TECENTRIQ®▼, the 1st Anti-PD-L1 cancer immunotherapy

Dear Professor,
Dear Doctor,

We are pleased to inform you that **TECENTRIQ® (atezolizumab) is reimbursed** as of **March 1st** as monotherapy for the treatment of adult patients with

- locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy[1]
- locally advanced or metastatic urothelial carcinoma who are considered cisplatin ineligible[1]
- locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy[1a]

Tecentriq offers you and your patients multiple unique features:

1st Anti-PD-L1

- Direct, complete, selective [1,2,3]
- Only cancer immunotherapy (CIT) directly targeting the tumor[1]

Durable Patient Benefit

- Proven efficacy in 1L mUC: **15.9 months median OS**[4,5]
- Durable responses in platinum pretreated mUC: **21.7 months median DOR**[6,7]
- Broad clinically relevant efficacy in 2L NSCLC: **13,8 months median OS**[8,9]
  Superior survival in all PD-L1 subgroups[b8,9]

Convenience

- 3-weekly, fixed dose[1]
- Only 30' infusion time[1]
- Well tolerated[1,7]

The reimbursement request is made via the eHealth-platform. More information regarding the reimbursement criteria can be found on www.riziv.fgov.be.

For more information please contact your Roche scientific representative or visit www.rochepro.be.

Sincerely,

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R.E.: Dr. Chr. Lenaerts - BE/TCNL/0218/0005a - 02/03/2018

▼ 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 adverse reactions.

[a] Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq [b] versus docetaxel
OS: Overall Survival; 1L: First-Line; DOR; Duration of Response; 2L; Second-Line; PD-L1: Programmed-Death Ligand 1

1. TECENTRIQ Summary of Product Characteristics, 2017, 2. Chen DS, et al. Clin Cancer Res. 2012, 3. Harris NL, et al. Immunol Cell Biol. 1999, 4. Hamilou Z, et al. Future Oncol. 2018, 5. Balar AV, et al. Lancet. 2017, 6. Loriot Y, et al. ESMO 2016, 7. Powles T, et al. Lancet. 2017, 8. Rittmeyer et al. Lancet. 2017, 9. Gadgeel et al., WCLC 2016

TECENTRIQ®▼
atezolizumab

▼ 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 adverse reactions. See full leaflet for how to report adverse reactions.

TECENTRIQ® 1200 mg - 1 vial of 20 ml with 60 mg/ml (*) : 5673,87 €

NAME OF THE MEDICINAL PRODUCT Tecentriq 1,200 mg concentrate for solution for infusion. QUALITATIVE AND QUATANTITATIVE COMPOSITION Each 20 mL vial of concentrate contains 1,200 mg atezolizumab*. After dilution (see section 6.6 of SmPC), one mL of solution contains approximately 4.4 mg of atezolizumab. *Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed deathligand 1 (PDL1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology. For the full list of excipients, see section 6.1 of SmPC. PHARMACEUTICAL FORM Concentrate for solution for infusion. Clear, colourless to slightly yellowish liquid. THERAPEUTIC INDICATIONS Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinumcontaining chemotherapy or who are considered cisplatin ineligible (see section 5.1 of SmPC). Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALKpositive tumour mutations should also have received targeted therapy before receiving Tecentriq (see section 5.1 of SmPC). POSOLOGY AND METHOD OF ADMINISTRATION Tecentriq must be initiated and supervised by physicians experienced in the treatment of cancer. Posology. The recommended dose of Tecentriq is 1,200 mg administered intravenously every three weeks. Duration of treatment. It is recommended that patients are treated with Tecentriq until loss of clinical benefit (see section 5.1 of the SmPC) or unmanageable toxicity. Delayed or missed doses. If a planned dose of Tecentriq is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3week interval between doses. Dose modifications during treatment. Dose reductions of Tecentriq are not recommended. Dose delay or discontinuation. (see also sections 4.4 and 4.8 of the SmPC) **Table 1: Dose modification advice for specified adverse drug reactions.** [Adverse reaction→Severity→Treatment modification]: **Pneumonitis**→grade 2→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤10mg prednisone or equivalent per day. Pneumonitis→grade 3 or 4→Permanently discontinue Tecentriq. **Hepatitis**→Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN)→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Hepatitis→Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)→Permanently discontinue Tecentriq. **Colitis**→Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis→Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone equivalent per day. Colitis→Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)→Permanently discontinue Tecentriq. **Hypothyroidism or hyperthyroidism**→Symptomatic→Withhold Tecentriq. Hypothyroidism: Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing. Hyperthyroidism: Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving. **Adrenal insufficiency**→Symptomatic→Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy. **Hypophysitis**→Grade 2 or 3→Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy. Hypophysitis→Grade 4→Permanently discontinue Tecentriq. **Type 1 diabetes mellitus**→Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)→Withhold Tecentriq. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy. **Infusion-related reactions**→Grade 1 or 2→Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved. Infusion-related reactions→Grade 3 or 4→Permanently discontinue Tecentriq. **Rash**→Grade 3→Withhold Tecentriq. Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Rash→Grade 4→Permanently discontinue Tecentriq. **Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis**→All Grades→Permanently discontinue Tecentriq. **Pancreatitis**→Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis→Withhold Tecentriq. Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Pancreatitis→Grade 4 or any grade of recurrent pancreatitis→Permanently discontinue Tecentriq. Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCICTCAE v.4.). Tecentriq should be permanently discontinued: for Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones, for any recurrent event at Grade ≥ 3 severity, if a treatmentrelated toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date, if a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatmentrelated toxicity beyond 12 weeks after adverse reaction onset date. Patients treated with Tecentriq must be given the Patient Alert Card and be informed about the risks of Tecentriq (see also package leaflet). Special populations. *Paediatric population.* The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. No data are available. *Elderly.* Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age. *Renal impairment.* Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2 of SmPC). Data from patients with severe renal impairment are too limited to draw conclusions on this population. *Hepatic impairment.* Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. Tecentriq has not been studied in patients with moderate or severe hepatic impairment (see section 5.2 of SmPC). *Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2.* Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in NSCLC and 2nd line UC (see sections 4.4 and 5.1 of SmPC). Method of administration. Tecentriq is for intravenous use. The infusions must not be administered as an intravenous push or bolus. The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. For instructions on dilution and handling of the medicinal product before administration, see section 6.6 of SmPC. CONTRAINDICATIONS Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1 of SmPC. UNDESIRABLE EFFECTS *Summary of the safety profile.* The safety of Tecentriq is based on pooled data in 2,160 patients with metastatic UC and NSCLC. The most common adverse reactions were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), rash (18.6%), pyrexia (18.3%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%). *Tabulated list of adverse reactions.* The Adverse Drug Reactions (ADRs) are listed below by MedDRA system organ class (SOC) and categories of frequency. The following categories of frequency have been used: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. **Table 2: Summary of adverse reactions occurring in patients treated with Tecentriq in clinical trials. Blood and lymphatic system disorders**: Common, thrombocytopenia. **Immune system disorders**: Common, hypersensitivity. **Endocrine disorders:** Common, hypothyroidism[a], hyperthyroidism[b] - Uncommon, diabetes mellitus[c], adrenal insufficiency[d] – Rare, hypophysitis. **Metabolism and nutrition disorders:** Very common, decreased appetite – Common, hypokalaemia, hyponatremia. **Nervous system disorders:** Uncommon, Guillain-Barré syndrome[e], noninfective meningitis[f] – Rare, noninfective encephalitis[g], myasthenic syndrome[h]. **Vascular disorders**: Common, hypotension. **Respiratory, thoracic, and mediastinal disorders:** Very Common, dyspnoea – Common, pneumonitis[i], hypoxia, nasal congestion. **Gastrointestinal disorders:** Very common, nausea, vomiting, diarrhoea - Common, abdominal pain, colitis[j], dysphagia - Uncommon, pancreatitis[k], lipase increased - Rare, amylase increase. **Hepatobiliary disorders**: Common, AST increased, ALT increased - Uncommon, hepatitis[l]. **Skin and subcutaneous tissue disorders**: Very Common rash[m], pruritus. **Musculoskeletal and connective tissue disorders**: Very common, arthralgia - Common, musculoskeletal pain. **General disorders and administration site conditions:** Very Common pyrexia, fatigue, asthenia – Common, infusion related reaction, influenza like illness, chills. [a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased. [b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, thyroid function test abnormal, thyroiditis acute, thyroxine decreased. [c] Includes reports of diabetes mellitus and type 1 diabetes mellitus. [d] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease. [e] Includes reports of GuillainBarré syndrome and demyelinating polyneuropathy. [f] Includes reports of meningitis. [g] Includes reports of encephalitis. [h] Reported in studies other than those in metastatic UC and NSCLC patients. The frequency is based on the exposure in 6,000 patients across all atezolizumab clinical trials. [i] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis. [j] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic. [k] Includes reports of pancreatitis and pancreatitis acute. [l] Includes reports of autoimmune hepatitis, hepatitis, hepatitis acute. [m] Includes reports of acne, eczema, erythema, erythema of eyelid, erythema multiforme, exfoliative rash, eyelid rash, folliculitis, furuncle, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, drug eruption, palmarplantar erythrodysaesthesia syndrome, rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash papulosquamous, rash pruritic, rash pustular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic skin eruption. Description of selected adverse reactions. The data below reflect exposure to atezolizumab for clinically significant adverse reactions in clinical studies (see section 5.1 of SmPC). The management guidelines for these adverse reactions are described in sections 4.2 and 4.4 of SmPC. *Immunerelated pneumonitis.* Pneumonitis occurred in 3.1% (68/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. Of the 68 patients, one experienced a fatal event. The median time to onset was 3.5 months (range 3 days to 20.5 months). The median duration was 1.5 months (range 0 days to 15.1 + months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 10 (0.5 %) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (34/2,160) of patients receiving atezolizumab. *Immunerelated hepatitis.* Hepatitis occurred in 0.3% (7/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 1.1 months (range 9 days to 7.9 months). The median duration was 1 month (range 9 days to 1.9+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 2 (< 0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2,160) of patients receiving atezolizumab. *Immunerelated colitis.* Colitis occurred in 1.1% (23/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 4 months (range 15 days to 15.2 months). The median duration was 1.4 months (range 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 5 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (10/2,160) of patients receiving atezolizumab. *Immunerelated endocrinopathies.* Hypothyroidism occurred in 4.7% (101/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.5 months (range 21 days to 31.3 months). Hyperthyroidism occurred in 1.7% (36/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 3.5 months (range 21 days to 31.3 months). Adrenal insufficiency occurred in 0.3% (7/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.7 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (6/2,160) of patients receiving atezolizumab. Hypophysitis occurred in < 0.1% (1/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset for this patient was 13.7 months. Diabetes mellitus occurred in 0.3% (6/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of atezolizumab in 1 (< 0.1%) patient. *Immunerelated meningoencephalitis.* Meningitis occurred in 0.1% (3/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset ranged from 15 to 16 days. All three patients required the use of corticosteroids and discontinued atezolizumab. Encephalitis occurred in < 0.1% (2/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The time to onset was 14 and 16 days. Encephalitis led to discontinuation of atezolizumab in 1 (< 0.1%) patient. Encephalitis requiring the use of corticosteroids occurred in < 0.1% (1/2,160) of patients receiving atezolizumab. *Immunerelated neuropathies.* GuillainBarré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (0+ day to 8.3+ months; + denotes a censored value). GuillainBarré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). GuillainBarré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/2,160) of patients receiving atezolizumab. *Myasthenic syndrome.* Myasthenia gravis occurred in < 0.1% (4/6,000) of patients across all atezolizumab clinical trials in multiple tumour types. The time to onset ranged from 20 days to 4 months. All four patients discontinued atezolizumab. Myasthenic syndrome/myasthenia gravis requiring the use of corticosteroids occurred in < 0.1% (3/6,000) of patients receiving atezolizumab. *Immunerelated pancreatitis.* Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (10/2,160) of patients who received atezolizumab for metastatic UC and NSCLC. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 19 days (range 3 days to 11.2+ months; + denotes a censored value). Pancreatitis requiring the use of corticosteroids occurred in < 0.1% (2/2,160) of patients receiving atezolizumab. *Immunogenicity.* In study IMvigor210, 43.9% of patients tested positive for antiatezolizumab antibodies (ATAs) at one or more postdose time points. In study OAK (GO28915), the treatmentemergent ATA rate was 30.4%. Overall, ATA positivity appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety. No data are available to allow conclusions to be drawn on any possible effect of neutralising antibodies. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. *België/Belgique* : Federaal agentschap voor geneesmiddelen en gezondheidsproducten /Agence fédérale des médicaments et des produits de santé - Afdeling Vigilantie / Division Vigilance -EUROSTATION II, Place Victor Hortaplein, 40/ 40 - B-1060 Brussel/ Bruxelles - Website: www.fagg.be / Site internet: www.afmps.be - e-mail: adversedrugreactions@fagg-afmps.be – *Luxembourg* : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html MARKETING AUTHORISATION HOLDER Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom MARKETING AUTHORISATION NUMBER EU/1/17/1220/001 MODE OF DELIVERY on medical prescription DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 21 September 2017 DATE OF REVISION OF TEXT. 10/11/2017 Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu . R.E. Dr. Chr. Lenaerts - BE/TCN/1117/0017 – 15/11/2017