PRODUCT INFORMATION

ZINPLAVA®

(bezlotoxumab)
Concentrated Injection

NAME OF THE MEDICINE

Bezlotoxumab

CAS No.: 1246264-45-8

DESCRIPTION

One vial contains bezlotoxumab 1,000 mg/40 mL.

ZINPLAVA (bezlotoxumab) is a specific fully human monoclonal antibody that binds with high affinity to *C. difficile* toxin B. Bezlotoxumab is an IgG_1 immunoglobulin with an approximate molecular weight of 148.2 kDa. Bezlotoxumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

ZINPLAVA concentrated injection is a sterile, preservative-free, clear to moderately opalescent, colourless to pale yellow liquid that requires dilution for intravenous infusion. Each vial contains bezlotoxumab and the following inactive ingredients: sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 80, pentetic acid, and Water for Injections. The vial may contain sodium hydroxide to adjust the pH to 6.0.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J06BB21

Mechanism of Action

Clostridium difficile colonizes and infects the large intestine. The bacterium expresses two exotoxins, toxin A and toxin B. In preclinical studies, the toxins have been shown to target host colonic epithelial cells, leading to tissue injury that disrupts the normal gut barrier function. In addition to their cytopathic/cytotoxic effects on cells, the toxins cause the release of pro-inflammatory mediators leading to the recruitment of neutrophils and other immune cells to the site of infection, which contributes to the persistence of tissue damage that underlies the symptoms of *Clostridium difficile* infection (CDI). CDI is generally treated with antibiotic therapy to kill the growing *C. difficile* bacteria that are expressing the toxins. Recurrence of CDI occurs due to persistent or newly-acquired *C. difficile* spores, whose outgrowth (leading to new toxin expression) is facilitated by the gut dysbiosis caused by antibiotics. In patients, endogenous antibody titres against *C. difficile* toxins have been reported to correlate with reduced recurrence of *C. difficile* infection. Bezlotoxumab is an antitoxin antibody that binds with high affinity ($Kd<1\times10^{-9}M$) to *C. difficile* toxin B and neutralises its activity by preventing it from binding to host cells. Bezlotoxumab does not bind to *C.difficile* toxin A. In MODIFY I and MODIFY II, ZINPLAVA prevented the recurrence of CDI when administered in combination with Standard of Care (SoC) antibiotics during an active episode of CDI. ZINPLAVA prevents CDI recurrence by providing enhanced passive immunity against toxin produced by the outgrowth of persistent or newly-acquired *C. difficile* spores.

Pharmacodynamic effects

Microbiology

Activity In Vitro and In Vivo
The epitope of bezlotoxumab is conserved, though not identical, across all known toxin sequences. Bezlotoxumab neutralizes the cytotoxic activities of toxin B from all clinical isolates of *C. difficile* tested (ribotypes 001, 002, 003, 012, 014, 017, 018, 023, 027, 053, 063, 077, 078, 081, 087, 106, 198, and 369).

In a gnotobiotic piglet model of CDI, bezlotoxumab reduced mortality and protected against intestinal damage and inflammation. Similar results were obtained in mice and hamster models of CDI, including recurrent CDI, although full protection in these models required co-administration of a toxin A-neutralising antibody.

Pharmacokinetics

The pharmacokinetics of bezlotoxumab were studied in 1,515 patients in MODIFY I and MODIFY II. After a single IV dose of 10 mg/kg bezlotoxumab, mean $AUC_{(0-\infty)}$ and C_{max} were 5,3000 mcg.h/mL and 185 mcg/mL, respectively. Bezlotoxumab exposures in healthy subjects increased in an approximately dose proportional manner across the 0.3 to 20 mg/kg dose range.

Absorption

Bezlotoxumab is dosed via the IV route and therefore is immediately and completely bioavailable.

Distribution

Bezlotoxumab has limited extravascular distribution. The mean volume of distribution of bezlotoxumab was 7.33 L (CV: 16%).

Metabolism

Bezlotoxumab is catabolised through protein degradation processes; metabolism does not contribute to its clearance.

Elimination

Bezlotoxumab is eliminated from the body primarily by protein degradation. The mean clearance of bezlotoxumab was 0.317 L/day (CV: 41%) and the terminal half-life (t½) was approximately 19 days (28%).

Special populations

The effects of various covariates on the pharmacokinetics of bezlotoxumab were assessed in a population pharmacokinetic analysis. The clearance of bezlotoxumab increased with increasing body weight; the resulting exposure differences are adequately addressed by the administration of a weight-based dose.

The following factors had no clinically meaningful effect on the exposure of bezlotoxumab and no dose adjustment is required: age (range 18 to 100 years), gender, race, ethnicity, renal impairment, hepatic impairment, and presence of co-morbid conditions.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bezlotoxumab was evaluated in patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), or severe (eGFR 15 to < 30 mL/min/1.73 m^2) renal impairment, or with end stage renal disease (eGFR < 15 mL/min/1.73 m^2), as compared to patients demonstrating normal (eGFR ≥90 mL/min/1.73 m^2) renal function. No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of bezlotoxumab was evaluated in patients with hepatic impairment (defined as having two or more of the following: [1] albumin ≤ 3.1 g/dL; [2] ALT ≥2X ULN; [3] total bilirubin ≥1.3X ULN; or [4] mild, moderate or severe liver disease as reported by the Charlson Co-morbidity Index), as compared to patients with normal hepatic function. No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with hepatic impairment and patients with normal hepatic function.

Geriatric

The effect of age on the pharmacokinetics of bezlotoxumab was evaluated in patients ranging from 18 to 100 years of age. No clinically meaningful differences in the exposure of bezlotoxumab were found between elderly patients 65 years and older and patients under 65 years of age.

CLINICAL TRIALS

The safety and efficacy of ZINPLAVA (bezlotoxumab) were investigated in two randomised, double-blind, placebo-controlled, multicenter, Phase 3 studies (MODIFY I and MODIFY II) in 2,655 patients receiving concomitant oral Standard of Care (SoC) antibiotic therapy for CDI.

Randomisation was stratified by SoC antibiotic and hospitalisation status (inpatient vs. outpatient) at the time of study entry. In MODIFY I, subjects were randomised in a 1:1:1:1 ratio to receive ZINPLAVA, anti-toxin A, ZINPLAVA plus anti-toxin A, or placebo. In MODIFY II, subjects were randomised in a 1:1:1 ratio to receive ZINPLAVA, ZINPLAVA plus anti-toxin A, or placebo. Anti-toxin A when given alone was not shown to prevent CDI recurrence compared to placebo, and ZINPLAVA plus anti-toxin A was not superior to ZINPLAVA in preventing CDI recurrence. Therefore, the anti-toxin A and ZINPLAVA plus anti-toxin A arms are not described.

Enrolled patients were 18 years of age or older and had a confirmed diagnosis of CDI, which was defined as diarrhoea (passage of 3 or more loose bowel movements in 24 or fewer hours) and a positive stool test for toxigenic *C. difficile* from a stool sample collected no more than 7 days before study entry. Patients were excluded if surgery for CDI was planned, or if they had uncontrolled chronic diarrhoeal illness. Patients received a 10- to 14-day course of oral SoC antibiotic for CDI (metronidazole, vancomycin or fidaxomicin) and a single infusion of ZINPLAVA or placebo was administered prior to completion of the SoC antibiotic therapy; patients were followed for 12-weeks following the infusion. Patients on oral vancomycin or oral fidaxomicin could have also received IV metronidazole. Choice of SoC antibiotic therapy was at the discretion of the health care provider.

The baseline characteristics of the 1,554 patients receiving ZINPLAVA or placebo were similar across treatment groups and in MODIFY I and MODIFY II. The median age was 65 years, 85% were white, 57% were female, and 68% were inpatients. A similar proportion of patients were receiving oral metronidazole (48%) or oral vancomycin (48%) as their SoC antibiotic. A small proportion of patients received oral fidaxomicin (4%) as the SoC antibiotic. The following risk factors associated with an increased risk of CDI recurrence or CDI-related adverse outcomes were

present in the study population at entry: 51% were ≥ 65 years of age, 39% received one or more systemic antibiotics (during the 12-week follow-up period), 28% had one or more episodes of CDI within the six months prior to the episode under treatment (15% had two or more episodes prior to the episode under treatment), 21% were immunocompromised and 16% presented with clinically severe CDI. A hypervirulent strain (ribotypes 027, 078 or 244) was isolated in 22% of patients who had a positive baseline culture, of which the majority (87%, 189 of 217 strains) were ribotype 027.

The primary efficacy endpoint was the proportion of patients with recurrence of CDI through 12 weeks following administration of the study infusion. CDI recurrence was defined as the development of a new episode of diarrhoea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode. Clinical cure was defined as no diarrhoea for 2 consecutive days following a ≤14 day regimen of SoC antibiotic. In a prospectively planned combined analysis of MODIFY I and MODIFY II, ZINPLAVA was superior to placebo in the prevention of CDI recurrence (see **Table 1**).

Table 1: CDI Recurrence Rate Through 12 Weeks After Infusion (MODIFY I and MODIFY II, Full Analysis Set [*])

ZINPLAVA with SoC [†] Percent (n/N)	Placebo with SoC [†] Percent (n/N)	Adjusted Difference (95% CI) [‡]	p-value
16.5 (129/781)	26.6 (206/773)	-10.0 (-14.0, -6.0)	<0.0001

n = Number of subjects in the analysis population meeting the criteria for endpoint

N = Number of subjects included in the analysis population

[*] Full Analysis Set = a subset of all randomised subjects with exclusions for: (i) did not receive infusion of study medication, (ii) did not have a positive local stool test for toxigenic C. difficile; (iii) did not receive protocol defined standard of care therapy within a 1 day window of the infusion

[†] SoC = Standard of Care antibiotic (metronidazole or vancomycin or fidaxomicin)

[‡] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (MODIFY I and MODIFY II), SoC antibiotic (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)

In a prospectively planned combined analysis of MODIFY I and MODIFY II, the CDI recurrence rates in pre-specified subgroups of patients predisposed to CDI recurrence and/or at risk for severe outcomes are presented in **Table 2**. In the subgroups studied, the proportion of patients with CDI recurrence in the ZINPLAVA treatment group was consistently lower than the proportion of patients with CDI recurrence in the placebo group.

Table 2: CDI Recurrence Rate by Subgroup (MODIFY I and MODIFY II, Full Analysis Set [*])

Characteristic at study entry	ZINPLAVA with SoC [†] Percent (n/m)	Placebo with SoC [†] Percent (n/m)	Difference (95% CI) [‡]
Age ≥ 65 years	15.4 (60/390)	31.4 (127/405)	-16.0 (-21.7, -10.2)
History of one or more episodes of CDI in past 6 months	25.0 (54/216)	41.1 (90/219)	-16.1 (-24.7, -7.3)
Immunocompromised [§]	14.6 (26/178)	27.5 (42/153)	-12.8 (21.7, -4.1)

Severe CDI ¶	10.7 (13/122)	22.4 (28/125)	-11.7 (-21.1, -2.5)
Infected with a Hypervirulent strain #	21.6 (22/102)	32.2 (37/115)	-10.6 (-22.1, 1.3)
Infected with 027 ribotype	23.6 (21/89)	34.0 (34/100)	-10.4 (-23.0, 2.6)

n = Number of subjects within subgroup that met the criteria for endpoint

m = Number of subjects within subgroup

* Full Analysis Set = a subset of all randomised subjects with exclusions for: (i) did not receive infusion of study medication, (ii) did not have a positive local stool test for toxigenic *C. difficile*; (iii) did not receive protocol defined standard of care therapy within a 1 day window of the infusion

† SoC = Standard of Care antibiotic (metronidazole or vancomycin or fidaxomicin)

‡ Based on the Miettinen and Nurminen method without stratification

§ Based on medical conditions or medications received that may result in immunosuppression

¶ Zar score ≥2

Hypervirulent strain included the following: 027, 078, or 244 ribotypes

A secondary endpoint was global cure, defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion. In the combined data across MODIFY I and MODIFY II, ZINPLAVA was superior to placebo in achieving global cure (64% for ZINPLAVA vs. 54% for placebo, one-sided p <0.0001).

INDICATIONS

ZINPLAVA® (bezlotoxumab) is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adult patients 18 years or older at high risk for recurrence of CDI who are receiving antibiotic therapy for CDI (see CLINICAL TRIALS).

ZINPLAVA is not indicated for the treatment of CDI. ZINPLAVA is not an antibacterial drug. ZINPLAVA should only be used in conjunction with antibacterial drug treatment of CDI.

The safety and efficacy of repeat administration of ZINPLAVA in patients with CDI have not been studied.

CONTRAINDICATIONS

ZINPLAVA is contraindicated in patients with hypersensitivity to bezlotoxumab or to any of the inactive ingredients.

PRECAUTIONS

Heart Failure

Heart failure was reported more commonly in the two Phase 3 clinical trials in ZINPLAVA-treated patients compared to placebo-treated patients. These adverse reactions occurred primarily in patients with underlying congestive heart failure (CHF). In patients with a history of CHF, 12.7% (15/118) of ZINPLAVA-treated patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure during the 12-week study period (see ADVERSE EFFECTS). Additionally, in patients with a history of CHF, there were more deaths in ZINPLAVA-treated patients, 19.5% (23/118) than in placebo-treated patients, 12.5% (13/104) during the 12-week study period. The causes of death varied and included cardiac failure, infections, and respiratory failure.

In patients with a history of CHF, ZINPLAVA should be reserved for use when the benefit outweighs the risk.

Treatment of acute CDI episode

ZINPLAVA is not an antibiotic, and is not indicated for the treatment of an acute episode of CDI.

ZINPLAVA should be administered during a course of antibiotic therapy for CDI [see DOSAGE AND ADMINISTRATION].

Effects on Fertility

Animal reproduction studies have not been conducted with bezlotoxumab. There were no notable effects in the male and female reproductive organs in mice based on repeat dose toxicity studies and no binding to reproductive tissues was observed in tissue cross-reactivity studies.

Use in Pregnancy (Category B2)

Bezlotoxumab targets a non-endogenous microbial toxin antigen and lacks toxicologically relevant cross-reactivity to human tissues including reproductive tissues. Animal reproduction studies have not been conducted with bezlotoxumab. Adequate and well controlled studies with ZINPLAVA have not been conducted in pregnant women. As it is not known whether ZINPLAVA can cause foetal harm or affect reproductive capacity in pregnant women, this drug should be used during pregnancy only if clearly needed.

Use in Lactation

It is unknown whether bezlotoxumab is secreted in human milk. Because monoclonal antibodies may be excreted in human milk, a decision should be made whether to discontinue nursing or to not administer ZINPLAVA, taking into account the importance of ZINPLAVA to the mother.

Paediatric Use

Safety and efficacy of ZINPLAVA in patients below 18 years of age have not been established.

Use in the elderly

Of the 786 patients treated with ZINPLAVA, 50% were 65 years of age and over. Safety and efficacy were demonstrated in these patients [see CLINICAL TRIALS]. No dose adjustment is necessary in this population [see PHARMACOLOGY].

Renal impairment

No dose adjustment is needed for patients with renal impairment [see PHARMACOLOGY].

Hepatic impairment

No dose adjustment is needed for patients with hepatic impairment [see PHARMACOLOGY].

Genotoxicity

The genotoxic potential of bezlotoxumab has not been evaluated.

Carcinogenicity

The carcinogenic potential of bezlotoxumab has not been evaluated in long-term animal studies.

INTERACTIONS WITH OTHER MEDICINES

No formal pharmacokinetic drug interaction studies have been conducted with bezlotoxumab. Since bezlotoxumab is eliminated by catabolism, no metabolic drug-drug interactions are expected.

ADVERSE EFFECTS

Clinical trials experience

The safety of ZINPLAVA was evaluated in two placebo-controlled, Phase 3 studies (MODIFY I and MODIFY II) in patients receiving a single dose of ZINPLAVA of 10 mg/kg and concomitant standard of care (SoC) antibiotic therapy (metronidazole, vancomycin or fidaxomicin) for CDI.

Adverse reactions (adverse events regardless of causality or severity) reported within the first 4 weeks after ZINPLAVA was administered are described for the pooled Phase 3 trial population of 786 patients. The median age of patients receiving ZINPLAVA was 65 years (range 18 to 100), 50% were age 65 years or older, 56% were female, and 83% were white.

The type and severity of adverse reactions in patients treated with ZINPLAVA was comparable to that in patients treated with placebo. The most common adverse reactions following treatment with ZINPLAVA (reported in ≥ 4% of patients within the first 4 weeks of infusion) were nausea, diarrhoea, pyrexia and headache. Adverse reactions reported in at least 4% of ZINPLAVA treated patients, with a frequency greater than placebo are shown in **Table 3**.

Table 3: Adverse Reactions Reported Within 4 Weeks of Infusion in ≥4% of ZINPLAVA-treated Patients and at a Frequency Greater than Placebo in the MODIFY I and MODIFY II Trials [*]

Adverse Reaction	ZINPLAVA with SoC [†] N=786 % (n)	Placebo with SoC [†] N=781 % (n)
Gastrointestinal disorders		
Diarrhoea	6 (47)	6 (45)
Nausea	7 (52)	5 (39)
General disorders and administration site conditions		
Pyrexia	5 (36)	3 (27)
Nervous system disorders		
Headache	4 (35)	3 (24)

*	All patients as treated population, defined as all randomised patients who received a dose of study medication, by treatment received
†	SoC = Standard of Care antibiotic (metronidazole or vancomycin or fidaxomicin)

Serious adverse reactions occurring within 12 weeks following infusion were reported in 29% of ZINPLAVA-treated patients and 33% in patients receiving placebo. Four of 786 patients treated with ZINPLAVA had serious adverse reactions that were considered to be drug-related (one report each of diarrhoea, ventricular tachyarrhythmia, haematuria, sepsis, and cerebral haemorrhage); all occurred within 4 weeks of receiving ZINPLAVA. Of these four patients, one patient discontinued the ZINPLAVA infusion due to the event (ventricular tachyarrhythmia). There were no other ZINPLAVA-treated patients who discontinued therapy due to adverse reactions.

Heart failure was reported as a serious adverse reaction in 2.3% of the ZINPLAVA-treated patients and 1.0% of the placebo-treated patients (see PRECAUTIONS).

Mortality rates were similar across treatment arms (7% in ZINPLAVA treatment arm and 8% in the placebo treatment arm) during the 12-week follow-up period.

In a Phase 1 clinical trial, healthy subjects received two consecutive doses of 10 mg/kg of bezlotoxumab separated by 12 weeks. The adverse reactions after the second dose were not markedly different from those observed after the first dose, and are consistent with adverse reactions observed in MODIFY I and MODIFY II during which all patients received a single dose.

Infusion Related Reactions
Overall, 10% of subjects in the ZINPLAVA group experienced one or more infusion specific adverse reactions on the day of, or the day after, the infusion compared to 8% in the placebo group. Infusion specific adverse reactions reported in ≥0.5% of subjects receiving ZINPLAVA and at a frequency greater than placebo were nausea (3%), fatigue (1%), pyrexia (1%), dizziness (1%), headache (2%), dyspnoea (1%) and hypertension (1%). Of the patients who experienced an infusion specific adverse reaction, the majority reported a reaction with a maximum intensity of mild (78%) or moderate (20%), and the majority of reactions resolved within 24 hours following onset.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity following administration of ZINPLAVA. Immunogenicity of ZINPLAVA was evaluated using an electrochemiluminescence (ECL) assay in MODIFY I and MODIFY II.

Following treatment with ZINPLAVA in MODIFY I and MODIFY II, none of the 710 evaluable patients tested positive for treatment-emergent anti-bezlotoxumab antibodies. Although ZINPLAVA is intended for single dose administration, the immunogenicity of bezlotoxumab following a second administration of 10 mg/kg, 12 weeks after the first dose, was assessed in 29 healthy subjects. No anti-bezlotoxumab antibodies were detected after the second dose.

DOSAGE AND ADMINISTRATION

ZINPLAVA® (bezlotoxumab) should be administered during a course of antibiotic therapy for CDI [see PRECAUTIONS].

Dose Recommendations in Adults

The recommended dose of ZINPLAVA is 10 mg/kg based on patient body weight administered as an intravenous (IV) infusion over 60 minutes as a single dose.

Preparation and Administration

Preparation of Diluted Solution

- Prepare the diluted solution immediately after removal of the vial(s) from refrigerated storage, or the vial(s) may be stored at room temperature protected from light for up to 24 hours prior to preparation of the diluted solution.
- Inspect vial contents for discoloration and particulate matter prior to dilution. ZINPLAVA is a clear to moderately opalescent, colorless to pale yellow liquid. Do not use the vial if the solution is discolored or contains visible particles.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) based on the patient's weight (in kg) and transfer into an IV bag containing either 0.9% Sodium Chloride Injection, or 5% Glucose Injection, to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Discard vial(s) and all unused contents.

Storage of Diluted Solution

- The product does not contain preservative. The diluted solution of ZINPLAVA may be stored either at room temperature for up to 16 hours or under refrigeration at 2°C to 8°C for up to 24 hours. Product is for single use in one patient only. Discard any residue. If refrigerated, allow the IV bag to come to room temperature prior to use.
- These time limits include storage of the infusion solution in the IV bag through the duration of infusion.
- Do not freeze the diluted solution.

Administration

- Administer the diluted solution for infusion intravenously over 60 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- The diluted solution can be infused via a central line or peripheral catheter. Do not administer ZINPLAVA as an intravenous push or bolus.
- Do not co-administer other drugs simultaneously through the same infusion line.

Paediatric Patients

Safety and efficacy of ZINPLAVA in patients below 18 years of age have not been established.

Geriatric Patients

No dose adjustment is necessary in geriatric patients.

Renal Impairment

No dose adjustment is necessary for patients with renal impairment.

Hepatic Impairment

No dose adjustment is necessary for patients with hepatic impairment.

OVERDOSAGE

There is no clinical experience with overdosage of ZINPLAVA. In clinical trials, healthy subjects received up to 20 mg/kg, which was generally well tolerated. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

PRESENTATION AND STORAGE CONDITIONS

ZINPLAVA® concentrated injection: carton containing one 1,000 mg/40 mL (25 mg/mL) single-dose vial.

Store at 2ºC to 8ºC (Refrigerate. Do not freeze). Store in original carton. Protect from light.

For storage of diluted solution, see DOSAGE AND ADMINISTRATION.

NAME AND ADDRESS OF THE SPONSOR

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Macquarie Park, NSW 2113, Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

13 November 2017

DATE OF MOST RECENT AMENDMENT

CCDS-MK6072-IV-112015