PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

IMFINZI 120 mg/2,4 ml concentrate for solution for infusion

IMFINZI 500 mg/10 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMFINZI 120 mg/2,4 ml: Each vial of 2,4 ml contains 120 mg of durvalumab

IMFINZI 500 mg/10 ml: Each vial of 10 ml contains 500 mg of durvalumab

Sugar-free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

IMFINZI is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.

IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

4.2 Posology and method of administration

Posology

The recommended dose of IMFINZI depends on the indication as presented in Table 1. IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended dosage of IMFINZI

Indication	**Recommended IMFINZI dosage**	**Duration of Therapy**
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	Until disease progression or unacceptable toxicity
ES-SCLC	1500 mg[b] in combination with chemotherapy[c,d] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

[b] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

[c] Administer IMFINZI prior to chemotherapy when given on the same day.

[d] When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information.

Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Guidelines for management of immune-mediated adverse reactions are described in Table 2. Refer to section 4.4, for further monitoring and evaluation information.

Table 2. Recommended Treatment Modifications for IMFINZI and Management Recommendations

Adverse Reactions	**Severity**[a]	**IMFINZI Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hepatitis	Grade 2 with ALT or AST >3-5xULN and/or total bilirubin >1.5-3xULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT > 5-≤8xULN or total bilirubin ≤5xULN or total bilirubin > 3-≤ 5 x ULN		

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	Grade 3 with AST or ALT >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Immune-mediated colitis or diarrhoea	Grade 2 or 3	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue[b]	
Immune-mediated hyperthyroidism or thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5-3x (ULN or baseline)	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine >3x baseline or >3-6xULN; Grade 4 with serum	Permanently discontinue	

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	creatinine >6xULN		
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis			Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[d]
	Grade 2- 4	Permanently discontinue	
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,e]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	
Myasthenia gravis	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4 or any Grade with signs of respiratory or autonomic insufficiency	Permanently discontinue	
Other immune-mediated adverse reactions[f]	Grade 3	Withhold dose[c]	Initiate1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

IMFINZIIMFINZIIMFINZI[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[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 withhold, IMFINZI 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. IMFINZI should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

[d] 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.

[e] Permanently discontinue IMFINZI if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

f Includes immune thrombocytopenia, and pancreatitis and encephalitis.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. For other immune-mediated adverse reactions not included in Table 1, IMFINZI should be discontinued for Grade 4 adverse reactions. Withholding of IMFINZI should be considered for Grade 3 immune- mediated adverse reactions, unless clinical judgment indicates discontinuation. Systemic corticosteroids should be considered.

For non-immune-mediated adverse reactions, withhold IMFINZI for Grade 2 and 3 adverse reactions until ≤ Grade 1 or baseline. IMFINZI should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment).

Special patient populations

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended based on patient age, body weight, gender and race (see section 5.2).

Paediatric and adolescents:

The safety and effectiveness of IMFINZI have not been established in children and adolescents aged less than 18 years.

Elderly (≥ 65 years):

No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.1 and 5.2).

Renal Impairment:

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended in patients with renal impairment (see section 5.2).

Hepatic Impairment:

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended for patients with mild hepatic impairment. IMFINZI has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Method of Administration

For intravenous administration.

For instructions on dilution of the medicine before administration, see below, Instructions for use, handling and disposal.

Instructions for use, handling and disposal

Preparation of solution:

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

- Visually inspect medicine for particulate matter and discolouration. IMFINZI is clear to 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 IMFINZI and transfer into an intravenous (IV) bag containing 0,9 % Sodium Chloride Injection, or 5 % Dextrose Injection. Mix diluted solution by

gentle inversion. The final concentration of the diluted solution should be between 1 mg/ml and 15 mg/ml. Do not freeze or shake the solution.

- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of medicine; only administer one dose per vial.
- Discard any unused portion left in the vial.

Administration:

- Administer 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 medicines through the same infusion line.

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

Incompatibilities

No incompatibilities between IMFINZI and 9 g/l (0,9 %) sodium chloride or 50 g/l (5 %) dextrose in polyvinylchloride or polyolefin IV bags have been observed.

This medicine must not be mixed with other medicines except those mentioned in Instructions for use, handling and disposal.

Do not co-administer other medicines through the same intravenous line.

4.3 Contraindications

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

4.4. Special warnings and precautions for use

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 IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis.

Patients with suspected pneumonitis should be evaluated and the diagnosis should be confirmed with radiographic imaging and other infections and disease-related aetiologies (example tuberculosis) excluded and managed as recommended in section 4.2.

Pneumonitis and radiation pneumonitis

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar.

In the PACIFIC Study, in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis including
both immune-mediated pneumonitis and radiation pneumonitis, occurred in patients
receiving IMFINZI. Pneumonitis or radiation pneumonitis occurred in 161 (33,9 %) patients in the IMFINZI treated group and 58 (24,8 %) in the placebo group; including Grade 3 in 16 (3,4 %) patients on IMFINZI vs. 7 (3,0 %) patients on placebo
and Grade 5 in 5 (1,1 %) patients on IMFINZI vs. 4 (1,7 %) patients on placebo.

The median time to onset in the IMFINZI-treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

Immune-mediated hepatitis:

Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI (see section 4.8).

Patients should be monitored for abnormal liver tests prior to and periodically during treatment with IMFINZI. 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 IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of colitis or diarrhoea and managed as recommended in section 4.2.

Immune-mediated endocrinopathies:

Hypothyroidism

Immune-mediated hypothyroidism occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in section 4.2.

Hyperthyroidism

Immune-mediated hyperthyroidism (including thyroiditis) occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in section 4.2.

Adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI (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.

Type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis occurred in patients receiving IMFINZI (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.

Hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMFINZI (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 IMFINZI (see section 4.8).

Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMFINZI 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 IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section 4.2.

Other immune mediated adverse reactions:

Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. Patients should be monitored for signs and symptoms and managed as recommended in section 4.2. IMFINZIIMFINZI Other immune-mediated adverse reactions are myasthenia gravis, myocarditis, myositis, polymyositis, immune thrombocytopenia, pancreatitis and encephalitis.

Human Immunodeficiency Virus (HIV):

Safety and efficacy in patients with HIV have not been established.

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 IMFINZI (see section 4.8).

4.5 interaction with other medicines and other forms of interaction

IMFINZI is an immunoglobulin, therefore no formal pharmacokinetic medicine-medicine interaction studies have been conducted with IMFINZI.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal reproduction studies, administration of IMFINZI to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery at exposure levels approximately 22 times higher than those observed at the clinical dose of 10 mg/kg of IMFINZI (based on AUC) was not associated with maternal toxicity or effects

on embryofoetal development, pregnancy outcome or postnatal development. There are no data on the use of IMFINZI in pregnant women. Based on its mechanism of action, IMFINZI has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier. IMFINZI 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.

Lactation

There is no information regarding the presence of IMFINZI in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG is excreted in human milk. In animal reproduction studies, administration of IMFINZI to pregnant cynomolgus monkeys was associated with dose-related low level excretion of IMFINZI in breast milk. Because of the potential for adverse reactions in breastfed infants from IMFINZI, advise a lactating woman not to breastfeed during treatment and for at least 3 months after the last dose.

Fertility

There are no data on the potential effects of IMFINZI on fertility in humans. In repeat-dose toxicology studies with IMFINZI in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs.

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, IMFINZI is unlikely to affect the ability to drive and use machines. However, if patients experience adverse reactions affecting their ability to concentrate and react, they should be advised to use caution when driving or operating machinery.

4.8 Undesirable effects

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies across multiple tumour types the most frequent adverse reaction were cough, diarrhoea and rash.
The safety of IMFINZI in combination with chemotherapy is based on data in 265 patients from the CASPIAN (SCLC) study and was consistent with IMFINZI monotherapy and known chemotherapy safety profile.

Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. The corresponding frequency category is based on the CIOMS III convention and is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not determined (cannot be estimated from available data).

Table 3. Adverse drug reactions in patients treated with IMFINZI at 10 mg/kg

System Organ Class	**Preferred Term**	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Respiratory, thoracic and mediastinal disorders	Cough/ Productive Cough	Very common	646 (21.5%)	Uncommon	11 (0.4%)
	Pneumonitis	Common	114 (3.8%)	Uncommon	26 (0.9%)
	Dysphonia	Common	93 (3.1%)	Uncommon	2 (<0.1%)
	Interstitial lung disease	Uncommon	18 (0.6%)	Uncommon	4 (0.1%)
Hepatobiliary disorders	Increased aspartate aminotransferase or increased alanine aminotransferase	Common	244 (8.1%)	Common	69 (2.3%)
	Hepatitis	Uncommon	25 (0.8%)	Uncommon	12 (0.4%)

System Organ Class	Preferred Term	Frequency of any Grade		Frequency of Grade 3-4	
Gastrointestinal disorders	Diarrhoea	Very common	491 (16.3%)	Uncommon	19 (0.6%)
	Abdominal pain	Very common	383 (12.7%)	Uncommon	53 (1.8%)
	Colitis	Uncommon	28 (0.9%)	Uncommon	10 (0.3%)
	Pancreatitis	Uncommon	6 (0.23%)	Uncommon	5 (0.17%)
Endocrine disorders	Hypothyroidism	Very common	305 (10.1%)	Uncommon	5 (0.2%)
	Hyperthyroidism	Common	137 (4.6%)		
	Thyroiditis	Uncommon	23 (0.8%)	Rare	2 (<0.1%)
	Adrenal insufficiency	Uncommon	18 (0.6%)	Rare	3 (<0.1%)
	Type 1 diabetes mellitus	Rare	1 (< 0,1 %)	Rare	1 (<0,1 %)
	Hypophysitis/ Hypopituitarism	Rare	2 (<0.1%)	Rare	2 (<0.1%)
	Diabetes insipidus	Rare	1 (< 0,1 %)	Rare	1 (<0,1 %)
Renal and urinary disorders	Increased blood creatinine	Common	105 (3.5%)	Rare	3 (<0.1%)
	Dysuria	Common	39 (1.3%)		0
	Nephritis	Uncommon	9 (0.3%)	Rare	2 (<0.1%)
	Rash	Very common	480 (16.0%)	Uncommon	18 (0.6%)

System Organ Class	Preferred Term	Frequency of any Grade		Frequency of Grade 3-4	
Skin and subcutaneous tissue disorders	Pruritus	Very common	325 (10.8%)	Rare	1 (<0.1%)
	Night sweats	Common	47 (1.6%)	Rare	1 (<0.1%)
	Dermatitis	Uncommon	22 (0.7%)	Rare	2 (<0.1%)
	Pemphigoid	Rare	3 (<0.1%)		0
Cardiac disorders	Myocarditis	Rare	1 (< 0,1 %)	Rare	1 (<0,1 %)
General disorders and administration site conditions	Pyrexia	Very common	414 (13.8%)	Uncommon	10 (0.3%)
	Peripheral oedema	Common	291 (9.7%)	Uncommon	9 (0.3%)
Infections and infestations	Upper respiratory tract infections	Very common	407 (13.5%)	Uncommon	6 (0.2%)
	Pneumonia	Common	269 (8.9%)	Common	106 (3.5%)
	Oral candidiasis	Common	64 (2.1%)		0
	Dental and oral soft tissue infections	Common	50 (1.7%)	Rare	1 (<0.1%)
	Influenza	Common	47 (1.6%)	Rare	2 (<0.1%)
Musculoskeletal and connective tissue disorders	Myalgia	Common	178 (5.9%)	Rare	2 (<0.1%)
	Myositis	Uncommon	6 (0.2%)	Rare	1 (<0.1%)
	Polymyositis	Not determined		Not determined	
Nervous system disorders	Myasthenia gravis	Rare			

System Organ Class	Preferred Term	Frequency of any Grade		Frequency of Grade 3-4	
	Encephalitis	Not determined		Not determined	
Blood and lymphatic system disorders	Immune thrombocytopenia	Rare	2 (<0.1%)	Rare	1 (<0.1%)
Injury, poisoning and procedural complications	Infusion related reaction	Common	49 (1.6%)	Uncommon	5 (0.2%)

Worsening laboratory abnormalities including increased alanine aminotransferase, increased aspartate aminotransferase, increases blood creatinine and thyroid stimulating hormone (TSH) changes were observed in patients treated with IMFINZI.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific treatment in the event of IMFINZI overdose, and symptoms of overdose are not established. In the event of an overdose, medical practitioners should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC28

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

In preclinical studies, PD-L1 blockade led to increased T-cell activation and decreased tumour size.

5.2 Pharmacokinetic properties:

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI as a single agent and in combination with chemotherapy.

The pharmacokinetics of durvalumab was studied in 2903 patients with solid tumours with doses ranging from 0,1 to 20 mg/kg administered once every two, three or four weeks. PK exposure increased more than dose-proportionally (non-linear PK) at doses < 3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg.

Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included 1878 patients in the dose range of ≥ 10 mg/kg Q2W, the geometric mean, steady state volume of distribution (Vss) was 5,64 l. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8,16 ml/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days.

There was no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy.

Special Populations:

Age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CRCL) 60 to 89 ml/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 ml/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1,0 to 1,5 × ULN and any AST), or ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab. The effect of severe renal impairment (CRCL 15 to 29 ml/min) or moderate hepatic impairment (bilirubin > 1,5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin > 3,0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

Elderly:

No dose adjustment is required for elderly patients (≥65 years of age). Of the 476 patients with locally advanced, unresectable NSCLC (primary efficacy population) treated with durvalumab, 215 patients were 65 years or older. Of the 265 patients with ES-SCLC treated with durvalumab in combination with chemotherapy, 101 (38%) patients were 65 years or older. No overall clinically meaningful differences in safety were reported between patients ≥65 years of age and younger patients.

Medicine Interaction Studies:

PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified.

Immunogenicity:

As with all therapeutic proteins, there is a potential for immunogenicity. Of the 2280 patients who were treated with durvalumab 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single agent and evaluable for the presence of anti-drug antibodies (ADAs), 3 % (69/2280) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 0,5 % (12/2280) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics or safety.

In the CASPIAN study, of the 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs. Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

For these reasons, comparison of incidence of antibodies to durvalumab with the incidence of antibodies to other medicines may be misleading.

6. PHARMACEUTICAL PARTICULARS

6.1 **List of excipients:**

L-histidine,

L-histidine hydrochloride monohydrate,

α,α-trehalose dihydrate,

polysorbate 80

Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months.

6.4 Special precautions for storage

Unopened Vial

Store vials under refrigeration between 2 °C and 8 °C in original carton to protect from light. Do not freeze. Do not shake.

Diluted Solution

IMFINZI does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, the total time from vial puncture to the start of administration should not exceed:

- 30 days at 2 °C - 8 °C
- 12 hours at or below 25 °C, up to 24 hours if dilution took place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

IMFINZI 120 mg/2,4 ml: 2,4 ml of concentrate in a 10 ml Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminum seal contains 120 mg durvalumab. Pack size of 1 vial.
IMFINZI 500 mg/10 ml: 10 ml of concentrate in a 10 ml Type 1 glass vial with an elastomeric stopper and a white flip-off aluminum seal contains 500 mg durvalumab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

See section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited
Building 2, Northdowns Office Park
17 Georgian Crescent West, Bryanston
Johannesburg, 2191

8. REGISTRATION NUMBER(S):

IMFINZI 120mg/2,4 ml: 54/30.1/0001
IMFINZI 500 mg/10 ml: 54/30.1/0002

9. DATE OF FIRST AUTHORISATION

23 February 2021

10. DATE OF REVISION OF THE TEXT

29 August 2022

AstraZeneca Logo