1. NAME OF THE MEDICINAL PRODUCT

ZINPLAVA® 25 mg/mL
Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 25 mg bezlotoxumab.
One 40 mL vial contains 1,000 mg of bezlotoxumab.

Bezlotoxumab is a human monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology. It binds to *C. difficile* toxin B.

Excipient with known effect

Each mL of concentrate contains 0.2 mmol sodium, which is 4.57 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear to moderately opalescent, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZINPLAVA is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults who are receiving antibacterial drug treatment of CDI and are at high risk for recurrence of CDI (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Posology

ZINPLAVA should be administered during the course of antibacterial therapy for CDI (see sections 4.4 and 5.1).

ZINPLAVA should be administered as a single intravenous infusion of 10 mg/kg (see below and section 6.6).

The experience with ZINPLAVA in patients is limited to a single CDI episode and single administration (see section 4.4).

Special populations

Elderly
No dose adjustment is necessary in patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of ZINPLAVA in patients below 18 years of age have not been established. No data are available.

Method of 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. ZINPLAVA should not be administered as an intravenous push or bolus.
- The diluted solution can be infused via a central line or peripheral catheter.
- ZINPLAVA must not be co-administered with other medicinal products simultaneously through the same infusion line.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

ZINPLAVA is not a treatment for CDI and has no effect on the current CDI episode. ZINPLAVA should be administered during the course of antibacterial therapy for CDI. There is no data regarding the efficacy of ZINPLAVA if given after the initial 10- to 14-days of antibacterial therapy for CDI.

ZINPLAVA should not be administered as an intravenous push or bolus.

There is no experience with repeat administration of ZINPLAVA in patients with CDI. In clinical trials, patients with CDI were only administered a single dose of ZINPLAVA (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

No formal interactions studies with other medicinal products were conducted. Therapeutic monoclonal antibodies do not typically have significant drug-drug interaction potential, as they do not directly affect cytochrome P450 enzymes and are not substrates of hepatic or renal transporters.

Bezlotoxumab-mediated drug-drug interactions are unlikely as the target of bezlotoxumab is an exogenous toxin.

Concomitant oral standard of care (SoC) antibacterial therapy for CDI was given together with ZINPLAVA.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of bezlotoxumab in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). ZINPLAVA should not be used during pregnancy unless the clinical condition of the woman requires treatment with bezlotoxumab.

Breast-feeding

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 breast-feeding or to not administer ZINPLAVA, taking into account the importance of ZINPLAVA to the mother.

Fertility

No clinical data are available on the possible effects of bezlotoxumab on fertility. Fertility studies have not been conducted in animals. There was no binding of bezlotoxumab to reproductive tissue in tissue cross reactivity studies, and no notable effects in the male and female reproductive organs in repeat dose toxicity studies in mice (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile of ZINPLAVA was assessed in two Phase 3 clinical studies. 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. These adverse reactions were reported at a similar frequency in placebo treated patients compared with ZINPLAVA treated patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions reported within 4 weeks of infusion in ZINPLAVA-treated patients and listed by System Organ Class. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 1: Adverse Reactions with ZINPLAVA

MedDRA System Organ Class	Frequency	Adverse Reaction(s)
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Nausea, diarrhoea
General disorders and administration site conditions	Common	Pyrexia
Injury, poisoning and procedural complications	Common	Infusion related reactions†

† See Description of selected adverse reactions below.

Description of selected adverse reactions

Serious adverse reactions
In clinical studies, serious adverse reactions occurring within 12 weeks following infusion were reported in 29 % of ZINPLAVA-treated patients and 33 % in patients receiving placebo.

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.

Immune-related adverse reactions
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 the two Phase 3 trials (MODIFY I and MODIFY II; see section 5.1) in which all patients received a single dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use, specific immunoglobulins. ATC code: J06BB21

Mechanism of action

Bezlotoxumab is a human monoclonal antitoxin antibody that binds with high affinity to *C. difficile* toxin B and neutralizes its activity. Bezlotoxumab prevents CDI recurrence by providing 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 toxin B epitope to which bezlotoxumab binds is conserved, though not identical, across all known toxin sequences.

Clinical trials

The efficacy of ZINPLAVA (bezlotoxumab) was investigated in two randomised, double-blind, placebo-controlled, multicentre, Phase 3 studies (MODIFY I and MODIFY II) where 810 patients were randomised to bezlotoxumab and 803 to placebo. The number of patients completing the studies and included in the full analysis set (FAS) was 781 in the ZINPLAVA group versus 773 in the placebo group. All patients received concomitant standard of care antibacterial therapy for CDI.

Randomisation was stratified by the antibacterial agent and hospitalisation status (inpatient vs. outpatient) at the time of study entry. Adult patients had a confirmed diagnosis of CDI, which was defined as diarrhoea (passage of 3 or more loose bowel movements as defined in the Bristol stool chart as types 5 through 7 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 received a 10- to 14-day course of oral antibacterial therapy for CDI (metronidazole, vancomycin or fidaxomicin, chosen by the investigator). Patients on oral vancomycin or oral fidaxomicin could have also received IV metronidazole.

A single infusion of ZINPLAVA or placebo was administered prior to completion of antibacterial therapy and patients were followed for 12 weeks following the infusion. The day of the infusion of ZINPLAVA or placebo ranged from prior to the start of antibacterial therapy up to day 14 of treatment, with a median on day 3.

The baseline characteristics of the 781 patients receiving ZINPLAVA and 773 receiving placebo were generally similar across treatment groups. 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 %) and only 4 % were receiving fidaxomicin as antibacterial treatment for CDI.

The CDI recurrence rates are shown in Table 2.

Table 2: 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 patients in the analysis population meeting the criteria for endpoint
N = Number of patients included in the analysis population

[*] Full Analysis Set = a subset of all randomised patients 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; (iiii) GCP non-compliance

[†] SoC = Standard of Care antibacterial (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 antibacterial (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)

Table 3 shows the results of a prospectively planned combined analysis of the CDI recurrence rates in pre-specified subgroups of patients at high risk for CDI recurrence across the two Phase 3 Trials. Overall, 51 % were ≥ 65 years, 29% were ≥ 75 years and 39 % received one or more systemic antibacterial agents during the 12 week follow-up period. Of the total 28 % had one or more episodes of CDI within the six months prior to the episode under treatment (18 % of the patients had one, 7 % had two and a few patients had 3 or more prior episodes). Twenty one (21) percent of the patients were immunocompromised and 16 % presented with clinically severe CDI. Among the 976/1554 (62 %) patients who had a positive baseline stool culture for *C. difficile* a hypervirulent strain (ribotypes 027, 078 or 244) was isolated in 22 % (217 of 976 patients), of which the majority (87 %, 189 of 217 strains) were ribotype 027.

These patients presented with risk factors primarily but not exclusively associated with higher risk of CDI recurrence. Efficacy results did not point towards a benefit of ZINPLAVA in patients with no known risk factors for CDI.

Table 3: CDI Recurrence Rate by Risk Factor 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 patients within subgroup that met the criteria for endpoint
m = Number of patients within subgroup
[*] Full Analysis Set = a subset of all randomised patients 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 antibacterial (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

In the studies, the clinical cure rates of the presenting CDI episode were comparable between the treatment arms.

Immunogenicity

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.

There are no data on repeated administration of bezlotoxumab in patients with CDI.

Paediatric population

The safety and efficacy of ZINPLAVA in patients below 18 years of age have not been established. No data are available.

5.2 Pharmacokinetic properties

Absorption

Bezlotoxumab is dosed via the IV route and therefore is immediately and completely bioavailable. After a single IV dose of 10 mg/kg bezlotoxumab, mean $AUC_{(0-\infty)}$ and C_{max} were 53,000 mcg.h/mL and 185 mcg/mL, respectively, in patients with CDI. Bezlotoxumab exposures in healthy subjects increased in an approximately dose proportional manner across the 0.3 to 20 mg/kg dose range.

Distribution

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

Biotransformation

Bezlotoxumab is catabolized 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.

Elderly

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Genotoxicity and carcinogenic potential have not been evaluated.

Animal reproduction or developmental toxicity 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate dihydrate
Citric acid monohydrate
Polysorbate 80
Diethylenetriaminepentaacetic acid
Water for injections
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Solution for infusion: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C or 16 hours at room temperature (at or below 25°C). These time limits include storage of the infusion solution in the IV bag through the duration of infusion. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours at 2°C – 8°C or 16 hours at room temperature (at or below 25°C).

6.4 Special precautions for storage

Store in a refrigerator 2°C to 8°C. Do not freeze. Keep vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Type I glass vial containing 40 mL solution, with a chlorobutyl stopper, and a flip-off cap seal.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

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, colourless to pale yellow liquid. Do not use the vial if the solution is discoloured 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 % Dextrose 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.
- If the diluted solution is refrigerated, allow the IV bag to come to room temperature prior to use.
- Do not freeze the diluted solution.

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

7. MANUFACTURER

Merck Sharp & Dohme Corp., New-Jersey, USA.

8. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

9. REGISTRATION NUMBER

161-24-35464

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in December 2018.