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 section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMJUDO 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 20 mg of tremelimumab.

One vial of 1.25 ml of concentrate contains 25 mg of tremelimumab.

One vial of 15 ml of concentrate contains 300 mg of tremelimumab.

Tremelimumab is a human anti-CTLA-4 immunoglobulin G2 IgG2a monoclonal antibody produced in murine myeloma cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles. The solution has a pH of approximately 5.5 and an osmolality of approximately 285 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.

Posology

The recommended dose of IMJUDO is presented in Table 1. IMJUDO is administered as an intravenous infusion over 1 hour.
Table 1: Recommended dose of IMJUDO

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended IMJUDO dosage</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced or unresectable HCC</td>
<td>IMJUDO 300 mg as a single dose administered in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
</tbody>
</table>

*For IMJUDO, HCC patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg until weight is greater than 40 kg. For durvalumab, patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until weight is greater than 30 kg. Dose escalation or reduction is not recommended during treatment with IMJUDO in combination with durvalumab. Treatment withholding or discontinuation may be required based on individual safety and tolerability.

Guidelines for management of immune-mediated adverse reactions are described in Table 2 (see section 4.4). Refer also to the summary of product characteristics (SmPC) for durvalumab.

Table 2. Treatment modifications and management recommendations for IMJUDO in combination with durvalumab

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Severity*</th>
<th>Treatment modification</th>
<th>Corticosteroid treatment unless otherwise specifiedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated pneumonitis/interstitial lung disease</td>
<td>Grade 2</td>
<td>Withhold dosec</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated hepatitis</td>
<td>ALT or AST &gt; 3 - ≤ 5 x ULN or total bilirubin &gt; 1.5 - ≤ 3 x ULN</td>
<td>Withhold dosec</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td></td>
<td>ALT or AST &gt; 5 - ≤ 10 x ULN</td>
<td>Withhold durvalumab and permanently discontinue IMJUDO (where appropriate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concurrent ALT or AST &gt; 3 x ULN and total bilirubin &gt; 2 x ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALT or AST &gt; 10 x ULN or total bilirubin &gt; 3 x ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated hepatitis in HCC (or secondary tumour)</td>
<td>ALT or AST &gt; 2.5 - ≤ 5 x BLV and ≤ 20 x ULN</td>
<td>Withhold dosec</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Severity</td>
<td>Treatment modification</td>
<td>Corticosteroid treatment unless otherwise specified</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>involvement of the liver with abnormal baseline values)(c)</td>
<td>ALT or AST &gt; 5 - 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 - 5 x BLV and ≤ 20 x ULN and total bilirubin &gt; 1.5 - &lt; 2 x ULN(d)</td>
<td>Withhold durvalumab and permanently discontinue IMJUDO (where appropriate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALT or AST &gt; 7 x BLV or &gt; 20 x ULN whichever occurs first or bilirubin &gt; 3 x ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated colitis or diarrhoea</td>
<td>Grade 2</td>
<td>Withhold dose(e)</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
<td>Consult a surgeon immediately if an intestinal perforation is suspected</td>
</tr>
<tr>
<td></td>
<td>Intestinal perforation of ANY grade</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated hyperthyroidism, thyroiditis</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
<td>Symptomatic management</td>
</tr>
<tr>
<td>Immune-mediated hypothyroidism</td>
<td>Grade 2-4</td>
<td>No changes</td>
<td>Initiate thyroid hormone replacement as clinically indicated</td>
</tr>
<tr>
<td>Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated</td>
</tr>
<tr>
<td>Immune-mediated Type 1 diabetes mellitus</td>
<td>Grade 2-4</td>
<td>No changes</td>
<td>Initiate treatment with insulin as clinically indicated</td>
</tr>
<tr>
<td>Immune-mediated nephritis</td>
<td>Grade 2 with serum creatinine &gt; 1.5-3 x (ULN or baseline)</td>
<td>Withhold dose(e)</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Severitya</td>
<td>Treatment modification</td>
<td>Corticosteroid treatment unless otherwise specifiedb</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------</td>
<td>------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Immune-mediated rash or dermatitis (including pemphigoid)</td>
<td>Grade 3 with serum creatinine &gt; 3 x baseline or &gt; 3-6 x ULN; Grade 4 with serum creatinine &gt; 6 x ULN</td>
<td>Permanently discontinue</td>
<td>equivalent followed by a taper</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune-mediated myocarditis</td>
<td>Grade 2 for &gt; 1 week or Grade 3</td>
<td>Withhold dosec</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune-mediated myocarditis</td>
<td>Grade 2-4</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Grade 1 or 2</td>
<td>Interrupt or slow the rate of infusion</td>
<td>Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated myasthenia gravis</td>
<td>Grade 2-4</td>
<td>Permanently discontinue</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Immune-mediated encephalitis</td>
<td>Grade 2-4</td>
<td>Permanently discontinue</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Other immune-mediated adverse reactionsb</td>
<td>Grade 2 or 3</td>
<td>Withhold dosec</td>
<td>Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Severitya</td>
<td>Treatment modification</td>
<td>Corticosteroid treatment unless otherwise specifiedb</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Non-immune-mediated adverse reactions</td>
<td>Grade 2 and 3</td>
<td>Withhold dose until ≤ Grade 1 or return to baseline</td>
<td>equivalent followed by a taper</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue(^1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value.

\(^b\) Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

\(^c\) After withholding, IMJUDO and/or durvalumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. IMJUDO and durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

\(^d\) For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

\(^e\) If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.

\(^f\) If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month.

\(^g\) Permanently discontinue IMJUDO and durvalumab if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

\(^h\) Includes immune thrombocytopenia and pancreatitis.

\(^i\) With the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue treatment should be based on accompanying clinical signs/symptoms and clinical judgment.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies.

**Special populations**

**Paediatric population**
The safety and efficacy of IMJUDO in children and adolescents below 18 years of age have not been established. No data are available.

**Elderly**
No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.2).

**Renal impairment**
No dose adjustment of IMJUDO is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 5.2).

**Hepatic impairment**
No dose adjustment of IMJUDO is recommended for patients with mild or moderate hepatic impairment. IMJUDO has not been studied in patients with severe hepatic impairment (see section 5.2).

**Method of administration**
IMJUDO is for intravenous use.
Administer IMJUDO prior to durvalumab on the same day.

IMJUDO and durvalumab are administered as separate intravenous infusions. Refer to the SmPC for durvalumab administration information.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in section 4.2.

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Monitor alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in section 4.2.

Immune-mediated colitis

Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Intestinal perforation and large intestine perforation were reported in patients receiving tremelimumab in combination with durvalumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in section 4.2.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving tremelimumab in combination with durvalumab, and hypothyroidism may follow hyperthyroidism (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed as recommended in section 4.2.
Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in section 4.2.

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in section 4.2.

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in section 4.2.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment and managed as recommended in section 4.2.

Immune-mediated rash

Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 and CTLA-4 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section 4.2.

Immune-mediated myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2.

Other immune-mediated adverse reactions

Given the mechanism of action of tremelimumab in combination with durvalumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with tremelimumab in combination with durvalumab: myasthenia gravis, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, cystitis noninfective and pancreatitis (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended in section 4.2.

Infusion-related reactions

Patients should be monitored for signs and symptoms of infusion-related reactions. Severe infusion-related reactions have been reported in patients receiving tremelimumab in combination with...
durvalumab (see section 4.8). Infusion-related reactions should be managed as recommended in section 4.2.

Patients excluded from clinical studies

Patients with the following were excluded from clinical studies: Child-Pugh Score B or C, main portal vein thrombosis, liver transplant, uncontrolled hypertension, history of, or current brain metastases, spinal cord compression, co-infection of viral hepatitis B and hepatitis C, active or prior documented gastrointestinal (GI) bleeding within 12 months, ascites requiring non-pharmacologic intervention within 6 months, hepatic encephalopathy within 12 months before the start of treatment, active or prior documented autoimmune or inflammatory disorders. In the absence of data, tremelimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The use of systemic corticosteroids or immunosuppressants before starting tremelimumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of tremelimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting tremelimumab to treat immune-related adverse reactions (see section 4.4).

No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab. Since the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception during treatment with tremelimumab and for at least 3 months after the last dose of tremelimumab.

Pregnancy

There are no data on the use of tremelimumab in pregnant women. Based on its mechanism of action, tremelimumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or any effects on maintenance of pregnancy or embryofoetal development (see section 5.3). Human IgG2 is known to cross the placental barrier. Tremelimumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

Breast-feeding

There is no information regarding the presence of tremelimumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG2 is excreted in human milk. Because of the potential for adverse reactions from tremelimumab in breast-fed infants, breast-feeding women are advised not to breast-feed during treatment and for at least 3 months after the last dose.
Fertility

There are no data on the potential effects of tremelimumab on fertility in humans or animals. However, mononuclear cell infiltration in prostate and uterus was observed in repeat-dose toxicity studies (see Section 5.3). The clinical relevance of these findings for fertility is unknown.

4.7 Effects on ability to drive and use machines

Tremelimumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of tremelimumab 300 mg as a single dose in combination with durvalumab, is based on pooled data in 462 HCC patients (HCC pool) from the HIMALAYA Study and another study in HCC patients, Study 22. The most common (> 10%) adverse reactions were rash (32.5%), pruritus (25.5%), diarrhoea (25.3%), abdominal pain (19.7%), aspartate aminotransferase increased/alanine aminotransferase increased (18.0%), pyrexia (13.9%), hypothyroidism (13.0%), cough/productive cough (10.8%), oedema peripheral (10.4%) and lipase increased (10.0%) (see Table 3).

The most common severe adverse reactions (NCI CTCAE Grade ≥ 3) are aspartate aminotransferase increased/alanine aminotransferase increased (8.9%), lipase increased (7.1%), amylase increased (4.3%) and diarrhoea (3.9%).

The most common serious adverse reactions are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

The frequency of treatment discontinuation due to adverse reactions is 6.5%. The most common adverse reactions leading to treatment discontinuation are hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%).

The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening and grade 5=death.

Tabulated list of adverse reactions

Table 3, unless otherwise stated, lists the incidence of adverse reactions (ADRs) in patients treated with tremelimumab 300 mg in combination with durvalumab in the HCC pool of 462 patients. Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the ADRs are presented in decreasing frequency. The corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/100 to < 1/1000); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 3. Adverse reactions in patients with HCC treated with tremelimumab 300 mg in combination with durvalumab

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Frequency of any Grade</th>
<th>Frequency of Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionsa</td>
<td>Common</td>
<td>39 (8.4%)</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>Common</td>
<td>20 (4.3%)</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Frequency of any Grade</td>
<td>Frequency of Grade 3-4</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td>Common 10 (2.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dental and oral soft tissue infections</strong></td>
<td>Common 6 (1.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral candidiasis</strong></td>
<td>Uncommon 3 (0.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Very common 60 (13.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td>Common 44 (9.5%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Thyroiditis</strong></td>
<td>Common 8 (1.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal insufficiency</strong></td>
<td>Common 6 (1.3%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypopituitarism/Hypophysitis</strong></td>
<td>Uncommon 4 (0.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes insipidus</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Type 1 diabetes mellitus</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Myasthenia gravis</strong></td>
<td>Uncommon 2 (0.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td>Uncommon 1 (0.2%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Guillain-Barré syndrome</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Encephalitis</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Myocarditis</strong></td>
<td>Uncommon 2 (0.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Cough/Productive cough</strong></td>
<td>Very common 50 (10.8%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td>Common 11 (2.4%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dysphonia</strong></td>
<td>Uncommon 4 (0.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Interstitial lung disease</strong></td>
<td>Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>Very common 117 (25.3%) Common 18 (3.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>Very common 91 (19.7%) Common 10 (2.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Lipase increased</strong></td>
<td>Common 46 (10.0%) Common 33 (7.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Amylase increased</strong></td>
<td>Common 41 (8.9%) Common 20 (4.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>Common 16 (3.5%) Common 12 (2.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Common 6 (1.3%) Uncommon 3 (0.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Intestinal perforation</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Large intestine perforation</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase increased/Alanine aminotransferase increased</strong></td>
<td>Very common 83 (18.0%) Common 41 (8.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>Common 23 (5.0%) Common 8 (1.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Very common 150 (32.5%) Common 14 (3.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>Very common 118 (25.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dermatitis</strong></td>
<td>Common 6 (1.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Night sweats</strong></td>
<td>Common 6 (1.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pemphigoid</strong></td>
<td>Uncommon 1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>Common 16 (3.5%) Uncommon 1 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Tremelimumab 300 mg in combination with durvalumab (n=462)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Frequency of any Grade</th>
<th>Frequency of Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myositis</td>
<td>Uncommon 3 (0.6%)</td>
<td>Uncommon 1 (0.2%)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Uncommon 1 (0.2%)</td>
<td>Uncommon 1 (0.2%)</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood creatinine increased</td>
<td>Common 21</td>
<td>Uncommon 2</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Common 7</td>
<td></td>
</tr>
<tr>
<td>Nephritis&lt;sup&gt;o&lt;/sup&gt;</td>
<td>Uncommon 3</td>
<td>Uncommon 2</td>
</tr>
<tr>
<td>Cystitis noninfective&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Oedema peripheral&lt;sup&gt;q&lt;/sup&gt;</td>
<td>Very common</td>
<td></td>
</tr>
</tbody>
</table>

**Injury, poisoning and procedural complications**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction&lt;sup&gt;r&lt;/sup&gt;</td>
<td>Common 6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.

<sup>b</sup> Includes pneumocystis jirovecii pneumonia and pneumonia.

<sup>c</sup> Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

<sup>d</sup> Adverse reaction was not observed in the HCC pool, but was reported in patients treated with durvalumab or durvalumab + tremelimumab in AstraZeneca-sponsored clinical studies.

<sup>e</sup> Includes blood thyroid stimulating hormone increased, hyperthyroidism and immune-mediated hypothyroidism.

<sup>f</sup> Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

<sup>g</sup> Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

<sup>h</sup> Includes immune-mediated pneumonitis and pneumonitis.

<sup>i</sup> Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

<sup>j</sup> Includes colitis, enteritis and enterocolitis.

<sup>k</sup> Includes pancreatitis and pancreatitis acute.

<sup>l</sup> Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

<sup>m</sup> Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.

<sup>n</sup> Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

<sup>o</sup> Includes dermatitis and immune-mediated dermatitis.

<sup>p</sup> Includes autoimmune nephritis and immune-mediated nephritis.

<sup>q</sup> Includes oedema peripheral and peripheral swelling.

<sup>r</sup> Includes infusion-related reaction and urticaria.

**Description of selected adverse reactions**

The data below reflects information for significant adverse reactions for tremelimumab 300 mg in combination with durvalumab in the HCC pool (n=462).

**Immune-mediated pneumonitis**

In the HCC pool (n=462), immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.
Immune-mediated hepatitis

In the HCC pool (n=462), immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients.

Immune-mediated colitis

In the HCC pool (n=462), immune-mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients.

Intestinal perforation was observed in patients receiving tremelimumab in combination with durvalumab (rare) in studies outside of the HCC pool.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

In the HCC pool (n=462), immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-mediated hyperthyroidism

In the HCC pool (n=462), immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteroids, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients.

Immune-mediated thyroiditis

In the HCC pool (n=462), immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 2 patients.

Immune-mediated adrenal insufficiency

In the HCC pool (n=462), immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients.

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus was observed in patients receiving tremelimumab in combination with durvalumab (uncommon) in studies outside of the HCC pool.
Immune-mediated hypophysitis/hypopituitarism

In the HCC pool (n=462), immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients.

Immune-mediated nephritis

In the HCC pool (n=462), immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

Immune-mediated rash

In the HCC pool (n=462), immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of tremelimumab is based on pooled data in 2075 patients who were treated with tremelimumab 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). Two-hundred fifty-two patients (12.1%) tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 10.0% (208/2075) patients. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety.

In the HIMALAYA study, of the 182 patients who were treated with tremelimumab 300 mg as a single dose in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

Elderly

Data from HCC patients 75 years of age or older are limited.

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 listed in Appendix V.

4.9 Overdose

There is no information on overdose with tremelimumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other monoclonal antibodies and antibody drug conjugates. ATC code: L01FX20

Mechanism of action

Cytotoxic T lymphocyte-associated antigen (CTLA-4) is primarily expressed on the surface of T lymphocytes. Interaction of CTLA-4 with its ligands, CD80 and CD86, limits effector T-cell activation, through a number of potential mechanisms, but primarily by limiting co-stimulatory signalling through CD28.

Tremelimumab is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour activity.

The combination of tremelimumab, a CTLA-4 inhibitor and durvalumab, a PD-L1 inhibitor results in improved anti-tumour responses in metastatic non-small cell lung cancer In murine syngeneic tumour models, dual blockade of PD-L1 and CTLA-4 resulted in enhanced anti-tumour activity.

Clinical efficacy

HCC - HIMALAYA Study

The efficacy of IMJUDO 300 mg as a single dose in combination with durvalumab was evaluated in the HIMALAYA Study, a randomised, open-label, multicentre study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with Barcelona Clinic Liver Cancer (BCLC) Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.

The study excluded patients with brain metastases or a history of brain metastases, co-infection of viral hepatitis B and hepatitis C; active or prior documented gastro-intestinal (GI) bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Patients with esophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry.

Randomisation was stratified by macrovascular invasion (MVI) (yes vs. no), aetiology of liver disease (confirmed hepatitis B virus vs. confirmed hepatitis C virus vs. others) and ECOG performance status (0 vs. 1). The HIMALAYA study randomized 1171 patients 1:1:1 to receive:

- D: durvalumab 1500 mg every 4 weeks
- IMJUDO 300 mg as a single dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks
- S: Sorafenib 400 mg twice daily

Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter. Survival assessments were conducted every month for the first 3 months following treatment discontinuation and then every 2 months.

The primary endpoint was Overall Survival (OS). Secondary endpoints included Progression-Free Survival (PFS), Investigator-assessed Objective Response Rate (ORR) and Duration of Response (DoR) according to RECIST v1.1.
The demographics and baseline disease characteristics were well balanced between study arms. The baseline demographics of the overall study population were as follows: male (83.7%), age < 65 years (50.4%) White (44.6%), Asian (50.7%), Black or African American (1.7%), Other race (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), baseline AFP < 400 ng/ml (63.7%), baseline AFP ≥ 400 ng/ml (34.5%), viral aetiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%), evaluable PD-L1 data (86.3%), PD-L1 Tumour area positivity (TAP) ≥ 1% (38.9%), PD-L1 TAP < 1% (48.3%) [Ventana PD-L1 (SP263) assay].

Results are presented in Table 4 and Figure 1.

Table 4. Efficacy Results for the HIMALAYA Study for IMJUDO 300 mg with durvalumab vs. S

<table>
<thead>
<tr>
<th>Follow-up duration</th>
<th>IMJUDO 300 mg + durvalumab (n= 393)</th>
<th>S (n= 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration</td>
<td>Median follow-up (months)(a)</td>
<td>33.2</td>
</tr>
<tr>
<td>OS</td>
<td>Number of deaths (%)</td>
<td>262 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Median OS (months) (95% CI)</td>
<td>16.4 (14.2, 19.6)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.78 (0.66, 0.92)</td>
</tr>
<tr>
<td>PFS</td>
<td>Number of events (%)</td>
<td>335 (85.2)</td>
</tr>
<tr>
<td></td>
<td>Median PFS (months) (95% CI)</td>
<td>3.78 (3.68, 5.32)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.90 (0.77, 1.05)</td>
</tr>
<tr>
<td>ORR</td>
<td>ORR n (%) (c)</td>
<td>79 (20.1)</td>
</tr>
<tr>
<td></td>
<td>Complete Response n (%)</td>
<td>12 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Partial Response n (%)</td>
<td>67 (17.0)</td>
</tr>
<tr>
<td>DoR</td>
<td>Median DoR (months)</td>
<td>22.3</td>
</tr>
</tbody>
</table>

\(a\) Calculated using reverse the Kaplan-Meier technique (with censor indicator reversed).

\(b\) Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMJUDO 300 mg + durvalumab vs. S was 0.0398 (Lan\textsuperscript{and} DeMets 1983).

\(c\) Confirmed complete response.

NR=Not Reached, CI=Confidence Interval
Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with tremelimumab in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms). See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tremelimumab was assessed for tremelimumab as monotherapy and in combination with durvalumab.

The PK of tremelimumab was studied in patients with doses ranging from 75 mg to 750 mg or 10 mg/kg administered intravenously once every 4 or 12 weeks as monotherapy, or at a single dose of 300 mg. PK exposure increased dose proportionally (linear PK) at doses ≥ 75 mg. Steady state was achieved at approximately 12 weeks. Based on population PK analysis that included patients who received tremelimumab monotherapy or in combination with other medicinal products in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the estimated tremelimumab clearance (CL) and volume of distribution (Vd) were 0.309 l/day and 6.33 l, respectively. The terminal half-life was approximately 14.2-days.

Special populations

Age (18–87 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, tumour type, race or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

Patients with renal impairment

Mild (creatinine clearance (CrCL) 60 to 89 ml/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 ml/min) had no clinically significant effect on the PK of tremelimumab. The effect of severe renal impairment (CrCL 15 to 29 ml/min) on the PK of tremelimumab is unknown.
Patients with hepatic impairment

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) and moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) had no clinically significant effect on the PK of tremelimumab. The effect of severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence tremelimumab exposure.

5.3 Preclinical safety data

Animal toxicology

In the chronic 6-month study in cynomolgus monkeys, treatment with tremelimumab was associated with dose-related incidence in persistent diarrhoea and skin rash, scabs and open sores, which were dose-limiting. These clinical signs were also associated with decreased appetite and body weight and swollen peripheral lymph nodes. Histopathological findings correlating with the observed clinical signs included reversible chronic inflammation in the cecum and colon, mononuclear cell infiltration in the skin and hyperplasia in lymphoid tissues.

A dose-dependent increase in the incidence and severity of mononuclear cell infiltration with or without mononuclear cell inflammation was observed in the salivary gland, pancreas (acinar), thyroid, parathyroid, adrenal, heart, esophagus, tongue, periportal liver area, skeletal muscle, prostate, uterus, pituitary, eye (conjunctiva, extra ocular muscles), and choroid plexus of the brain. No NOAEL was found in this study with animals treated with the lowest dose of 5 mg/kg/week, however the intermediate dose of 15 mg/kg week was considered the highest non-severely toxic dose (HNSTD). This dose provided an exposure-based safety margin of 1.77 to clinical relevant exposure.

Carcinogenicity and mutagenicity

The carcinogenic and genotoxic potential of tremelimumab has not been evaluated.

Reproductive toxicology

Animal fertility studies have not been conducted with tremelimumab. Mononuclear cell infiltration in prostate and uterus was observed in repeat dose toxicity studies. Since animal fertility studies have not been conducted with tremelimumab, the clinical relevance of these findings for fertility is unknown. In reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or effects pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Disodium edetate dihydrate
Polysorbate 80
Water for injections
6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

4 years at 2 °C - 8 °C.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 28 days at 2 °C to 8 °C and for up to 48 hours at room temperature (up to 25 °C) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 12 hours at room temperature (up to 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

Lack of microbial growth in the prepared solution for infusion has been demonstrated for up to 28 days at 2 °C to 8 °C and for up to 48 hours at room temperature (up to 25 °C) from the time of preparation.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Two pack sizes of IMJUDO are available:

- 1.25 ml (a total of 25 mg tremelimumab) concentrate in a Type I glass vial with an elastomeric stopper and a violet flip-off aluminum seal. Pack size of 1 single-dose vial.

- 15 ml (a total of 300 mg tremelimumab) concentrate in a Type I glass vial with an elastomeric stopper and a dark blue flip-off aluminum seal. Pack size of 1 single-dose vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of solution

IMJUDO is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.

- Visually inspect medicinal product for particulate matter and discolouration. IMJUDO is clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
• Withdraw the required volume from the vial(s) of IMJUDO and transfer into an intravenous bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 0.1 mg/ml and 10 mg/ml. Do not freeze or shake the solution.

• Care must be taken to ensure the sterility of the prepared solution.

• Do not re-enter the vial after withdrawal of the medicinal product.

• Discard any unused portion left in the vial.

Administration

• Administer the infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

• Do not co-administer other medicinal products through the same infusion line.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1713/001 25 mg vial
EU/1/22/1713/002 300 mg vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
Boehringer Ingelheim Pharma GmBH & Co. KG
Birkendorfer Strasse 65
88397, Biberach An Der Riss
Germany

Name and address of the manufacturers responsible for batch release
AstraZeneca AB
Gärtnunägen
SE-151 85 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product
Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION
- Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of
Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC
and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6
months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT
- Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in
the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed
subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information
  being received that may lead to a significant change to the benefit/risk profile or as the result of
  an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures
Prior to the launch of IMJUDO in each Member State the MAH will agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The additional risk minimisation measure is aimed at increasing awareness and providing information concerning the symptoms of immune-mediated adverse reactions.

The MAH shall ensure that in each Member State where IMJUDO is marketed, all physicians who are expected to use IMJUDO have access to/are provided with the following to provide to their patients:

**Patient card**

Key messages of the Patient Card include:

- A warning that immune-mediated adverse reactions (in lay terms) may occur and that they can be serious.
- A description of the symptoms of immune-mediated adverse reactions.
- A reminder to contact a healthcare professional provider immediately to discuss signs and symptoms.
- Space for contact details of the prescriber.
- A reminder to carry the card at all times.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMJUDO 20 mg/ml concentrate for solution for infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 20 mg of tremelimumab.
One vial of 1.25 ml of concentrate contains 25 mg of tremelimumab.
One vial of 15 ml of concentrate contains 300 mg of tremelimumab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

25 mg/1.25 ml
300 mg/15 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1713/001 25 mg vial
EU/1/22/1713/002 300 mg vial

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC
SN
NN
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL LABEL**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
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<td>IMJUDO 20 mg/ml sterile concentrate</td>
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<tr>
<td>tremelimumab</td>
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<td>IV</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>EXP</td>
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<th>4. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>Lot</td>
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</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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</thead>
<tbody>
<tr>
<td>25 mg/1.25 ml</td>
</tr>
<tr>
<td>300 mg/15 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

IMJUDO 20 mg/ml concentrate for solution for infusion
tremelimumab

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMJUDO is and what it is used for
2. What you need to know before you are given IMJUDO
3. How you are given IMJUDO
4. Possible side effects
5. How to store IMJUDO
6. Contents of the pack and other information

1. What IMJUDO is and what it is used for

IMJUDO is an anti-cancer medicine. It contains the active substance tremelimumab, which is a type of medicine called a monoclonal antibody. This medicine is designed to recognise a specific target substance in the body. IMJUDO works by helping your immune system fight your cancer.

IMJUDO in combination with durvalumab is used to treat a type of liver cancer, called advanced or unresectable hepatocellular carcinoma (HCC). It is used when your HCC:
- cannot be removed by surgery (unresectable), and
- may have spread within your liver or to other parts of the body.

As IMJUDO will be given in combination with other anti-cancer medicines, it is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given IMJUDO

You should not be given IMJUDO if you are allergic to tremelimumab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor before you are given IMJUDO if:
- you have an autoimmune disease (an illness where the body’s immune system attacks its own cells)
- you have had an organ transplant
- you have lung or breathing problems
- you have liver problems.
Talk to your doctor before you are given IMJUDO if any of these could apply to you.

When you are given IMJUDO, you can have some serious side effects.

Your doctor may give you other medicines that prevent more severe complications and to help reduce your symptoms. Your doctor may delay the next dose of IMJUDO or stop your treatment with IMJUDO. Talk to your doctor straight away if you get any of the following side effects:

- new or worsening cough; shortness of breath; chest pain (may be signs of lung inflammation)
- feeling sick (nausea) or vomiting; feeling less hungry; pain on the right side of your stomach; yellowing of skin or whites of eyes; drowsiness; dark urine or bleeding or bruising more easily than normal may be signs of liver inflammation)
- diarrhoea or more bowel movements than usual; stools that are black, tarry or sticky with blood or mucus; severe stomach pain or tenderness (may be signs of bowel inflammation, or a hole in the bowel)
- fast heart rate; extreme tiredness; weight gain or weight loss; dizziness or fainting; hair loss; feeling cold; constipation; headaches that will not go away or unusual headaches (may be signs of glands being inflamed, especially the thyroid, adrenal, pituitary or pancreas)
- feeling more hungry or thirsty than usual; passing urine more often than usual; high blood sugar; fast and deep breathing; confusion; a sweet smell to your breath; a sweet or metallic taste in your mouth or a different odour to your urine or sweat (may be signs of diabetes)
- decrease in the amount of urine you pass (may be sign of kidney inflammation)
- rash; itching; skin blistering or ulcers in the mouth or on other moist surfaces (may be signs of skin inflammation)
- chest pain; shortness of breath; irregular heartbeat (may be signs of heart muscle inflammation)
- muscle pain or weakness or rapid tiring of the muscles (may be signs of inflammation or other problems of the muscles)
- chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever (may be signs of infusion-related reactions)
- seizures; neck stiffness; headache; fever, chills; vomiting; eye sensitivity to light; confusion and sleepiness (may be signs of inflammation of the brain or the membrane around the brain and spinal cord)
- pain; weakness and paralysis in the hands, feet or arms (may be signs of inflammation of the nerves, Guillain-Barré syndrome)
- bleeding (from the nose or gums) and/or bruising (may be signs of low blood platelets).

Talk to your doctor straight away if you have any of the symptoms listed above.

Children and adolescents
IMJUDO should not be given to children and adolescents below 18 years of age as it has not been studied in these patients.

Other medicines and IMJUDO
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Pregnancy and fertility
This medicine is not recommended during pregnancy. Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. If you are a woman who could become pregnant, you must use effective contraception while you are being treated with IMJUDO and for at least 3 months after your last dose.

Breast-feeding
Tell your doctor if you are breast-feeding. It is not known if IMJUDO passes into human breast milk. You may be advised to not breast-feed during treatment and for at least 3 months after your last dose.
Driving and using machines
IMJUDO is not likely to affect your driving or use of machines. However, if you have side effects that affect your ability to concentrate and react, be careful when driving or operating machines.

IMJUDO has a low sodium content
IMJUDO contains less than 1 mmol sodium (23 mg) in each dose, that is to say essentially sodium-free.

3. How you are given IMJUDO
IMJUDO will be given to you in a hospital or clinic under the supervision of an experienced doctor. It is given in combination with durvalumab.

The recommended dose
- If you weigh 40 kg or more, the dose is 300 mg as a one-time single dose.
- If you weigh less than 40 kg, the dose will be 4 mg per kg of your body weight.

Your doctor will give you IMJUDO as a drip into your vein (infusion) lasting about an hour.

When IMJUDO is given in combination with durvalumab for your liver cancer, you will be given IMJUDO first, then durvalumab.

If you miss an appointment
It is very important that you do not miss a dose of this medicine. If you miss an appointment, call your doctor straight away to reschedule your appointment.

If you have any further questions about your treatment, ask your doctor.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get IMJUDO, you can have some serious side effects. See section 2 for a detailed list of these.

Talk to your doctor straight away if you get any of the following side effects that have been reported in a clinical study with patients receiving IMJUDO in combination with durvalumab.

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab:

Very common (may affect more than 1 in 10 people)
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- diarrhoea
- stomach pain
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- skin rash
- itchiness
- fever
- swelling of legs (oedema peripheral)
Common (may affect up to 1 in 10 people)

- infections of the upper respiratory tract
- lung infection (pneumonia)
- flu-like illness
- tooth and mouth soft tissue infections
- overactive thyroid gland that can cause fast heart rate or weight loss
- inflammation of the thyroid gland (thyroiditis)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- inflammation of the lungs (pneumonitis)
- abnormal pancreas function tests
- inflammation of the gut or intestine (colitis)
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver (hepatitis)
- inflammation of the skin
- night sweats
- muscle pain (myalgia)
- abnormal kidney function test (blood creatinine increased)
- painful urination (dysuria)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)

- fungal infection in the mouth
- underactive pituitary gland; inflammation of pituitary gland
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the membrane around the spinal cord and brain (meningitis)
- inflammation of the heart (myocarditis)
- hoarse voice (dysphonia)
- scarring of lung tissue
- blistering of the skin
- inflammation of the muscles (myositis)
- inflammation of the muscles and vessels
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

- low number of platelets with signs of excessive bleeding and bruising (immune thrombocytopenia)
- diabetes insipidus
- type 1 diabetes mellitus
- inflammation of the nerves (Guillain-Barré syndrome)
- inflammation of the brain (encephalitis)
- hole in the bowel (intestinal perforation)
- inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

Talk to your doctor straight away if you get any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in
Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMJUDO

IMJUDO will be given to you in a hospital or clinic and the healthcare professional will be responsible for its storage.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

Do not use if this medicine is cloudy, discoloured or contains visible particles.

Do not store any unused portion of the infusion solution for re-use. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What IMJUDO contains
The active substance is tremelimumab.

Each ml of concentrate for solution for infusion contains 20 mg of tremelimumab.

One vial contains either 300 mg of tremelimumab in 15 ml of concentrate or 25 mg of tremelimumab in 1.25 ml of concentrate.

The other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate (see section 2 “IMJUDO has a low sodium content”), polysorbate 80 and water for injections.

What IMJUDO looks like and contents of the pack
IMJUDO concentrate for solution for infusion (sterile concentrate) is a preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from visible particles.

It is available in packs containing either 1 glass vial of 1.25 ml of concentrate or 1 glass vial of 15 ml of concentrate.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>AstraZeneca S.A./N.V. Tel: +32 2 370 48 11</td>
</tr>
<tr>
<td>Lietuva</td>
<td>UAB AstraZeneca Lietuva Tel: +370 5 2660550</td>
</tr>
<tr>
<td>България</td>
<td>AstraZeneca България ЕООД Тел.: +359 24450000</td>
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<tr>
<td>Luxemburg/Luxemburg</td>
<td>AstraZeneca S.A./N.V. Tél/Tel: +32 2 370 48 11</td>
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<tr>
<td>Česká republika</td>
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</tr>
<tr>
<td>Malta</td>
<td>Associated Drug Co. Ltd Tel: +356 2277 8000</td>
</tr>
<tr>
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<td>AstraZeneca A/S Tlf: +45 43 66 64 62</td>
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<td>Nederland</td>
<td>AstraZeneca BV Tel: +31 79 363 2222</td>
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<td>Eesti</td>
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<td>Polska</td>
<td>AstraZeneca Pharma Poland Sp. z o.o. Tel.: +48 22 245 73 00</td>
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<td>France</td>
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<tr>
<td>Ireland</td>
<td>AstraZeneca Pharmaceuticals (Ireland) DAC Tel: +353 1609 7100</td>
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<td>Slovenija</td>
<td>AstraZeneca UK Limited Tel: +386 1 51 35 600</td>
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<tr>
<td>Suomi/Finland</td>
<td>AstraZeneca Oy Puh/Tel: +358 10 23 010</td>
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Preparation and administration of the infusion

- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to opalescent, colourless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discoloured or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume of concentrate from the vial(s) and transfer into an intravenous bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for injection, to prepare a diluted solution with a final concentration ranging from 0.1 to 10 mg/ml. Mix diluted solution by gentle inversion.
- Use the medicinal product immediately once diluted. The diluted solution must not be frozen. If not used immediately, the total time from vial puncture to start of the administration should not exceed 24 hours at 2 °C to 8 °C or 12 hours at room temperature (up to 25 °C). If refrigerated, intravenous bags must be allowed to come to room temperature prior to use. Administer the infusion solution intravenously over 1 hour using a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other medicinal products through the same infusion line.
- IMJUDO is single dose. Discard any unused portion left in the vial.

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