receive platinum-containing medications or patients who progress during or after the first line chemotherapy may benefit from the use of immune checkpoint inhibitors. The PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab are approved as first-line therapy in patients who are not cisplatin-eligible and as second-line treatments. The PD-1 inhibitor nivolumab and tislelizumab and the PD-L1 inhibitors avelumab and durvalumap are approved as second-line therapy only. The aim of these immunotherapy agents is to inhibit the specific tumor-associated antigens checkpoint molecule PDL1, which inhibits the immune response by T-cells. As mentioned above other immune checkpoint inhibitors are available for the treatment of UC. Focusing on the second-line treatment after failure of platinum-based chemotherapy, pembrolizumab demonstrated a better OS and quality of life (QoL) compared with further lines of chemotherapy (KEYNOTE-045 trial, 542 participants: median OS 10.1 vs 7.3 months, HR 0.70, 95% CI 0.57 to 0.85; time to health-related QoL deterioration 3.5 vs 2.3 months). Atezolizumab did not demonstrate any significant improvement in OS over other lines of chemotherapy (Van der Heijden 2021), while no data from phase III trials are available for nivolumab (both as monotherapy and in combination with nivolumab) and avelumab. Immune checkpoint inhibitors were never directly compared in clinical trials. The Model List currently includes most of the components of the cisplatin-based

	systemic chemotherapy widely used for the treatment of several neoplasms. The Model List does not include any immune checkpoint inhibitors for the treatment of UC. An Application for the inclusion of the anti-PD1 immune-checkpoint inhibitors for the treatment of locally advanced and metastatic non-small cell lung cancer has been submitted and under evaluation by the Expert panel. With the exception of the Guidelines of Chinese Society of Clinical Oncology (2020 edition), tislelizumab is not recommended for the treatment of patients with high PD-L1 expression with locally advanced or metastatic UC.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: It seems all relevant concluded studies have been included in the Application. However, the evidence supporting the efficacy and safety of tislelizumab for the treatment of patients with high PD-L1 expression with locally advanced or metastatic UC is currently poor. Several ongoing studies on the use of tislelizumab in UC are listed in ClinicalTrials.gov (May 2021). The most relevant for this Application is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study designed to compare the efficacy and safety of tislelizumab plus chemotherapy (either cisplatin or carboplatin/gemcitabine) versus placebo plus chemotherapy in approximately 420 participants with locally advanced or metastatic UC who have not received prior systemic therapy (NCT03967977). Other ongoing/active, not recruiting studies are: ▪ Chidamide With Immunotherapy for Patients With Locally Advanced or Metastatic Urothelial Carcinoma (phase 2, single arm chidamide plus tislelizumab) NCT04562311 ▪ Tislelizumab Combined With Nab-Paclitaxel for High-Risk Non-Muscle-Invasive Urothelial Bladder Carcinoma Which is Not Completely Resectable (phase 2, single arm Tislelizumab plus Nab-Paclitaxel) NCT04730232 Neoadjuvant setting ▪ Primary Excision Combined With Preoperative Neoadjuvant and Adjuvant Therapy for Oligometastasis of Urothelial Carcinoma (phase 2 RCT tislelizumab vs gentamicin+cisplatin) NCT04570410 ▪ Neoadjuvant Tislelizumab Combined With Nab-Paclitaxel for Muscle-invasive Urothelial Bladder Carcinoma (phase 2 single arm) NCT04730219 ▪ Neoadjuvant PD-1 Monoclonal Antibody in Locally Advanced Upper Tract Urothelial Carcinoma (phase 2 single arm) NCT04672330 ▪ Neoadjuvant PD-1 Monoclonal Antibody Plus Cisplatin-based Chemotherapy in Locally Advanced Upper Tract Urothelial Carcinoma (phase 2 single arm) NCT04672317

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable **Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).** The Application does not report any phase 3 trials, comparative data or data on hard endpoints. Available data are limited to two phase 1/2 studies and one single arm, non-randomised, open label phase 2 study (BGB-A317-204, Ye 2020). This study included 113 participants PD-L1 positive who received tislelizumab for a median of 15 weeks and were followed up for a median of 9.4 month. Of 104 evaluable patients, a confirmed objective response was observed in 25 patients (ORR=24%, 95% CI 16 to 33), including 10 complete response and 15 partial response. The median duration of response was not reached at the time of data analysis. An estimation of OS is provided: 9.8 months (95% CI 7.5 to 12.5) with 6-mo and 12-mo OS rates of 67% (95% CI 57 to 74) and 43% (95% CI 33 to 52), respectively. However, the usefulness of this estimation is low given the lack of a control arm and an adequate sample size. The qualitative indirect comparison of data on efficacy with Tislelizumab and other PD-1/PD-L1 monoclonal antibodies is of limited value. **Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?** The Application reports only studies conducted on the Chinese population. No data on people under 18 years are presented
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Overall, the safety population comprises less than 6000 patients treated with tislelizumab. In the pivotal study (BGB-A317-204, Ye 2020) 94% of the participants had at least one drug-related adverse event. Anemia and pyrexia were the most common treatment-related AEs (TRAEs). Most reported TRAEs were grade 1-2 in severity. Immune-related AEs included skin reactions, hypothyroidism and hyperthyroidism. The most common serious TRAEs were pyrexia and upper respiratory tract infection, urinary tract infection, and drug eruption. Other studies reporting use of tislelizumab based regimen in other cancers reported an incidence of AEs of all grades of 71%, with an incidence greater than or equal to 10% including fatigue, rash, hypothyroidism, increased alanine aminotransferase, and increased aspartate aminotransferase. The incidence of grade 3 and above adverse reactions was 18.4%, and the incidence of more than 1% reported hematological toxicity as prevalent (anemia, neutropenia, decreased blood cell and neutrophil counts).

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Data on safety are limited and it is difficult to conclude on which adverse effects may require special monitoring. Hepatic failure appear to be a major concern.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The evidence included in the Application suggests that the benefit-harm balance for tislelizumab in the treatment of locally advanced or metastatic UC is unfavourable.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Overall, the quality of the evidence supporting the use of tislelizumab in the treatment of locally advanced or metastatic UC is low. The main concerns regard: - lack of data on adequate sample of participants (imprecision of the estimates); - lack of data on hard outcomes; - lack of comparative assessment over other treatments approved for the same indication.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Tislelizumab is approved in China for locally advanced or metastatic UC in patients who have failed platinum containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) and have a high PD-L1 expression. In the pivotal study, during the participant screening, archival tissue/fresh biopsies were tested by a central laboratory using the VENTANA PD-L1 (SP263) immunohistochemistry. Although the role of PD-L1 expression as a predictive biomarker is still matter of debate and the decision to pursue testing must be carefully implemented for clinical decision, it is likely that testing PD-L1 protein expression will be needed before using tislelizumab. This may hamper the availability and affordability in some context.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: As stated above, tislelizumab was approved only by the Chinese medicine authority NMPA for the treatment of patients with high PD-L1 expression with locally advanced or metastatic UC who have failed platinum containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months. In China tislelizumab is also approved for third-line classical Hodgkin's lymphoma and, according to a press release from BeiGene Co., the company is seeking the approval for other indications, such as non-small cell lung and oesophageal cancer patients (https://www.fiercepharma.com/marketing/beigene-novartis-pd-1-tislelizumab-beat-chemotherapy-esophageal-cancer) Tislelizumab is not authorized anywhere in the European Union or in the United

	States. Both EMA and FDA granted an orphan designation for oesophageal cancer.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	No cost-effectiveness analyses are available. According to the Application, the cost of tislelizumab is ¥10,688 (100mg/ vials), approximately 1,700 US dollars or 1,400 Euros. Given that tislelizumab is only licensed in China where other immune checkpoint inhibitors are not marketed, any attempts to compare the cost of treatments are difficult. The Application includes an indirect international price comparison of monoclonal antibody for the treatment of advanced UC that suggests some price advantage. However, the reliability of this comparison is poor given the lack of comparative data and use in similar context.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	At the moment, this Reviewer does not support the inclusion of tislelizumab in the WHO Model List. The main reason for this opinion is the lack of sufficient data on its efficacy, safety, and place in therapy compared to other similar treatments for the same indication. Possible reduced cost of treatment is not supported by convincing evidence; thus, it cannot contribute to a positive opinion toward inclusion. Accumulating evidence for tislelizumab in this and other tumours could lead to a change in this opinion. Ongoing and future clinical trials will clarify the possible benefits of tislelizumab also in combination with other drugs.
References (if required)	Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 2015;**136**(5):E359-86. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncology 2017;**3**(4):524-48. Van der Heijden MS, Loriot Y, Duran I, et al. Atezolizumab Versus Chemotherapy in Patients with Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: A Long-term Overall Survival and Safety Update from the Phase 3 IMvigor211 Clinical Trial. Eur Urol. 2021 Apr 23:S0302-2838(21)00230-X. Von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. Journal of Clinical Oncology 2005;**23**(21):4602-8. Ye D, Liu J, Zhou A, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer science. 2020.