AUSTRALIAN PRODUCT INFORMATION – EMPLICITI® (ELOTUZUMAB)

1 NAME OF THE MEDICINE

Elotuzumab.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EMPLICITI 300 mg powder for concentrate for solution for intravenous infusion.

EMPLICITI 400 mg powder for concentrate for solution for intravenous infusion.

Each vial contains either 300 mg or 400 mg elotuzumab. After reconstitution, each mL of concentrate contains 25 mg elotuzumab.

Elotuzumab is a humanized recombinant monoclonal antibody directed to SLAMF7, a cell surface glycoprotein. Elotuzumab consists of the complementary determining regions (CDR) of the mouse antibody MuLuc63 grafted onto human IgG1 heavy and kappa light chain frameworks. Elotuzumab is produced in NS0 cells by recombinant DNA technology. Purified elotuzumab IgG1 has been shown to have an affinity to SLAMF7 in the range of 30 to 45 nM.

EMPLICITI for Injection vials require reconstitution with Sterile Water for Injection, BP (13 mL and 17 mL, respectively) to obtain a solution with a concentration of 25 mg/mL. After reconstitution, each vial contains overfill to allow for withdrawal of 12 mL (300 mg) and 16 mL (400 mg). The reconstituted solution has a pH of 5.7 – 6.3 in sterile water for injection BP and is intravenously administered as an isotonic solution upon further dilution with 0.9% sodium chloride or 5% glucose.

Note: "quantitative composition" only relates to the quantity of the therapeutically active ingredient.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

EMPLICITI is a nonpyrogenic lyophilized powder that is a white to off-white, whole or fragmented cake that is provided in two strengths.

EMPLICITI for Injection, 400 mg per vial and EMPLICITI for Injection, 300 mg per vial are single-use, sterile, nonpyrogenic lyophilized products.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EMPLICITI (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

EMPLICITI therapy should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

Patients must receive premedication before each dose of EMPLICITI. (see PREMEDICATION in 4.2 DOSE AND METHOD OF ADMINISTRATION).

Adminstration with lenalidomide and dexamethasone

The recommended dose of EMPLICITI is 10 mg/kg administered intravenously every week (28-day cycle), on days 1, 8, 15, and 22 for the first two cycles and every 2 weeks thereafter on days 1 and 15 when administered with lenalidomide and dexamethasone. Treatment should continue until disease progression or unacceptable toxicity.

The dosing schedule is presented in Table 1

Table 1: Recommended Dosing Schedule of EMPLICITI in Combination with Lenalidomide and Dexamethasone

Cycle	**28-Day Cycles 1 & 2**				**28-Day Cycles 3+**			
Day of Cycle	1	8	15	22	1	8	15	22
Premedication*	✓	✓	✓	✓	✓		✓	
EMPLICITI (mg/kg) Intravenous	10	10	10	10	10		10	
Lenalidomide† (25 mg) Oral	Days 1-21				Days 1-21			
Dexamethasone‡ (mg) Oral	28	28	28	28	28	40	28	40
Dexamethasone‡ (mg) Intravenous	8	8	8	8	8		8	
Day of Cycle	1	8	15	22	1	8	15	22

* Premedicate with the following 45-90 minutes prior to EMPLICITI infusion: 8 mg intravenous dexamethasone‡, H1 blocker: diphenhydramine (25-50 mg orally) or equivalent; H2 blocker: ranitidine (50 mg intravenous or 150 mg oral) or equivalent; paracetamol (650-1000 mg orally).

† The recommended dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles, and at least 2 hours after EMPLICITI administration when on the same day.

‡ Dexamethasone should be administered as follows: On days that EMPLICITI is administered, dexamethasone should be given as 28 mg orally once daily between 3 and 24 hours before EMPLICITI plus 8 mg intravenously between 45 and 90 minutes before EMPLICITI; on days that EMPLICITI is not administered, it should be given as 40 mg orally once weekly.

For additional information concerning lenalidomide and dexamethasone, see the corresponding Product Information.

Premedication

Premedication consisting of dexamethasone, H1 blocker, H2 blocker, and paracetamol should be administered prior to elotuzumab infusion.

When elotuzumab is used in combination with lenalidomide, dexamethasone 40 mg should be divided into an oral and intravenous dose and administered as shown in Table 1.

In addition, the following premedication must be administered 45-90 minutes prior to EMPLICITI infusion:

- H1 blocker: diphenhydramine (25-50 mg orally once daily) or equivalent H1 blocker.
- H2 blocker: ranitidine (50 mg intravenous or 150 mg orally once daily) or equivalent H2 blocker.
- Paracetamol (650-1000 mg orally once daily).

Dose delay, interruption, or discontinuation

If the dose of one medicine in the regimen is delayed, interrupted, or discontinued, the treatment with the other medicines may continue as scheduled. However, if dexamethasone is delayed or discontinued, the administration of EMPLICITI should be based on clinical judgment (based on risk of hypersensitivity).

Infusion rate should be modified following a ≥ Grade 2 infusion reaction (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

SPECIAL POPULATIONS

Paediatric population

There is no relevant use of EMPLICITI in the paediatric population in the indication of multiple myeloma.

Elderly patients

No dose adjustment is required for elotuzumab in patients over 65 years of age (see 5.3 PHARMACOKINETICS PROPERTIES).

Patients with renal impairment

In a study evaluating EMPLICITI in patients with renal impairment, the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone did not significantly differ between patients with normal renal function, severe renal impairment not requiring dialysis, or end-stage renal disease requiring dialysis. No dose adjustment of EMPLICITI is required for patients with mild, moderate, severe renal impairment or end stage renal disease requiring dialysis (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with hepatic impairment

EMPLICITI is an IgG1 monoclonal antibody, which is likely eliminated via several pathways similar to that of other antibodies. Hepatic excretion is not expected to play a dominant role in the excretion of EMPLICITI. Based on a population pharmacokinetic analysis, no dose adjustment for EMPLICITI is recommended for patients with mild hepatic impairment. EMPLICITI has not been studied in patients with moderate or severe hepatic impairment (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

METHOD OF ADMINISTRATION INFUSION RATES

EMPLICITI is for intravenous use only.

The administration of the diluted reconstituted solution must be initiated at an infusion rate of 0.5 mL per minute. If the infusion is well tolerated the infusion rate may be increased in a stepwise fashion as described in Table 2. The maximum infusion rate should not exceed 5 mL per minute.

Table 2: Infusion Rate for EMPLICITI

Cycle 1, Dose 1		**Cycle 1, Dose 2**		**Cycle 1, Dose 3 and 4 And all subsequent Cycles**
Time Interval	**Rate**	**Time Interval**	**Rate**	**Rate**
0-30 min	0.5 mL/min	0-30 min	3 mL/min	5 mL/min*
30-60 min	1 mL/min	≥ 30 min	4 mL/min*	
≥ 60 min	2 mL/min*	-	-	

* *Continue this rate until infusion is completed, approximately 1 hour based on patient weight.*

If a ≥ Grade 2 infusion reaction occurs during EMPLICITI administration, the infusion must be interrupted. Upon resolution to ≤ Grade 1, EMPLICITI should be restarted at 0.5 mL/min and may be gradually increased at a rate of 0.5 mL/min every 30 minutes as tolerated to the rate at which the infusion reaction occurred. If there is no recurrence of the infusion reaction, the escalation can be resumed (see Table 2).

In patients who experience an infusion reaction vital signs should be monitored every 30 minutes for 2 hours after the end of the EMPLICITI infusion. If the infusion reaction recurs, the EMPLICITI infusion must be stopped and not restarted on that day (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Very severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment.

Dose delay and modification for dexamethasone and lenalidomide or bortezomib should be performed as clinically indicated.

For instructions on reconstitution and dilution of EMPLICITI before administration. (see Preparation of the intravenous infusion in 4.2 DOSE AND METHOD OF ADMINISTRATION)

Calculating the dose

Calculate the dose (mg) and determine the number of vials needed for the 10 mg/kg dose based on patient weight. More than one vial of EMPLICITI may be needed to give the total dose for the patient.

- The total elotuzumab dose in mg = the patient's weight in kg x 10.

Preparation of the Intravenous Infusion.

Use Aseptic technique

Aseptically reconstitute each EMPLICITI vial with a syringe of adequate size and an 18 gauge or smaller needle as shown in Table 3. A slight back pressure may be experienced during administration of the sterilised water for injections, which is considered normal.

Table 3: Reconstitution Instructions

Strength	**Amount of Sterile Water forInjections BP, required for reconstitution**	**Final volume of reconstituted EMPLICITI in the vial (including volume displaced by the solid cake)**	**Post-reconstitution concentration**
300 mg vial	13.0 mL	13.6 mL	25 mg/mL
400 mg vial	17.0 mL	17.6 mL	25 mg/mL

- Hold the vial upright and swirl the solution by rotating the vial to dissolve the lyophilized cake. Then invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Avoid vigorous agitation, DO NOT SHAKE. The lyophilized powder should dissolve in less than 10 minutes.
- After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. The reconstituted preparation results in a colourless to slightly yellow, clear to very opalescent solution. EMPLICITI should be inspected visually for particulate matter and discolouration prior to administration. Discard the solution if any particulate matter or discolouration is observed.

Dilute the reconstituted EMPLICITI solution as described below:

Once the reconstitution is completed, withdraw the necessary volume for the calculated dose from each vial, up to a maximum of 16mL from 400 mg vial and 12mL from 300 mg vial.

- Dilute the reconstituted solution with 230 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection, into an infusion bag made of polyvinyl chloride or polyolefin.
- The volume of 0.9% sodium chloride injection BP or 5% glucose injection BP should be adjusted so as not to exceed 5 mL/kg of patient weight at any given dose of EMPLICITI.
- EACH VIAL OF EMPLICITI IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE

ADMINISTRATION

The entire EMPLICITI infusion should be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 µm) using an automated infusion pump. EMPLICITI should be initiated at an infusion rate of 0.5 mL per minute. If well tolerated, the infusion rate may be increased in a stepwise fashion as described in Table 2. The maximum infusion rate should not exceed 5 mL per minute.

The EMPLICITI infusion must be completed within 24 hours of preparation of the infusion solution. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°C-8°C and

protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours can be at room temperature: 20°C-25°C and room light).

4.3 CONTRAINDICATIONS

EMPLICITI should not be administered to patients with known hypersensitivity to the active substance elotuzumab or to any of the excipients (see 2 QUANLITATIVE AND QUANITATIVE COMPOSITION and 6.1 LIST OF EXCIPIENTS).

EMPLICITI is used in combination with other medicinal products; therefore, the contraindications applicable to those medicinal products also apply to EMPLICITI combination therapy.

The Product information for all medicinal products used in combination with EMPLICITI must be consulted before starting therapy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

INFUSION REACTION

EMPLICITI can cause infusion reactions. Infusion reactions have been reported in patients receiving EMPLICITI (see 4.8 ADVERSE EFFECTS (Undesirable effects). For severe infusion reactions, infusion should be stopped and EMPLICITI permanently discontinued (see 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients with mild or moderate infusion reaction may continue to receive EMPLICITI with close monitoring.

Premedication consisting of dexamethasone, H1 blocker, H2 blocker, and paracetamol must be administered prior to EMPLICITI infusion. The frequency of infusion reactions was much higher in patients who were not premedicated (see DESCRIPTION OF SELECT ADVERSE REACTIONS in 4.8 ADVERSE EFFECTS (Undesirable effects)).

In case of a Grade ≥ 2 infusion reaction, EMPLICITI infusion must be interrupted and appropriate medical and supportive measures instituted. Vital signs should be monitored every 30 minutes for 2 hours after the end of the EMPLICITI infusion. Once the reaction has resolved (≤ Grade 1), EMPLICITI can be restarted at the initial infusion rate of 0.5 mL per minute. If symptoms do not recur, the infusion rate may be gradually escalated every 30 minutes to a maximum of 5 mL per minute.

Very severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment. Patients with mild infusion reactions may receive EMPLICITI with a reduced infusion rate and close monitoring (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

USE OF EMPLICITI WITH LENALIDOMIDE AND DEXAMETHASONE

EMPLICITI is recomended for use in combination with lenalidomide and dexamethasone. **The product information for lenalidomide and dexamethasone must be consulted before starting therapy with EMPLICITI.**

Patients receiving EMPLICITI in combination with lenalidomide should adhere to the pregnancy prevention programme of lenalidomide (see USE in PREGNANCY in 4.6 FERTILITY, PREGNANCY AND LACTATION).

INFECTIONS

The incidence of infections, including pneumonia, was higher with EMPLICITI treatment than with control. In the largest clinical trial of patients with multiple myeloma (N=635), infections were reported in 81.4% of patients in the EMPLICITI combined with lenalidomide and dexamethasone (E-Ld) arm and 74.4% in lenalidomide and dexamethasone (Ld). Grade 3-4 infections were noted in 28% and 24.3% of E-Ld and Ld treated patients, respectively. Fatal infections were infrequent and were reported in 2.5% of E-Ld and 2.2% of Ld treated patients.

Monitor patients for development of infections and treat promptly.

The need for anti-viral, or pneumocystis jiroveci pneumonia, prophylaxis should be assessed on a case by case basis by the treating physician in accordance with local treatment policies.

SECOND PRIMARY MALIGNACIES (SPMs)

In a clinical trial of patients with multiple myeloma (N=635), invasive second primary malignancies (SPM) have been observed in 6.9% of patients treated with E-Ld and 4.1% of patients treated with Ld. The rate of hematologic malignancies were the same between E-Ld and Ld treatment arms (1.6%). Solid tumors were reported in 2.5% and 1.9% of E-Ld- and Ld-treated patients, respectively. Non-melanoma skin cancer was reported in 3.1% and 1.6% of patients treated with E-Ld and Ld, respectively.

Monitor patients for the development of second primary malignancies.

HEPATOTOXICITY

Elevations in liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT] greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were reported in 2.5% and 0.6% of E-Ld- and Ld-treated patients in a clinical trial of patients with multiple myeloma (N=635). Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment. In 7 out of the 8 patients, there were confounding risk factors such as concurrent steatic hepatitis, cholelithiasis or infection.

Monitor liver enzymes periodically. Stop EMPLICITI upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

INTERFERENCE WITH DETERMINATION OF COMPLETE RESPONSE

EMPLICITI is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein. Therefore, the M-protein assay should not be used in isolation in the clinical assessment of response in patients with IgG kappa disease.

USE OF EMPLICITI WITH LENALIDOMIDE

When EMPLICITI is used with lenalidomide there is a risk of fetal harm, including severe life-threatening human birth defects associated with these agents, and the need to follow requirements regarding pregnancy avoidance, including testing and contraception. Lenalidomide is present in the blood and sperm of patients receiving the drug.

Please refer to the Product Information for requirements regarding contraception due to presence and transmission in sperm and for additional detail. Patients receiving EMPLICITI in combination with lenalidomide should adhere to the pregnancy prevention programme of lenalidomide.

Use in hepatic impairment

EMPLICITI is an IgG1 monoclonal antibody, which is likely eliminated via several pathways similar to that of other antibodies. Hepatic excretion is not expected to play a dominant role in the excretion of EMPLICITI. Based on a population pharmacokinetic analysis, no dose adjustment of EMPLICITI is recommended for patients with mild hepatic impairment. EMPLICITI has not been studied in patients with moderate or severe hepatic impairment (see 5.3 PHARMACOKINETICS PROPERTIES).

Use in renal impairment

In a study evaluating EMPLICITI in patients with renal impairment, the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone did not significantly differ between patients with normal renal function, severe renal impairment not requiring dialysis, or end-stage renal disease requiring dialysis. Dose adjustments of EMPLICITI are not needed in patients with mild,

moderate, severe renal impairment or end-stage renal disease requiring dialysis (see 5.3 PHARMACOKINETICS PROPERTIES).

Use in the elderly

Of the 785 patients across treatment groups in Studies Eloquent-2 (CA204-004) and CA204-009, 57% were ≥65 years of age; the number of patient's ≥65 years was similar between treatment groups for either study. No overall differences in safety or efficacy were observed between patients ≥65 years and younger patients (<65 years) in either study.

Paediatric use

The safety and effectiveness of EMPLICITI in paediatric patients have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Elotuzumab is a humanised monoclonal antibody. Therefore, pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of elotuzumab.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies to evaluate the effect of elotuzumab on fertility have not been performed. Thus, the effect of elotuzumab on male and female fertility is unknown.

Use in pregnancy (CATEGORY C)

There are no data from the use of elotuzumab in pregnant women. Animal reproduction studies have not been conducted with elotuzumab. It is also not known whether elotuzumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

EMPLICITI should not be used during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefit to the patient clearly outweighs the potential risk to the fetus.

Use in lactation.

It is unknown whether elotuzumab is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. However, because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breastfeeding or to discontinue from EMPLICITI therapy, taking into account the benefit of breastfeeding for the child and the benefit of EMPLICITI therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. On the basis of reported adverse reactions, EMPLICITI is not expected to influence the ability to drive or use machines. Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety data of elotuzumab have been assessed from a total of 554 patients with multiple myeloma treated with elotuzumab in combination with lenolidomide and dexamethasone or bortezomib and

dexamethasone pooled across 6 clinical trials. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The most serious adverse reaction that may occur during elotuzumab treatment is pneumonia.

The most common adverse reactions (occurring in > 10% of patients) with elotuzumab treatment were cough, herpes zoster, nasopharyngitis, pneumonia, upper respiratory tract infection and weight decreased.

ADVERSE EVENTS REPORTED IN STUDY CA204-004

Adverse events reported in patients with multiple myeloma at a frequency of 10% or higher in the EMPLICITI arm and 5% or higher than the lenalidomide and dexamethasone arm in study CA204-004 are presented in Table 4.

Table 4: Adverse Events Reported with a 10% or Higher Incidence for EMPLICITI-Treated Patients and a 5% or Higher Incidence than Lenalidomide and Dexamethasone-Treated Patients (All Grades) in Study CA204-004

	EMPLICITI + Lenalidomide and Dexamethasone N=318		Lenalidomide and Dexamethasone N=317	
Primary Term	All Grades	Grade3/4	All Grades	Grade 3/4
Fatigue*	61.6	12.6	51.7	11.7
Diarrhoea	46.9	5.0	36.0	4.1
Pyrexia	37.4	2.5	24.6	2.8
Constipation	35.5	1.3	27.1	0.3
Cough†	34.3	0.3	18.9	0
Peripheral Neuropathy‡	26.7	3.8	20.8	2.2
Nasopharyngitis	24.5	0	19.2	0
Upper Respiratory Tract Infection	22.6	0.6	17.4	1.3
Decreased Appeitite	20.8	1.6	12.6	1.3
Pneumonia§	20.1	14.2	14.2	9.5
Pain in Extemities	16.4	0.9	10.1	0.3
Headache	15.4	0.3	7.6	0.3
Vomiting	14.5	0.3	8.8	0.9
Weight Decreased	13.8	1.3	6.0	0
Lymphopenia	13.2	8.8	6.9	3.2
Catarcts	11.9	6.3	6.3	2.8
Oropharyngeal Pain	10.1	0	4.4	0

* The term fatigue is a grouping of the following terms: fatigue and asthenia.

† The term cough is a grouping of the following terms: cough, productive cough, and upper airway cough.

‡ The term peripheral neuropathy is a grouping of the following terms: peripheral neuropathy, axonal neuropathy, peripheral motor neuropathy, peripheral senosry neuropathy, and polyneuropathy.

§ The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

Table 5: Laboratory Abnormalities Worsening from Baseline and with a 10% or Higher Incidence for EMPLICITI-Treated Patients and a 5% Higher Incidence than Lenalidomide and Dexamethasone-Treated Patients.

	EMPLICITI + Lenalidomide and Dexamethasone N=318		Lenalidomide and Dexamethasone N=317	
Laboratory Parameter	All Grades	Grade3/4	All Grades	Grade 3/4
Haematology				
Lymphopenia	99.4	76.7	98.4	48.7
Leukopenia	90.6	32.4	88.3	25.6

	EMPLICITI + Lenalidomide and Dexamethasone N=318		Lenalidomide and Dexamethasone N=317	
Thrombocytopenia	83.6	19.2	77.8	20.3
Liver and Renal Function Tests				
Hypoalbuminaemia	73.3	3.9	65.6	2.3
Elevated Alkaline Phosphatase	38.7	1.3	29.8	0
Chemistry				
Hyperglycaemia	89.3	17.0	85.4	10.2
Hypocalcaemia	78.0	11.3	76.7	4.7
Low Bicarbonate	62.9	0.4	45.1	0
Hyperkalaemia	32.1	6.6	22.2	1.6

DESCRIPTION OF SELECT ADVERSE REACTIONS

Infusion reactions

In a clinical trial of patients with multiple myeloma (Study CA204-004), infusion reactions were reported in approximately 10% of premedicated patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The frequency of infusion reactions was much higher in patients who were not premedicated. All reports of infusion reaction were ≤ Grade 3. Grade 3 infusion reactions occurred in 1% of patients. The most common symptoms of an infusion reaction included fever, chills, and hypertension. Five percent (5%) of patients required interruption of the administration of EMPLICITI for a median of 25 minutes due to infusion reaction, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had the reaction during the first dose.

Infections

The incidence of infections, including pneumonia, was higher with Empliciti treatment than with control (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In a clinical trial of patients with multiple myeloma (Study CA204-004), infections were reported in 81.4% of patients in the EMPLICITI combined with lenalidomide and dexamethasone arm (N=318) and 74.4% in lenalidomide and dexamethasone arm (N = 317). Grade 3-4 infections were noted in 28% and 24.3% of EMPLICITI combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Fatal infections were infrequent and were reported in 2.5% of EMPLICITI combined with lenalidomide and dexamethasone and 2.2% of lenalidomide and dexamethasone treated patients. The incidence of pneumonia was higher in the EMPLICITI combined with lenalidomide and dexamethasone arm compared to lenalidomide and dexamethasone arm reported at 15.1% vs. 11.7% with a fatal outcome at 0.6% vs. 0%, respectively.

Second Primary Malignancies (SPMs)

The incidence of SPMs was higher with Empliciti treatment than with control (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In a clinical trial of patients with multiple myeloma (Study CA204-004), invasive SPMs have been observed in 6.9% of patients treated with EMPLICITI combined with lenalidomide and dexamethasone (N = 318) and 4.1% of patients treated with lenalidomide and dexamethasone (N = 317).

Second Primary Malignancies are known to be associated with lenalidomide exposure which was extended in patients treated with EMPLICITI combined with lenalidomide and dexamethasone vs. lenalidomide and dexamethasone. The rate of haematologic malignancies were the same between the two treatment arms (1.6%). Solid tumours were reported in 2.5% and 1.9% of EMPLICITI combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Non-melanoma skin cancer was reported in 3.1% and 1.6% of patients treated with EMPLICITI combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone, respectively.

ADVERSE REACTIONS REPORTED ACROSS CLINICAL TRIALS

The safety data of elotuzumab have been assessed from a total of 554 patients with multiple myeloma treated with elotuzumab in combination with lenolidomide and dexamethasone or bortezomib and dexamethasone pooled across 6 clinical trials. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Across the clinical studies adverse reactions reported in patients treated with EMPLICITI with at a cut off ≥ 10% included:

Investigations: weight decreased
Respiratory, thoracic, and mediastinal disorders: Cough (including productive cough, and upper-airway cough syndrome)
Blood and lymphatic system disorders: lymphopenia (including lymphocyte count decreased)

Other clinically important adverse reactions reported in patients treated with EMPLICITI with a cut-off of ≤ 10%) were:

Musculoskeletal and connective tissue disorders: chest pain
Nervous system disorders: hypoesthesia
Psychiatric disorders: mood altered
Skin and subcutaneous tissue disorders: night sweats
Immune system disorders: hypersensitivity
Infections and infestations: herpes zoster
Injury, poisoning, and procedural complications: infusion-related reaction

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

One patient was reported to be overdosed with 23.3 mg/kg of elotuzumab in combination with lenalidomide and dexamethasone. The patient had no infusion reaction, no symptoms, did not require any treatment for the overdose, and was able to continue on elotuzumab therapy.

The maximum tolerated dose has not been determined. In clinical studies, approximately 78 patients were evaluated with elotuzumab at 20 mg/kg without apparent toxic effects.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Elotuzumab is an immunostimulatory humanised, IgG1 monoclonal antibody that specifically targets the SLAMF7 (signaling lymphocyte activation molecule family member 7) protein. SLAMF7 is highly expressed on multiple myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer cells, natural killer T cells, plasma cells, and at lower levels on some CD8+ T cells and other specific immune cell subsets, but is not detected on normal solid tissues or hematopoietic stem cells.

Elotuzumab targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells (via Fc receptors) to mediate the killing of myeloma cells through

antibody-dependent cellular cytotoxicity (ADCC). Elotuzumab also directly activates natural killer cells through the SLAMF7 pathway to enhance anti-myeloma activity *in vitro*. In preclinical models, elotuzumab has demonstrated synergistic activity when combined with lenalidomide or bortezomib.

Clinical trials

Eloquent-2 (Study CA204-004)

A randomised, open-label study was conducted to evaluate the efficacy and safety of EMPLICITI in combination with lenalidomide and dexamethasone in patients with multiple myeloma who have received one to three prior therapies. All patients had documented progression following their most recent therapy.

Eligible patients were randomised in a 1:1 ratio to receive either EMPLICITI in combination with lenalidomide and low dose dexamethasone or lenalidomide and low dose dexamethasone. Treatment was administered in 4-week cycles until disease progression or unacceptable toxicity. EMPLICITI 10 mg/kg was administered intravenously each week for the first 2 cycles and every 2 weeks thereafter. Prior to EMPLICITI infusion, dexamethasone was administered as a divided dose: an oral dose of 28 mg and an intravenous dose of 8 mg. In the control group and on weeks without EMPLICITI, dexamethasone 40 mg was administered as a single oral dose weekly. Lenalidomide 25 mg was taken orally once daily for the first 3 weeks of each cycle. Assessment of tumour response was conducted every 4 weeks.

A total of 646 patients were randomised to receive treatment: 321 to EMPLICITI in combination with lenalidomide and dexamethasone and 325 to lenalidomide and low dose dexamethasone.

Demographics and baseline characteristics were well balanced between treatment arms. The median age was 66 years (range 37 to 91); 57% of patients were older than 65 years; 60% of patients were male; Caucasians comprised 84% of the study population, Asians 10%, and Blacks 4%. The ISS Stage was I in 43%, II in 32% and III in 21% of patients. The high risk cytogenetic categories of del17p and t(4;14) were present in 32% and 9% of patients, respectively. The median number of prior therapies was 2. Thirty-five percent (35%) of patients were refractory (progression during or within 60 days of last therapy) and 65% were relapsed (progression after 60 days of last therapy). Prior therapies included: stem cell transplant (54%), bortezomib (70%) melphalan (65%), thalidomide (48%), and lenalidomide (6%).

The primary endpoints of this study, progression-free survival (PFS), as assessed by hazard ratio, and overall response rate (ORR) were determined based on assessments made by a blinded Independent Review Committee. The median number of treatment cycles was 19 for the EMPLICITI arm and 14 for the comparator arm. Efficacy results are presented in Table 6 and Figure 1.

Table 6: Efficacy Results for Eloquent-2 (Study CA204-004)

	EMPLICITI + Lenalidomide/ Dexamethasone N = 321	**Lenalidomide/ Dexamethasone N = 325**
PFS (ITT)		
Hazard Ratio [97.61% CI]	0.68 [0.55, 0.85]	
Stratified log-rank test p-value[a]	0.0001	
1-Year PFS rate (%) [95% CI]	68 [63, 73]	56 [50, 61]
2-Year PFS rate (%) [95% CI]	39 [34, 45]	26 [21, 31]

	EMPLICITI + Lenalidomide/ Dexamethasone N = 321	Lenalidomide/ Dexamethasone N = 325
Median PFS in months [95% CI]	18.5 [16.5, 21.4]	14.3 [12.0, 16.0]
Response		
Overall Response (ORR)[b] n (%) [95% CI]	252 (78.5) [73.6, 82.9]	213 (65.5) [60.1, 70.7]
p-value[c]	0.0002	
Complete Response (CR + sCR)[d] n (%)	14 (4.4)[e]	24 (7.4)
Very Good Partial Response (VGPR) n (%)	91 (28.3)	67 (20.6)
Partial Response (RR/PR) n (%)	147 (45.8)	122 (37.5)
Combined Responses (CR+sCR+VGPR) n (%)	105 (32.7)	91 (28.0)

a p-alue based on the log-rank test stratified by B2 microglobulins (<3.5 mg/L versus ≥ 3.5mg/L), number of prior lines of therapy (1 versus 2 or 3), and prior immunomodulatory therapy (no versus prior thalidomide only versus other)

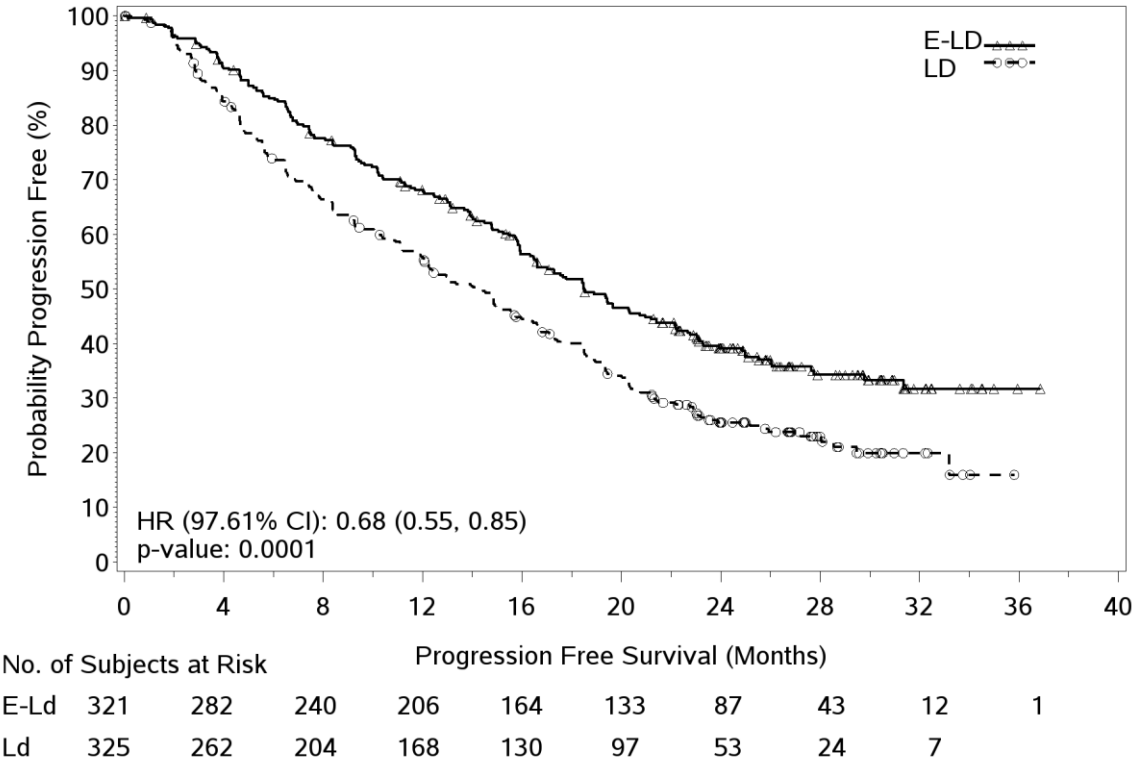
b European Group for Blood and Marrow Transplantation (EBMT) criteria

c p-value based on the Cochran-Mantel-Haenzel chi-square test stratified by B2 microglobulins (<3.5 mg/L versus ≥3.5 mg/L), number of prior lines of therapy (1 versus 2 or 3), and prior immunomodulatory therapy (no versus prior thalidomide only versus other)

d complete response (CR) + stringent complete response (sCR)

e complete response rates in EMPLICITI group may be underestimated due to interference of elotuzumab monoclonal antibody with immunofixation assay and serum protein electrophoresis assay.

Figure 1: Progression Free Survival for Eloquent-2 (Study CA204-004)



E-Ld = elotuzumab/lenalidomide/low-dose dexamethasone combination regimen
Ld = lenalidomide/low-dose dexamethasone combination regimen

With a minimum follow-up time of 23.4 months, the 1- and 2-year rates of PFS for EMPLICITI in combination with lenalidomide and dexamethasone treatment were 68% and 39%, respectively, compared with 56% and 26%, respectively, for lenalidomide and dexamethasone treatment.

Improvements observed in PFS were consistent across subsets regardless of cytogenetic category (presence or absence of cytogenetic categories del 17p or t (4;14)), age (<65 versus ≥65), ISS stage, prior immunomodulatory agent exposure, prior bortezomib exposure, relapsed or refractory status, or renal function.

The 1- and 2-year rates of Overall Survival (OS) for EMPLICITI in combination with lenalidomide and dexamethasone treatment were 91% and 73%, respectively, compared with 83% and 69%, respectively, for lenalidomide and dexamethasone treatment.

Study CA204-009

In a Phase 2, randomised open label study in a total of 152 subjects, the 1-year rate of PFS for EMPLICITI in combination with bortezomib and dexamethasone treatment was 39% compared with 33% for bortezomib and dexamethasone treatment (hazard ratio = 0.72 70% CI [0.59, 0.88]; median = 9.7 months 95% CI [7.4, 12.2]) compared to bortezomib and dexamethasone (median = 6.9 months 95% CI [5.1, 10.2]).

Improvements observed in PFS were consistent across subsets regardless of age (< 65 versus ≥ 65), cytogenic categories (presence or absence of del 17p or t(4;14)), ISS Stage, prior immunomodulatory exposure, prior proteasome inhibitor exposure, or renal function.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to EMPLICITI.

Of 390 patients across four clinical studies who were treated with EMPLICITI and evaluable for the presence of anti-product antibodies, 72 patients (18.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 19 of 299 patients in Eloquent-2 (Study CA204-004). In the majority of patients, immunogenicity occurred early in treatment and was transient, resolving by 2 to 4 months. There was no clear causal evidence of altered pharmacokinetic, efficacy, or toxicity profiles with anti-product antibody development based on the population pharmacokinetic and exposure-response analyses.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Elotuzumab is administered intravenously.

Distribution

The pharmacokinetics of elotuzumab was studied in patients with multiple myeloma who received doses ranging from 0.5 to 20 mg/kg. Elotuzumab exhibits nonlinear pharmacokinetics with clearance of elotuzumab decreasing from 19.2 to 5.3 17.5 to 5.8 mL/day/kg with an increase in dose from 0.5 to 20 mg/kg, suggesting target-mediated clearance, resulting in greater than proportional increases in Area under the Concentration time curve (AUC). The volume of distribution for elotuzumab approximated the serum volume and appeared to be independent of dose. Upon discontinuation of elotuzumab, concentrations will decrease to approximately 3% (approximately 97% washout) of the population predicted steady-state maximal serum concentration by 3 months. Administration of 10 mg/kg elotuzumab treatment resulted in steady-state trough concentrations in excess of 70 μg/mL, the target threshold concentration for maximal efficacy observed in the preclinical xenograft human multiple myeloma mouse model.

Special Populations

Based on a population PK analysis using data from 375 patients, the clearance of elotuzumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of elotuzumab: age (37 to 88 years), gender, race, baseline LDH, albumin, renal impairment, and mild hepatic impairment.

Renal Impairment

An open-label study evaluated the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone in patients with multiple myeloma with varying degrees of renal impairment (classified using the CrCL values). The effect of renal impairment on the pharmacokinetics of elotuzumab was evaluated in patients with normal renal function (CrCl > 90 mL/min; n = 8), severe renal impairment not requiring dialysis (CrCl <30 mL/min; n = 9), or end-stage renal disease requiring dialysis (CrCl < 30 mL/min; n = 9). No clinically important differences in the pharmacokinetics of elotuzumab were found between patients with severe renal impairment (with and without dialysis) and patients with normal renal function (see 4.2 DOSE & METHOD OF ADMINSTRATION).

Hepatic Impairment

The effect of hepatic impairment on the clearance of EMPLICITI was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n = 33). No clinically important differences in the clearance of EMPLICITI were found between patients with mild hepatic impairment and patients with normal hepatic function. Elotuzumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST) (see 4.2 DOSE & METHOD OF ADMINSTRATION).

Cardiac Electrophysiology

No changes in mean QT interval were detected in EMPLICITI-treated patients based on Fridericia correction method. The potential effect of elotuzumab on QTc interval prolongation was evaluated in 41 patients at doses of 10 and 20 mg/kg either as monotherapy or in combination with lenalidomide and dexamethasone.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity data are available for elotuzumab. As a large molecular weight protein, elotuzumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity data are available for elotuzumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate
Citric acid monohydrate,
Sucrose,
Polysorbate 80.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

EMPLICITI lyophilized powder must be refrigerated at 2°C-8°C. Do not freeze or shake.

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

For storage conditions after reconstitution for the fully diluted product(see ADMINSTRATION in 4.2 DOSE AND METHOD OF ADMINISTRATION).

After reconstitution: chemical and physical in use stability of the reconstituted solution has been demonstrated for 24 hours, under refrigerated conditions (2°C-8°C) and protected from light.

From a microbiological point of view, the product should be used as soon as possible, but within 8 hours if stored at room temperature. (see ADMINSTRATION in 4.2 DOSE AND METHOD OF ADMINISTRATION)

6.5 NATURE AND CONTENTS OF CONTAINER

EMPLICITI is a lyophilized powder for intravenous infusion; it is supplied as a single-use vial in a 20 ml Type I glass vials, closed with 20 mm stoppers and sealed with aluminium flip off seals.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

CAS number: 915296-00-3

Chemical structure

Elotuzumab has a theoretical mass of 148.1 kDa for the intact antibody. The elotuzumab molecule consists of two identical heavy chain subunits and two identical light chain subunits which are covalently linked through disulfide bridges. The light and heavy chains have masses of 23.4 kDa and 50.6 kDa, respectively. These molecular weights exclude the contributions of glycosylation and other posttranslational modifications.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
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9 DATE OF FIRST APPROVAL (ARTG ENTRY)

22 September 2016

10 DATE OF REVISION OF THE TEXT

11 April 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2 Dose and Method of Administration	Added a row for 'Dexamethasone Intravenous' in Table 1 Corrected dose frequency for dexamethasone footnote in Table 1

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