TO BE SOLD ON THE PRESCRIPTION OF A "MEDICAL SPECIALIST" ONLY

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Zidebactam and Cefepime for Injection 3g per vial

ZAYNICH®

1. GENERIC NAME

Zidebactam and Cefepime for Injection 3g per vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains
Zidebactam ..... 1 g
Cefepime Hydrochloride I.P. equivalent to Cefepime ..... 2 g
Inactive Ingredient: 1.4 g of L-arginine I.P.

Excipients:
There are no added excipients. L-arginine is an excipient in Cefepime for Injection (a premix of cefepime hydrochloride and L-arginine), added to control the pH of the reconstituted solution.

3. DOSAGE FORM AND STRENGTH

ZAYNICH for Injection is supplied as a sterile, non-pyrogenic, preservative-free dry powder in a single-dose vial. Each vial contains 1 g of zidebactam and 2 g of cefepime in a fixed 1:2 ratio. Each vial must be reconstituted with a primary diluent and further diluted with a suitable secondary diluent prior to intravenous infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications and Usage

ZAYNICH is a fixed dose combination of zidebactam, a β-lactam enhancer and cefepime, a fourth generation cephalosporin. Zidebactam augments cefepime's antibacterial activity against cefepime-resistant Gram negative bacteria through β-lactam enhancer mechanism involving complementary binding to Penicillin Binding Protein (PBP) 2 and PBP3 by zidebactam and cefepime, respectively (see section 5.1). Cefepime is approved in India as well as globally for several indications including complicated urinary tract infections, complicated intra-abdominal infections and pneumonia.

ZAYNICH is indicated for the treatment of adult (18 years of age or older) patients with complicated urinary tract infections (cUTI) or pyelonephritis, including concurrent Gram-negative bacteremia.

4.1.1. Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZAYNICH and other antibacterial drugs, ZAYNICH should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may guide empirical selection of therapy.

4.2. Posology and Method of Administration

4.2.1. Posology

Table 1 shows the recommended intravenous dosage regimens of ZAYNICH for adult patients with absolute estimated glomerular filtration rate [calculated based on Modification of Diet in Renal Disease (MDRD) equation] (deindexed eGFR) of 60-120 mL/min.

Table 1: Recommended Intravenous Dose for Adult Patients with deindexed eGFR of 60-120 mL/min[a]

Type of infections	Dose of ZAYNICH (zidebactam/ cefepime)	Frequency	Infusion Time	Duration of Treatment
Complicated Urinary Tract Infections including Pyelonephritis (cUTI/AP) with or without Concurrent Bacteraemia	3 g (1 g / 2 g)	Every 8 hours	1 hour	7 to 10 days

[a]As calculated using the MDRD formula

Dosage Adjustments in Adult Patients with Altered Renal Function

Dosage adjustment of ZAYNICH is recommended for patients with deindexed eGFR less than 60 mL/min, including patients receiving intermittent hemodialysis (HD) and patients with deindexed eGFR of more than 120 mL/min (see sections 4.6 and 5.2).

The recommended dosage of ZAYNICH in adults with altered renal function is described in Table 2. For patients with changing renal function, monitor serum creatinine concentrations and deindexed eGFR at least daily and adjust the dosage of ZAYNICH accordingly (see section 4.6).

Table 2: Recommended Dosage for Adult Patients with Altered Renal Function[1]

Deindexed eGFR[2] (mL/min)	Dose of ZAYNICH (zidebactam/ cefepime)[3]	Dosing Interval	Infusion Time
30-59	1.5 g (0.5 g / 1 g)	Every 8 hours	1 hour
15-29	1.5 g (0.5 g / 1 g)	Every 12 hours	1 hour
8-14 with or without intermittent hemodialysis[4]	1.5 g (0.5 g / 1 g)	Every 24 hours	1 hour
more than 120	3 g (1 g / 2 g)	Every 6 hours	1 hour

[1] Based on ≥99% Probability of Target Attainment (PTA) of zidebactam and cefepime pharmacodynamic targets (see section 5)
[2] As calculated using the MDRD formula
[3] Refer to Table 1 for the recommended duration of treatment
[4] In patients requiring intermittent hemodialysis or already under intermittent hemodialysis, ZAYNICH should be administered after the completion of hemodialysis or 24 hours after the earlier dose. Whenever possible, administer ZAYNICH at the same time each day.

4.2.2. Method of Administration

ZAYNICH is administered by intravenous infusion over 1 hour.

Preparation

ZAYNICH is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted prior to intravenous infusion as outlined below. ZAYNICH does not contain preservatives. Aseptic technique must be used for reconstitution and dilution. Prepare the required dose for intravenous infusion using the steps described below:

1. Reconstitute the powder in the ZAYNICH vial with 10 mL of 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or Lactated Ringer's solution from a 100 mL infusion bag or with 10 mL of sterile Water for Injection
2. Mix gently to the dissolve the content of the vial to get a clear solution. The reconstituted ZAYNICH solution will have a resultant concentration of approximately 240 mg/mL. The final volume is approximately 13 mL. The reconstituted solution is not for direct injection.
3. The reconstituted solution must be diluted further in the 100 mL infusion bag used in Step 1. The same injection solution should be used for both reconstitution and dilution (e.g., if reconstitution in Step 1 is performed with 5% dextrose, the dilution in Step 3 should be performed with a 100 mL infusion bag of 5% dextrose). To dilute the reconstituted solution, withdraw the full or partial reconstituted vial contents and add it back into the infusion bag in accordance with Table 3.

- If the powder is reconstituted in sterile Water for Injection, withdraw 10 mL volume from 100 mL infusion bag (0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or Lactated Ringer's solution), discard and use this bag for the dilution of the reconstituted solution.

Table 3: Preparation of ZAYNICH Doses

ZAYNICH (zidebactam/ cefepime) Dose	Number of Vials to Reconstitute for Further Dilution	Volume to Withdraw from Each Reconstituted Vial for Further Dilution	Approximate Volume of Infusion Bag*
3 g (1 g / 2 g)	1 vial	13 mL	100 mL
1.5 g (0.5 g / 1 g)	1 vial	6.5 mL#	100 mL

Discard unused portion
*If 250 mL infusion bag is used, discard 150 mL and follow the same steps listed above.

CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

Administration

Visually inspect the diluted ZAYNICH solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Similar to other cephalosporins, the reconstituted solution of ZAYNICH in the vial or the final solution for infusion may develop a yellow to amber color. However, this has no negative influence on the potency of the product. The final solution for the infusion should be used within 12 hours if stored at 20°C to 25°C (68°F to 77°F) or within 24 hours if stored at 2°C to 8°C (36°F to 46°F). The entire volume of the final solution for infusion should be infused over 1 hour.

4.3. Contraindications

ZAYNICH is contraindicated in patients with a history of serious hypersensitivity reactions to the components of ZAYNICH (zidebactam and cefepime) or other β-lactam antibiotics (see section 4.4).

4.4. Special Warnings and Precautions for Use

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients treated with ZAYNICH (see section 4.8). Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, and serious skin reactions have been reported in patients receiving β-lactam antibiotics. Before therapy with ZAYNICH is instituted, carefully inquire about previous hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other β-lactams because cross-hypersensitivity among β-lactam antibacterial drugs has been reported. The patient must be carefully monitored during the first administration. If an allergic reaction to ZAYNICH occurs, discontinue the drug and institute appropriate supportive measures.

Renal Impairment

In patients with deindexed eGFR less than 60 mL/min, adjust the dose of ZAYNICH to compensate for the slower rate of renal elimination (see sections 4.2 and 4.6). Since prolonged higher zidebactam and cefepime concentrations can result from usual standard dosages in patients with renal impairment, ZAYNICH dose should be reduced for such patients. The elderly patients are more likely to have decreased renal function, therefore deindexed eGFR should be monitored and accordingly the dosage regimen should be adjusted. Neurotoxicity has been reported with cefepime when the dose has not been appropriately reduced in patients with renal impairment. Renal function should be monitored periodically if medicinal products with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered concomitantly with ZAYNICH.

Neurotoxicity

Neurotoxicity has been reported during treatment with cefepime (a component of ZAYNICH), including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus. Most such cases occurred in patients with reduced renal function who did not receive appropriately reduced doses. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity is observed during ZAYNICH treatment, discontinue ZAYNICH and institute appropriate supportive measures.

***Clostridioides difficile*-associated diarrhea**

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZAYNICH, and may range in severity from mild diarrhea to fatal colitis (see section 4.8). Treatment with antibacterial agents disrupt the normal flora of the colon, leading to overgrowth of *C. difficile*. The organism produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, on-going antibacterial drugs including ZAYNICH may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. Medicinal products that inhibit peristalsis should not be given.

Positive Direct Coombs' Tests

A positive direct or indirect Coombs test without evidence of haemolysis may develop during treatment with ZAYNICH as seen with cefepime (see section 4.5).

Interactions with Urine Glucose Testing

Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used (see section 4.5).

Prolonged Prothrombin Time

Many cephalosporins, including cefepime, have been associated with a decrease in prothrombin activity. Those at risk of developing prolonged prothrombin time include patients with renal or hepatic impairment or poor nutritional state as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K should be administered as indicated.

Development of Drug-Resistant Bacteria

Prescribing ZAYNICH in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria (see section 4.1).

Limitations of the Spectrum of Antibacterial Activity

Cefepime has activity against certain Gram-positive as well as anaerobes. Against Gram-positive organisms, addition of zidebactam to cefepime has no impact on the latter's antibacterial activity. Additional antibacterial agents should be used when Gram-positive pathogens or anaerobes not susceptible to cefepime are known or suspected to be contributing to the infectious process.

4.5 Drug Interactions

Based on the in vitro data related to CYPs and key human renal or hepatic transporters, pharmacokinetic drug interaction between ZAYNICH and other coadministered drugs is not anticipated.

Drug Metabolism

In vitro metabolism studies demonstrated that zidebactam is not a substrate of CYP isoforms and did not undergo oxidative or non-oxidative metabolism. Therefore, clinically-relevant alteration in zidebactam pharmacokinetics due to co-administered drugs which are inducer or inhibitor of CYPs is unlikely. In vitro studies also demonstrated that zidebactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at its therapeutic plasma concentrations. Therefore, zidebactam is unlikely to alter the pharmacokinetics of co-administered drugs that are substrates of these CYP enzymes.

Membrane Transporters

Zidebactam and cefepime are not substrates of MRP4, OAT1, OAT3 or OCT2. Zidebactam is also not a substrate of MDR1 or BCRP, in vitro at therapeutic concentrations. Therefore, co-administration of drugs that are inhibitors of these transporters is unlikely to alter the pharmacokinetics of ZAYNICH.

In vitro data revealed that zidebactam does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MRP4, BSEP, OAT1, or OAT3 in vitro at therapeutic plasma concentrations.

In vitro data indicate that cefepime does not inhibit MDR1, MRP4, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or OCTN2 transporters at therapeutic plasma concentrations. Due to non-substrate or lack of inhibition potential towards membrane transporters, drug-drug interactions for ZAYNICH and co-administered drugs are highly unlikely.

Interaction with Aminoglycosides and Diuretics

Renal function should be monitored carefully if aminoglycosides are to be administered with ZAYNICH because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Periodically monitor renal function when ZAYNICH is concomitantly administered with potent diuretics. Nephrotoxicity has been reported following the administration of other cephalosporins with potent diuretics such as furosemide (see section 4.4).

Drug/Laboratory Test Interactions

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest™ tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™) be used (see section 4.4).

4.6 Use in Special Populations

Pregnancy

Pregnancy Category B

There are no data available with the use of ZAYNICH, or zidebactam during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Available data from published observational studies and case reports over several decades with cephalosporin use, including cefepime, in pregnant women have not established the drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Animal Data

Zidebactam was evaluated in rats and rabbits to assess pregnancy risks associated with the drug. Zidebactam did not induce any changes during the organogenesis period in pregnant female rats up to the dose of 800 mg/kg/day, where the plasma AUC on gestation day (GD) of 17 was 4.7 times the human therapeutic exposure. In the rabbit study, there was no teratogenic potential observed with zidebactam up to the highest dose of 600 mg/kg/day, however developmental changes such as an increase in late resorption and post-implantation loss were observed at this dose. Based on the study findings, the No-Observed-Adverse- Effect level (NOAEL) dose for maternal toxicity and teratogenicity was adjudged at 600 mg/kg/day, where the highest AUC value of zidebactam on GD6 was 7.4 times the human therapeutic exposure. The fetal developmental NOAEL dose was adjudged at 300 mg/kg/day, where the plasma AUC value on GD18 was 3.19 times the human therapeutic exposure. In pre- and post-natal developmental studies of zidebactam in rats at the highest dose of 800 mg/kg/day, zidebactam did not cause any adverse change to the developing pups till lactation day (LD) 21. The NOAEL dose in the study was therefore adjudged as 800 mg/kg/day, where the AUC at GD 6, GD 20 and LD 21 was 1510, 2220 and 1310 µg·h/mL, respectively. These AUC values were 3.2, 4.7 and 2.8 times the human therapeutic exposure, respectively.

Available published data of cefepime showed no adverse developmental outcomes in rats, mice, or rabbits when administered by parenteral route during organogenesis. The doses used in these studies were 1000, 1200 and 100 mg/kg for rats, mice and rabbits, respectively. These doses generated AUCs that were 1.6 times in rats, approximately equal to clinical exposure in mice, and 0.3 times clinical exposure in rabbits.

Based on lack of adequate and well-controlled study of ZAYNICH in pregnant women and because animal reproduction studies are not always predictive of human response, ZAYNICH should be used during pregnancy only if benefit outweighs the risk.

Nursing Mothers

Cefepime is excreted in human milk in low concentrations. It is not known whether zidebactam is excreted into human milk. No information is available on the effects of zidebactam and cefepime on the breastfed child or on milk production.

The treatment of ZAYNICH should therefore be based on the developmental and health benefits of breastfeeding along with the mother's clinical need for ZAYNICH and any potential adverse effects on the breastfed child from ZAYNICH.

Paediatric Use

The safety and effectiveness of ZAYNICH in paediatric patients (younger than 18 years of age) has not been established in randomized clinical trials. However, under compassionate use, 4 paediatric patients (age: 11-15 years) with Gram-negative infections have been successfully treated by ZAYNICH. The treatment duration in 3 patients was between 20 to 24 days and in 1 patient, it was extended to 49 days. ZAYNICH was well tolerated by all patients with no adverse events (see section 7).

Animal Data

In a 28-day repeat-dose toxicity study of zidebactam at doses of 250, 500 and 1000 mg/kg/day by subcutaneous route in male and female Beagle dog pups (2 months old), there was hyaline droplet accumulation with increased weight of kidneys without alterations in correlative biochemical parameters at the mid and high doses. Increased liver weights in females at the 1000 mg/kg/day dose were observed but without any histopathological alterations. The NOAEL of the study was adjudged as 250 mg/kg/day, where the highest systemic $AUC_{0\text{-}24h}$ was 1.33 times of therapeutic exposure.

Geriatric Use

Of the 352 patients treated with ZAYNICH in the Phase 3 cUTI trial (Trial 1), 213 (60.5%) patients were 65 years of age and older, while 111 (31.5%) patients were 75 years of age and older. No overall differences in drug efficacy were observed between these patients and younger adult patients. The incidence of adverse events was comparable between patients aged 65 years or older and patients less than 65 years. The adverse event rates were higher in the patients who were 75 years of age or older compared to patients lower than 75 years. However, for both age subgroups, the incidences of adverse events were similar between ZAYNICH and the comparator.

No dosage adjustment based on age is required. ZAYNICH is known to be substantially excreted by the kidneys as unchanged drug, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function with no proper dose adjustment. Because elderly patients are more likely to have decreased renal function, care should be taken in ZAYNICH dose selection, and renal function should be monitored as appropriate or preferably on daily basis. Dosage adjustment for elderly patients should be based on renal function (see sections 4.2, 4.4 and 5). Serious neurological adverse events, including life-threatening or fatal occurrences of encephalopathy, myoclonus, and seizures have been reported in elderly patients with renal insufficiency when unadjusted doses of cefepime were administered to such patients (see sections 4.4).

Renal Impairment

Pharmacokinetic studies with ZAYNICH in subjects with renal impairment have demonstrated that the plasma exposures of both zidebactam and cefepime increases with decreasing renal function as both drugs undergo renal elimination as intact drugs. Dosage adjustment is therefore required in patients with impaired renal function (deindexed eGFR less than 60 mL/min) including patients on hemodialysis (see sections 4.2 and 5). For patients with changing renal function, serum creatinine and deindexed eGFR should be monitored at least daily, particularly early in treatment, and the dosage of ZAYNICH should be adjusted accordingly. In patients with augmented renal function (deindexed eGFR > 120 mL/min), plasma exposures of both zidebactam and cefepime may decrease. Therefore, dosage adjustments are recommended to compensate for the higher rate of renal clearance in these patients (see sections 4.2, 4.4 and 5).

Hepatic Impairment

The pharmacokinetics of ZAYNICH in patients with any degree of hepatic impairment has not been studied.

As cefepime and zidebactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either medicine is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ZAYNICH is recommended for patients with hepatic impairment.

4.7 Effect on Ability to Drive and Use Machine

The effects of ZAYNICH on the ability to drive and use machines have not been studied. Possible adverse effects such as dizziness, headache, altered state of consciousness, confusional state, or hallucinations may occur following ZAYNICH administration, which may influence the ability to drive and use machines (see sections 4.4, 4.8 and 4.9).

4.8 Undesirable Effect

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and also may not reflect the rates observed in practice. ZAYNICH was evaluated in a Phase 3 trial involving cUTI patients and a Phase 2 trial involving patients with cUTI, including pyelonephritis, cIAI or HABP/VABP, with or without concurrent bloodstream infections.

Phase 3 Trial

The Phase 3 randomized, comparator-controlled cUTI, including acute pyelonephritis (AP) trial (referred to as Trial 1) included 352 adult patients in the ZAYNICH arm and 177 patients in meropenem arm (2:1 randomization). In patients with creatinine clearance of 60 to 120 mL/min, ZAYNICH was administered intravenously at a dose of 3 g (1 g zidebactam and 2 g cefepime) infused over 1 hour at an interval of 8 hours (q8h). In case of meropenem, patients with creatinine clearance (CrCl) >50 mL/min were administered a dose of 1 g every 8 hours (q8h) infused over 30 minutes. Patients with altered renal function (CrCl <60 mL/min for ZAYNICH and ≤50 mL/min for meropenem) received appropriate dosage adjustments based on their CrCl. Approximately 63% of ZAYNICH-treated patients had CrCl <90 mL/min. No switch to oral therapy was permitted. The total duration of treatment was 7 to 10 days, including for concurrent bacteremia. The median age of patients treated with ZAYNICH was 69 years (18 to 90 years) and 61% of patients were 65 years of age or older. Patients were predominantly male (56%) and white (88.4%). The study sites were located in India, Europe, China, US and Mexico.

Serious Adverse Reactions and Adverse Reactions Leading to Drug Discontinuation

Serious adverse events (SAEs) were reported by 2.3% (8/352) patients in the ZAYNICH treatment group and 0.6% (1/177) in the meropenem treatment group. Drug-related SAEs were reported by 1.1% (4/352) of patients in the ZAYNICH group and none in the meropenem group. Treatment was discontinued due to adverse reactions in 1.4% (5/352) patients receiving ZAYNICH and in 1.1% (2/177) patients receiving meropenem. The adverse reactions resulting in discontinuation of ZAYNICH were *pseudomembranous colitis*, urinary tract infection, anaphylactic reaction, hypersensitivity reaction and hyperbilirubinaemia. In the meropenem arm, the discontinuations in the patients were due to systemic candida and mechanical ileus. There were no deaths reported in either of the treatment groups. The safety profile of ZAYNICH is consistent with that of cefepime and other β-lactam antibiotics.

Common Adverse Reactions

The most common adverse reactions occurring in more than 3% of cUTI or AP patients treated with ZAYNICH were diarrhea, headache and hypertension. Table 4 lists adverse reactions occurring in 1% or more of patients receiving ZAYNICH in the cUTI trial.

Table 4: Incidence of Adverse Drug Reactions Occurring in 1% or More of Patients Receiving ZAYNICH in the Phase 3 cUTI Trial

Preferred Term	ZAYNICH N=352	Meropenem N=177
Diarrhea	4.3%	4.0%
Headache	3.1%	5.1%
Hypertension	3.1%	1.1%
Hypokalaemia	2.8%	1.1%
Constipation	1.4%	1.1%
Abdominal pain upper	1.1%	0.6%
Haematuria	1.1%	0.0%

Other Adverse Reactions Associated with ZAYNICH

The following selected adverse reactions were reported in ZAYNICH-treated patients at a rate of less than 1% in the cUTI trial:

Gastrointestinal disorders: nausea, vomiting, abdominal pain, dyspepsia

Nervous system disorders: dizziness, hypoaesthesia, parosmia

Infection and Infestations: pseuomembraneous colitis, urinary tract candidiasis

Vascular disorders: hypotension

General disorder and administration site conditions: pyrexia, asthenia, chills, non-cardiac chest pain and infusion site erythema

Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hypercalcaemia

Renal and urinary disorders: acute kidney injury, nephrolithiasis

Psychiatric disorders: insomnia, anxiety, delirium

Skin and subcutaneous tissue disorders: rash

Blood and lymphatic system disorders: anaemia, neutropenia, thrombocytopenia

Immune system disorders: drug hypersensitivity, anaphylactic reaction

Musculoskeletal and connective tissue disorders: back pain, arthralgia, myalgia

Investigations: blood creatinine increase, alanine aminotransferase increase, aspartate aminotransferase increase, blood urea increase

Additionally, adverse reactions reported with standalone cefepime that were not reported in ZAYNICH-treated patients in the Phase 3 trial are listed below:

Nervous system disorders: convulsions, disguesia

Psychiatric disorders: hallucination

Skin and subcutaneous tissue disorders: erythema, urticaria, pruritus

Investigations: positive Coomb's test, alkaline phosphatase increased, prothrombin time prolonged, partial thromboplastin time prolonged

Metabolism and nutrition disorders: increased phosphorus, decreased phosphorus, decreased calcium

Phase 2 Trial

This prospective, multicenter, single arm Phase 2 trial (Trial 2) enrolled adult Indian patients with serious infections caused by carbapenem-resistant Gram-negative bacteria. In total 15 sites from India enrolled 72 patients with serious infections like HABP/VABP with or without concurrent bloodstream infection (ccBSI), cIAI with or without ccBSI, cUTI, including AP with or without ccBSI or BSI of unknown origin. Patients with normal renal function and mild renal impairment had received a 1-hour intravenous infusion of ZAYNICH (zidebactam 1 g and cefepime 2 g) every 8 hours. In patients with CrCl<60 mL/min, the dosage of ZAYNICH was adjusted based on their renal function. Approximately 52.8% of ZAYNICH-treated patients had CrCl ≤90 mL/min. The duration of ZAYNICH treatment was 7 to 21 days. The median age of patients treated with ZAYNICH was approximately 50.5 years (20 to 81 years) and approximately 18.1% of patients were 65 years of age or older.

Serious adverse events were reported by 11% (8/72) of patients, of which drug-related were in 2.8% (2/72) of patients, which were *Clostridioides difficile* infection and thrombocytopenia. ZAYNICH treatment was discontinued due to adverse reactions in 2.8% (2/72) of patients. In total 3 deaths were reported due to drug-unrelated SAEs (lower respiratory tract infection, aspiration pneumonia and sepsis).

The most common adverse reactions occurring in more than 3% of patients treated with ZAYNICH were vomiting (13.9%), pyrexia (12.5%), anaemia (11.1%), constipation (11.1%), nausea (8.3%), hypokalaemia (8.3%), pruritus (5.6%), pain (6.9%), diarrhea (6.9%), hypoalbuminaemia (5.6%), haematochezia (4.2%), urinary tract infection (4.2%), decreased appetite (4.2%), back pain (4.2%), cough (4.2%), accelerated hypertension (4.2%) and thrombocytopenia (4.2%).

Other Adverse Reactions Associated with ZAYNICH

The following selected adverse reactions were reported in ZAYNICH-treated patients at a rate of less than 3% in the Phase 2 trial:

Gastrointestinal disorders: abdominal distension, abdominal pain, abdominal pain upper

Nervous system disorders: dizziness, encephalopathy, headache, somnolence

Infection and Infestations: *Clostridioides difficile* infection, respiratory tract infection, urinary tract infection fungal

Vascular disorders: hypotension, vasculitis

General disorder and administration site conditions: injection site thrombosis

Metabolism and nutrition disorders: hyperglycaemia, hypocalcaemia, hypomagnesaemia

Renal and urinary disorders: acute kidney injury

Psychiatric disorders: insomnia, anxiety

Immune system disorders: drug hypersensitivity, anaphylactic reaction

Musculoskeletal and connective tissue disorders: back pain, arthralgia, myalgia

Investigations: blood creatinine increased

4.9. Overdose

Patients who receive an overdose of ZAYNICH should be carefully observed and given supportive treatment. Accidental overdosing may occur when large doses are given to patients with impaired renal function. In case of severe overdose, especially in patients with compromised renal function, haemodialysis will aid in the removal of cefepime and zidebactam from the body; peritoneal dialysis is of no use. Symptoms of overdose may include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures and neuromuscular excitability (see sections 4.4 and 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ZAYNICH (zidebactam-cefepime) is active in vitro against carbapenem-resistant Enterobacterales (CREs) including strains producing KPC or MBLs (NDM, VIM or IMP) or OXA-48-like or dual carbapenemases (such as those coproducing NDM and OXA-48-like or NDM and KPC, or VIM and OXA-48-like or VIM and KPC) with impermeability, carbapenem-resistant *P. aeruginosa* (CRPA) with hyper-efflux and porin loss, including those producing serine carbapenemases or MBLs (NDM, VIM, DIM, IMP), carbapenem-resistant *A. baumannii* (CRAB) producing class D carbapenemases and multi-drug resistant (MDR) *S. maltophilia* and *Burkholderia cepacia*.

Mechanism of Action

ZAYNICH is a novel combination of zidebactam, a first-in-class β-lactam enhancer (BLE) and cefepime, a cephalosporin antibiotic. Zidebactam shows potent and selective affinity for penicillin-binding protein-2 (PBP2) in key Gram-negative bacterial pathogens, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacterales (*E. coli, K. pneumoniae* and others). Cefepime, on the other hand, primarily targets PBP3 in these pathogens and also PBP1a/b and PBP2 in Enterobacterales. When both zidebactam and cefepime are present, they act synergistically, inactivating multiple PBPs in a complementary manner, leading to rapid bacterial killing. This synergy occurs even in the presence of β-lactamases, including metallo-β-lactamases (MBLs), which are not inhibited by zidebactam. This is due to cefepime's ability to bind to its PBP targets at a faster rate than it is hydrolyzed by β-lactamases. Additionally, zidebactam being a non-β-lactam is stable against β lactamases as well as shows adequate permeation even in strains expressing efflux and/or impermeability and therefore effectively inactivates PBP2 without interference. As a result of this mechanism, both in vitro and in vivo, zidebactam significantly enhances the pharmacodynamics of cefepime. In the in vivo studies, zidebactam in combination brought about a significant lowering of cefepime's percentage free time above minimum inhibitory concentration (%*f*T>MIC) required for bactericidal action. Such lowering of cefepime's %*f* T>MIC in presence of zidebactam creates a scope of coverage of strains with much higher ZAYNICH MICs by the combination, which has been demonstrated in diverse neutropenic murine infection models. Due to this novel β-lactam enhancer mechanism, ZAYNICH exhibits broad spectrum coverage of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug- resistant (PDR) Gram-negative bacteria, regardless of the β-lactamases they produce. Additionally, the enhancer mechanism of ZAYNICH helps overcome non-enzymatic resistance mechanisms, such as hyper-efflux and downregulation of outer membrane porin channels.

Mechanisms of Resistance

In order to assess the resistance suppression potential of ZAYNICH in a robust manner, a series of experiments were performed involving Enterobacterales, *P. aeruginosa* and *A. baumannii* strains expressing diverse resistance mechanisms. The frequency of resistance (FOR) to ZAYNICH was low for Enterobacterales (8×10^{-8} to 3.3×10^{-11} at 4x MIC), *P. aeruginosa (*1×10^{-9} to 9.1×10^{-10} at 4x MIC) and against carbapenem-resistant *A. baumannii* (8×10^{-8} to 3.3×10^{-10} at 4x MIC). The MICs of parent and ZAYNICH-selected mutants remained unchanged for meropenem, ceftazidime/avibactam and colistin indicating the absence of cross-resistance.

Genomic analyses of ZAYNICH-selected Enterobacterales revealed single nucleotide polymorphism (SNP) associated with 21 diverse genes encoding cell division, amino acid t-RNA synthesis, protein biosynthesis, and the electron transport system. Mutations in t-RNA synthetase gene have been reported to elevate the levels of guinosine-3', 5'-bisdiphosphate (ppGpp) implicated in physiological stress response, in turn linked with biological cost of fitness resulting in compromised growth properties and infectivity. In Hollow-fibre infection model, a lower human-simulated regimen (HSR) of zidebactam-cefepime (2 g + 250 mg, q8h) effectively suppressed resistance selection and eliminated resistance amplification against two KPC-producing isolates when challenged with high inoculum of 10^8 CFU/mL. ZAYNICH-selected mutant of MBL-producing *P. aeruginosa* (bla_{NIM-2}) showed mutations in gene encoding PBP2 (pbpA), however, the majority of mutants showed severe fitness cost as evidenced by slower rate of growth and poor infectivity. Moreover, the study also established that the expression level of the bla_{NIM-2} gene did not impact the activity of ZAYNICH. For Enterobacterales, the terminal MICs of ZAYNICH after 15 days of serial transfer were 0.25 to 0.5 mg/L for wild type isolates and 16 mg/L for clinical isolates. ZAYNICH -selected mutants of KPC and OXA-48-like producing *K. pneumoniae* showed loss of in vivo infectivity.

Against *P. aeruginosa*, resistance development was lower for ZAYNICH and high-level resistance was only achieved for hyper-mutator, PAOMS. High MIC mutants showed multiple mutations in genes encoding MexAB-OprM and its regulators as well as PBP2 and PBP3. Cumulatively, these mutations inflicted significant fitness cost as such mutants showed sub-optimal growth rate in media as well as in *Caenorhabditis elegans* model and remained in vivo susceptible to ZAYNICH-HSR as observed in the neutropenic mouse pneumonia model. In the in vivo resistance selection assessment study, none of the carbapenem-resistant *A. baumannii* and *P. aeruginosa* isolates recovered over 3 days of ZAYNICH treatment showed a shift in ZAYNICH MICs.

Interaction with Other Antimicrobials

ZAYNICH exhibits a positive synergistic antibacterial effect with sulbactam against carbapenem-resistant *A. baumannii* and with aztreonam against carbapenem-resistant Enterobacterales. In combination with other antibiotics from diverse antibacterial classes, including β-lactams, aminoglycosides, tetracyclines, fluoroquinolones, and polymyxins, ZAYNICH exhibited either additive antibacterial effect or indifference, indicating no evidence of antagonism.

Pharmacodynamic Properties

PK/PD Targets

The PK/PD features of ZAYNICH are principally driven by zidebactam's novel β-lactam enhancer mechanism. When zidebactam is combined with cefepime, it substantially enhances the pharmacodynamic activity of cefepime due to complementary inactivation of multiple PBPs by zidebactam and cefepime. The zidebactam-driven pharmacodynamic boost to cefepime is evident through a significant reduction in the %*f*T>MIC requirement of cefepime for eliciting the bactericidal activity. For instance, in neutropenic mouse lung infection model against 5 *A. baumannii* and 3 *P. aeruginosa* strains, the %*f*T>MIC requirement for standalone cefepime for 1-$\log_{10}$ kill or more was 38.9% and 68.2%, which reduced to 15.5% and 16%, respectively in presence of zidebactam.

The PK/PD targets of ZAYNICH constituents, zidebactam and cefepime were identified from dose-fractionation studies conducted in neutropenic mouse lung infection model. This model was considered appropriate as the exposures of zidebactam and cefepime in lung epithelial lining fluid relative to plasma were comparable between mouse and human. Moreover, in other infection sites, zidebactam and cefepime attain much higher concentrations, thus lung infection model serves as a conservative PK/PD model to identify the PK/PD targets. Due to substantial reduction in %*f*T>MIC of ZAYNICH for bactericidal effect, for most pathogens, the targets of zidebactam and cefepime were defined as %*f*T>sub-MIC (fractionated MICs). The sub-MIC based targets were determined employing multiple carbapenem-resistant strains of Enterobacterales, *P. aeruginosa* and *A. baumannii*. Many of these strains were also resistant to ceftazidime/avibactam, aztreonam/avibactam, ceftolozane/tazobactam, imipenem/relebactam, meropenem/vaborbactam and cefiderocol. MICs of ZAYNICH against these strains were higher so as to provide a challenging experimental condition for determining the PK/PD targets. Furthermore, to increase the stringency, PK/PD targets for a higher 2-$\log_{10}$ kill or 1.5 $\log_{10}$ kill effect as against routinely followed 1-$\log_{10}$ kill target were identified. The identified co-model based zidebactam targets were 30.9% for *f*T>1/128x MIC, 25.1% for *f*T>1/8x MIC, 23.9% for *f* T>1/8x MIC for *A. baumannii, P. aeruginosa* and Enterobacterales, respectively. Likewise, identified co-modeled cefepime targets for the same pathogen group were 39.2% for *f*T>1/8x MIC, 71.9% for *f*T>1/64x MIC, 86.1% for *f*T>1/64

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to zidebactam-cefepime. The zone size should be determined using a standardized test method. This procedure uses paper disks impregnated with 30/30 µg of zidebactam/cefepime to test the susceptibility of bacteria to ZAYNICH. The zone diameter values should be interpreted according to criteria provided in Table 5.

Table 5: Susceptibility Interpretive Criteria for Zidebactam-Cefepime

Pathogens	Minimum inhibitory concentrations (mg/L)*			Disk diffusion (Zone diameter in mm)*		
	S	I	R	S	I	R
Enterobacterales	≤64	-	-	≥13	-	-
Pseudomonas aeruginosa	≤64	-	-	≥12	-	-
Acinetobacter baumannii	≤64	-	-	≥12	-	-

*Susceptible-only criteria

S= susceptible; I= intermediate; R= resistant

For MIC determination of zidebactam-cefepime ratio is 1:1

For disk diffusion, use paper disks impregnated with 30/30 µg of zidebactam-cefepime

Since concurrent administration of sulbactam with ZAYNICH further improves the clinical outcome in patients with infection caused by documented carbapenem-resistant *A. baumannii*, susceptibility of ZAYNICH for *A. baumannii*, should be tested in combination with sulbactam. For broth micro-dilution based MIC determination, triple combination of zidebactam/cefepime/sulbactam is employed in 1:1:1 ratio using tryptic soy broth medium. To test the susceptibility by disc method, disc containing zidebactam/cefepime/sulbactam 30/30/30 µg is employed using tryptic soy agar medium.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test [1,2,3]. Standard zidebactam-cefepime powder should provide the following range of MIC values noted in Table 6 against the quality control (QC) isolates. For the diffusion technique using the 30/30 µg of zidebactam-cefepime disk, the criteria in Table 6 should be achieved.

Table 6: CLSI Approved Quality Control Ranges for Zidebactam-Cefepime

QC organisms	Minimum Inhibitory Concentrations range (mg/L)	Disk Diffusion (zone diameters range in mm)
E. coli ATCC 25922	0.016 - 0.06	33 - 40
P. aeruginosa ATCC 27853	0.5 – 2	29 - 35
K. pneumoniae ATCC 700603	0.06 - 0.25	28 - 34
E. coli NCTC 13353	0.06 - 0.5	29 - 35
A. baumannii NCTC 13304*	4 – 16	19- 25

A.baumannii NCTC 13304 is the QC strain recommended for routine QC

MICs determined in 1:1 ratio of zidebactam-cefepime

For disk diffusion, use paper disks impregnated with 30/30 µg of zidebactam-cefepime

Cardiac Electrophysiology

In a randomized, positive and placebo-controlled thorough QT study, 48 healthy subjects received a single 1-hour intravenous infusion of a supratherapeutic dose of zidebactam 4 g and cefepime 2 g in combination. At the given dose, there was no significant effect observed on heart rate, PR, QRS, or QTc interval. Thus, ZAYNICH lacks effect on cardiac repolarization.

5.2. Pharmacokinetic Properties

The mean steady-state pharmacokinetic parameters of zidebactam and cefepime in healthy subjects receiving 1-hour intravenous infusions of ZAYNICH 3 g (zidebactam 1 g and cefepime 2 g) every 8 hours are summarized in Table 7.

Table 7: Mean (%CV) Steady-State Plasma Pharmacokinetic Parameters of Zidebactam and Cefepime after Multiple Intravenous 1-hour Infusions of ZAYNICH 3 g (Zidebactam 1 g and Cefepime 2 g) Every 8 Hours in Healthy Adult Subjects

PK Parameters	ZAYNICH 3 g (zidebactam 1 g - cefepime 2 g) (N=5)	
	Zidebactam	Cefepime
C_{max} (µg/mL)	64.3 (6.3)	152.6 (2.6)
$AUC_{0\text{-}8h,\ SS}$ (µg·h/mL)	153.4 (5.6)	362.0 (6.3)

$AUC_{0\text{-}8h,\ SS}$ = Steady state area under the plasma concentration time curve from time of dosing to 8 hours (one dosage interval); C_{max} = maximum concentration

The pharmacokinetic parameters of zidebactam and cefepime were similar following single- or multiple-dose administrations of ZAYNICH and were similar when zidebactam or cefepime were administered standalone. In the multiple dose study, zidebactam administered alone or in combination with cefepime demonstrated dose-proportional increase in C_{max} and AUC. No accumulation of zidebactam or cefepime was observed upon 10 days of q8h dosing.

Distribution

The binding of zidebactam and cefepime to human plasma proteins is less than 20% and is independent of concentrations. In healthy adults following multiple doses of ZAYNICH 3 g (zidebactam 1 g and cefepime 2 g) infused every 8 hours for 10 days, the mean (CV%) steady-state volume of distribution of zidebactam and cefepime across the dosing intervals ranged from 15 to 17 L (10 to 17%) and 14 to 15 L (5 to 16%), respectively, which is comparable to extracellular fluid volume.

Following 1-hour intravenous infusions of ZAYNICH 3 g (zidebactam 1 g and cefepime 2 g) to healthy adult subjects (N=36) every 8 hours for 3 days (total 7 doses), the intrapulmonary penetration of zidebactam and cefepime based on $AUC_{0\text{-}8}$ values of mean epithelial lining fluid and total plasma concentrations were similar at 38% and 39%, respectively. The intrapulmonary penetration of zidebactam and cefepime based on $AUC_{0\text{-}8}$ values of mean alveolar macrophage and total plasma concentrations was 10% and 27%, respectively.

Metabolism

Zidebactam does not undergo oxidative or non-oxidative metabolism, suggesting it is not a substrate for CYP enzymes. Zidebactam in healthy adults undergoes minimal metabolism through hydrolysis of the bridging urea moiety to yield zidebactam impurity-1, which accounts for approximately 2.5% of the dose in urine.

Cefepime is metabolized to a small extent in healthy adults. Cefepime is metabolized to N-methylpyrrolidinium, being converted quickly to N-oxide. Less than 1% of the administered dose is eliminated in urine as N-methylpyrrolidinium, 6.8% as N-oxide and 2.5% as cefepime epimer. The majority (>90%) of zidebactam and cefepime is eliminated as unchanged drug in urine.

Elimination

Zidebactam and cefepime are primarily eliminated from the body by renal excretion with a mean half-life ($t_{1/2}$) of approximately 2 hours. The elimination half-life of zidebactam and cefepime is independent of dose.

Excretion

Both zidebactam and cefepime are primarily excreted by the kidneys. After intravenous administration of a single dose of ZAYNICH 3 g (zidebactam 1 g plus cefepime 2 g) to healthy adults, greater than 95% of zidebactam was excreted in the urine as an unchanged drug. Likewise, more than 90% of cefepime was excreted unchanged in the urine. The renal clearance of zidebactam was 5.5 to 6.7 L/h and of cefepime was 5.0 to 6.1 L/h, which was similar to their respective plasma clearances (zidebactam: 6.3 to 6.9 L/h; cefepime: 5.2 to 5.9 L/h) and was also similar to the glomerular filtration rate, suggesting that both zidebactam and cefepime are essentially eliminated by the kidneys via glomerular filtration.

Specific Populations

Dose adjustment for ZAYNICH is not warranted on the basis of age, weight, gender, race or ethnicity. No significant differences in the pharmacokinetics of zidebactam and cefepime were observed based on age, weight, gender, race or ethnicity.

Patients with Renal Impairment

In a single-dose pharmacokinetic study of ZAYNICH in subjects with renal impairment, the dose-normalized geometric mean $AUC_{0\text{-}t}$ of zidebactam increased by 1.33-fold, 3.30-fold and 5.03-fold in subjects with mild (CrCl 89-60 mL/min), moderate (CrCl 59-30 mL/min) and severe (CrCl<30 mL/min) renal impairment, respectively, while it increased by 10.41-fold in subjects with stable end-stage renal disease (ESRD) on hemodialysis compared to healthy subjects with normal renal function. Likewise, the respective cefepime dose normalized geometric mean AUC increased approximately by 1.36-fold, 2.97-fold, 4.04-fold and 8.20-fold compared to healthy subjects with normal renal function. To maintain the systemic exposures comparable with normal renal function, dosage adjustment is required for ZAYNICH in patients with CrCl less than 60 mL/min. (see sections 4.2, 4.4 and 4.6).

Augmented Renal Clearance

Probability of target attainment (PTA) analyses of zidebactam-cefepime based on population pharmacokinetic derived from Phase 1 and 3 pharmacokinetic data and Monte Carlo simulations indicated that in patients with deindexed eGFR more than 120 mL/min, reduction of the dosing interval to every 6 hours is recommended in order to maintain appropriate systemic exposure for achieving the ≥ 99% joint PTA (see section 4.2).

Patients with Hepatic Impairment

ZAYNICH does not undergo hepatic metabolism, therefore the systemic clearance of ZAYNICH is unlikely to be affected by hepatic impairment. Dose adjustment for ZAYNICH is not recommended in subjects with hepatic impairment.

6. NONCLINICAL PROPERTIES

Animal Toxicology and Pharmacology

Safety pharmacology studies with zidebactam alone or in combination with cefepime at supratherapeutic exposures showed no effects on functions of key organ systems like respiratory, cardiovascular and central nervous system. Zidebactam's safety was evaluated through intravenous repeat dosing in rats, consecutive for 28 days at the doses of 200, 400 and 800 mg/kg/day. Mild alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in male rats at mid and high doses on day 29, which was reversible at the end of the 14-day recovery period. These changes were not associated with histopathological alteration in the liver and therefore were not considered as drug-related. Dose-dependent accumulation of hyaline droplets in kidneys was observed on day 29. These findings persisted into the recovery period (day 43) but appeared less severe. Hyaline droplet accumulation evaluated on day 29 and 43 was not associated with observable morphological renal damage or altered renal clinical chemistry and was therefore not considered as an adverse effect. The NOAEL dose established was 800 mg/kg/day, at which the highest AUC on day 29 in males was 4.11 times and in females was 4.17 times the human therapeutic AUC. Further, a 28-day repeat dose toxicity study of cefepime standalone (300 mg/kg/day), zidebactam standalone (200, 300 and 750 mg/kg/day) and zidebactam-cefepime combination (zidebactam + cefepime: 150 + 300 and 300 + 300 mg/kg/day) was performed in male and female Beagle dogs by intravenous infusion. Male animals in zidebactam showed dose dependent increase in AST on day 29, with value <2x of upper normal limit in the high dose group. The elevated levels of AST completely recovered in all dose groups at 14 days of drug withdrawal period. Further, there were no histopathological alterations observed especially in liver attributable to increased AST levels. The NOAEL of zidebactam alone was established at 750 mg/kg/day, where the highest average plasma AUC exposures in male and female dogs were 3.5 and 4.2 times of therapeutic exposure, respectively. On the other hand, NOAEL of combination (zidebactam+cefepime) in dog was established at 300 + 300 mg/kg/day, where the maximum plasma AUC of zidebactam was 3.5 (male) and 1.5 (female) times and of cefepime was nearly comparable to that in human at the proposed therapeutic dose.

A 90-day intravenous study of zidebactam in Beagle dogs was also undertaken at doses of 250, 500 and 1000 mg/kg/day with a 1-month recovery period. Up to 30 days of zidebactam treatment, there were no changes in hematological and biochemical parameters even at the highest dose (1000 mg/kg). However, on days 59 and 91, there was a statistically significant but biologically inconsequential increase in ALT in males and on day 91 in females at a 500 mg/kg/day dose. At the 1000 mg/kg dose, there was an ALT rise with vacuolar changes in the liver in males and females. Liver related findings were usually found reversible in nature. Hyaline droplet accumulation was seen in kidneys in dose dependent manner with few histopathological alterations from the dose of 500 mg/kg/day, without affecting the renal-specific serum biochemical parameters. The histopathological changes in the kidney at 1000 mg/kg/day were partially recovered within 1 month of drug withdrawal period. Based on the findings, the NOAEL and LOAEL were adjudged at 250 and 500 mg/kg/day, respectively. The maximum $AUC_{0\text{-}24h}$ attained at NOAEL dose was 1.4 times the therapeutic exposure.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenesis studies of zidebactam or cefepime or ZAYNICH have not been performed in view of any such regulatory recommendations for short-term therapies, including antibiotics.

Mutagenesis

Zidebactam

Zidebactam was evaluated through a battery of *in vitro* (bacterial reverse mutation assay and chromosomal aberration in human lymphocytes) and *in vivo* (mouse micronucleus test) genotoxicity tests. Zidebactam did not show mutagenic or clastogenic potential in both in vitro and in vivo genotoxicity studies. In the mouse micronucleus test, the exposure in terms of mean AUC at the NOEL dose (1302 mg/kg) was 3.09 times in males and 2.56 times in females compared to therapeutic exposure. Further, in the gene mutation study employing the mouse Lymphoma cell line (L5178Y tk+/- 3.7.2C), zidebactam was found to be negative for both in the presence and absence of metabolic activation up to concentration of 2000 µg/mL.

Cefepime (Published Data)

In chromosomal aberration studies, cefepime was found to be positive for clastogenicity in primary human lymphocytes; however, it was negative in Chinese hamster ovary (CHO) cells. In other in vitro assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes, and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Additionally, cefepime in the micronucleus and chromosomal assay was found negative.

Impairment of Fertility

Zidebactam

Zidebactam did not impair male or female fertility in terms of spermology and fertility index when administered in Wistar rats at the doses of 200, 400 and 800 mg/kg/day. At these doses, early embryonic development to implantation was found to be unaffected, as indicated by normal parturition and litter size. NOEL for fertility and reproduction performance in rats was established at 800 mg/kg/day. At this dose, the highest AUC in males was 3.53 times and in females was 3.06 times the therapeutic AUC observed in the humans.

Cefepime (Published Data)

No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously up to 1000 mg/kg/day dose.

7. CLINICAL STUDIES

7.1 Complicated Urinary Tract Infections, including Acute Pyelonephritis

In a Phase 3 multinational, double-blind, non-inferiority trial (Trial 1), a total of 530 adults with cUTI or pyelonephritis were randomized 2:1 to receive ZAYNICH 3 g (1 g zidebactam and 2 g cefepime) intravenously (IV) every 8 hours (infused over 1 hour) and meropenem 1 g every 8 hours (infused over 30 minutes). Dose adjustments based on CrCl were required for ZAYNICH treated patients with a CrCl < 60 mL/min and for meropenem treated patients with a CrCl ≤ 50 mL/min. The treatment duration was 7 to 10 days for the both treatment groups, which also includes patients with concurrent bacteremia. No switch from IV to oral antibacterial therapy was permitted. The microbiological modified intent-to-treat population (mMITT) was the primary efficacy analysis population and included all randomized patients who received any study drug and had at least 1 baseline Gram-negative pathogen with $\geq 10^5$ colony-forming units (CFU)/mL in urine culture or the same pathogen in blood and urine cultures that is not resistant to ZAYNICH or meropenem.

The mMITT population included 417 patients: 282 patients with cUTI (190 on ZAYNICH and 92 on meropenem) and 135 patients with pyelonephritis (91 on ZAYNICH and 34 on meropenem). Patient demographic and baseline characteristics were balanced between treatment groups in the mMITT population. Majority of patients were white (90%), Asian (8.2%) and males (55.4%). The median age of patients was 69 years (ranged 18 to 94 years) and 62.1% patients were 65 years of age and older. The mean body mass index was approximately 28.4 kg/m^2. The majority of patients were enrolled from India, Europe, and relatively smaller numbers of patients were enrolled from Mexico, US and China. The numbers of patients enrolled from India were 36.

The primary efficacy endpoint was composite response defined as concurrently achieving both clinical cure and microbiological eradication at the Test-of-Cure (TOC) visit (Day 17 **±2**) in the mMITT population. Clinical cure was defined as complete resolution (or return to premorbid state) of the cUTI or AP symptoms that were present at screening (with no new cUTI or AP symptoms). Microbiological response was defined as the baseline qualifying Gram-negative pathogen(s) reduced to < 10^3 CFU/mL in urine culture.

ZAYNICH was non-inferior to meropenem for the primary efficacy endpoint of composite response in mMITT population as the lower limit of the 95% confidence interval (CI) for the treatment difference (ZAYNICH versus meropenem) was greater than the non-inferiority margin of -15% at TOC visit (Table 8).

Table 8: Composite Response (Clinical Cure, and Microbiological Response) Rates at TOC in Trial 1 of cUTI or Pyelonephritis (mMITT Population)

Response	ZAYNICH n/N (%)	Meropenem n/N (%)	Difference (%) (95% CI)*
Composite Response (Clinical Cure and Microbiological Response)	250/281 (89.0)	93/136 (68.4)	20.6 (12.3, 29.5)
Clinical Cure	272/281 (96.8)	129/136 (94.9)	1.9 (-1.9, 7.3)
Microbiological Response	256/281 (91.1)	96/136 (70.6)	20.5 (12.6, 29.2)

CI = confidence interval, *The 95% CIs (2-sided) are computed using the unstratified Miettinen-Nurminen method.

Furthermore, ZAYNICH demonstrated superiority over meropenem in the preplanned superiority analysis for the primary efficacy endpoint.

For the most common baseline cUTI or AP pathogens, the composite response rates at TOC in the ZAYNICH treatment group were either higher or similar to the meropenem group (Table 9).

Table 9: Composite Response (Microbiological Response and Clinical Cure) Rates at TOC by Pathogen in Trial 1 of cUTI, including Pyelonephritis (mMITT Population)

Gram-negative Group or Pathogen	ZAYNICH n/N (%)	Meropenem n/N (%)
Escherichia coli	162/176 (92)	60/87 (69)
Klebsiella pneumoniae	41/52 (78.8)	15/24 (62.5)
Pseudomonas aeruginosa	4/7 (57.1)	1/5 (20)
Proteus mirabilis	22/25 (88)	6/7 (85.7)
Enterobacter cloacae complex	11/13 (84.6)	3/6 (50)

7.2. Serious Infections Caused by Carbapenem-Resistant Pathogens

This prospective, multicenter India Phase 2 trial (Trial 2) was designed to determine the efficacy and safety of ZAYNICH in adult patients with serious infections caused by carbapenem-resistant Gram-negative bacteria, including those with underlying kidney dysfunction precluding the use of colistin/polymyxin B. In India, there is a high prevalence of MBL-mediated β-lactam resistance among Gram-negative pathogens against which only colistin/polymyxin B has in vitro activity. However, due to inconsistent efficacy and higher rates of renal toxicity reported with colistin/polymyxin B, the investigators considered them inappropriate as comparator study drug. Hence the Phase 2 study design was non-comparative.

As cefepime is approved for the treatment of pneumonia, cUTI and cIAI, patients with these infections were enrolled in the study. The study enrolled 72 patients; however, 60 patients met the criteria for inclusion in the clinically and microbiologically evaluable population (CME), a primary efficacy analysis population. Out of the 60 patients, 11 patients had HABP/VABP with or without concurrent bacteraemia (ccBSI), 12 patients had cIAI with or without ccBSI, 33 patients had cUTI or AP with or without ccBSI and 4 patients had bloodstream infection of unknown origin (uBSI). Overall, 12 patients had bacteraemia.

Patients with normal renal function and mild renal impairment received a 1-hour intravenous infusion of ZAYNICH (zidebactam 1 g and cefepime 2 g) every 8 hours. Whereas patients with altered renal function received adjusted dosages based on their CrCl. Approximately 53.4% of ZAYNICH-treated patients had CrCl ≤90 mL/min. Most of the cIAI patients had received intravenous metronidazole. The duration of treatment of ZAYNICH was 7 to 21 days. However, in the majority (81.7%) of patients, the treatment was completed by day 15. The median age of patients in the CME population was 51 years (range 20 to 81 years) and 18.3% of patients were 65 years of age or older.

The primary efficacy endpoint was clinical cure at the TOC visit in the CME population. A clinical cure for HABP/VABP was defined as resolution or substantial improvement of baseline signs and symptoms of pneumonia including a reduction in either Sequential Organ Failure Assessment (SOFA) score or Clinical Pulmonary Infection Scores (CPIS), and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy is required for the treatment of the index infection. A clinical cure for cIAI was defined as resolution or substantial improvement of baseline signs and symptoms of cIAI including a reduction in SOFA scores such that no antibacterial therapy is required for the treatment of the index infection. A clinical cure for cUTI or AP was defined as resolution or substantial improvement of baseline signs and symptoms of cUTI, or a return to the pre-infection baseline, such that no antibacterial therapy is required for the treatment of the index infection.

The baseline Gram-negative pathogens identified in the CME population (N=60) were *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*. In approximately 82% of the CME population, the infection was caused by MBL- producing Gram-negative pathogens. By indication and overall clinical cure rates at the TOC visit in the CME population with serious infection caused by carbapenem-resistant pathogens were high (>90%) (Table 10). The microbiological response in the CME population at the TOC visit was also high (>80%) for each indication and overall indications. In patients with bacteremia, the clinical cure and microbiological response were observed in 11/12 (91.7%) patients. By pathogen clinical cure rate in the CME population for different indications and overall is given in Table 11.

Table 10: Clinical Cure Rates and Microbiological Response by Indications and Overall Indications at the TOC Visit in CME Population

Response	HABP/VABP n/N (%)	cIAI n/N (%)	cUTI/AP n/N (%)	uBSI n/N (%)	Overall n/N (%)
Clinical cure	10/11 (90.9)	11/12 (91.7)	30/33 (90.9)	4/4 (100)	55/60 (91.7)
Microbiological response	9/11 (81.8)	11/12 (91.7)	30/33 (90.9)	4 /4 (100)	54/60 (90)

Table 11: Clinical Cure Rate by Pathogens for Each Indications and Overall Indications at the TOC Visit in the CME Population

Carbapenem-resistant Gram-negative pathogens	HABP/VABP n/N (%)	cIAI n/N (%)	cUTI/AP n/N (%)	uBSI n/N (%)	Overall n/N (%)
E. coli	3/3 (100)	4/5 (80)	10/10 (100)	1/1 (100)	18/19 (94.7)
K. pneumoniae	6/7 (85.7)	6/6 (100)	12/13 (92.3)	3/3 (100)	27/29 (93.1)
P. aeruginosa	2/2 (100)	1/1 (100)	9/11 (81.8)	1/1 (100)	13/15 (86.7)
A. baumannii	3/3 (100)	1/1 (100)	-	-	4/4 (100)

ZAYNICH MIC ranges by pathogen type in patients with clinical cure are provided in Table 12.

Table 12: ZAYNICH MIC Range in the Identified Carbapenem-Resistant Gram-Negative Pathogens Achieving Clinical Cure

Carbapenem-resistant Gram-negative pathogens	ZAYNICH MIC range (mg/L)
E. coli	<=0.06-0.5
K. pneumoniae	0.5-32
P. aeruginosa	1-32
A. baumannii	8-64

7.3. Compassionate Use / Expanded Use

Under the compassionate use, ZAYNICH was administered to 50 patients (48 from India and 2 from the US) with serious infections caused by MDR/XDR/PDR Gram-negative pathogens. These cases were referred by clinicians for compassionate use of ZAYNICH after failure of clinically available antibiotics such as meropenem, tigecycline, fosfomycin, ceftazidime/avibactam, aztreonam, polymyxin B, colistin, cefiderocol, eravacycline or combinations thereof for which no other treatment options were available. There was a high likelihood of disease progression in these patients, leading to a heightened risk of mortality. The patient's age ranged from 11 to 87 years, of which 14 patients were 65 years of age or older and 4 patients were less than 18 years. The sites of infections were bloodstream, respiratory, urinary, meninges, endovascular, endocardium, skin, bone, liver and spleen. Out of 50 patients, 10 patients had multiple site infections and 4 patients had polymicrobial infections. Patients had multiple co-morbidities/risk factors such as bone marrow transplant, acute T cell lymphoblastic leukaemia, chronic tuberculosis, bilateral lung transplant, kidney transplant, Hodgkin's lymphoma, and liver transplant, further enhancing their risk of mortality. The pathogens that were isolated from patients were *P. aeruginosa, E. coli, K. pneumoniae, A. baumannii, S. marcescens*, which were all carbapenem-resistant but were susceptible to ZAYNICH. The genomic analysis of certain representative isolates revealed the presence of carbapenemases such as NDM-1, NDM-5 and KPC-2 as well as non-enzymatic resistance mechanisms that include 4 amino acid insertion in PBP3, mutations in genes encoding PBP3, efflux and porin proteins, thus reflecting the real-world treatment challenges. The treatment duration of ZAYNICH in patients ranged from 4 days to 95 days. In 15 patients with osteomyelitis, ZAYNICH treatment was given for a minimum period of 2 weeks and a maximum of up to 13 weeks. Owing to synergistic antibacterial effect, patients with documented carbapenem-resistant *A. baumannii* infections were co-administered sulbactam (along with ZAYNICH). Overall, ZAYNICH was well tolerated by all patients.

Out of the 50 patients, the clinical as well as microbiological cure was observed in 46 patients. The following tables mentions the several indications treated with ZAYNICH under compassionate grounds (Table 13) and the diversity of baseline pathogens (Table 14) in these patients.

Table 13: Serious Gram-Negative Infections Treated by ZAYNICH Under Compassionate Use

Infection site/s*	Number of Patients Treated	Pathogens involved
Hospital-acquired bacterial pneumonia/ Ventilator associated bacterial pneumonia	11	*P. aeruginosa, A. baumannii, K. pneumoniae*
Complicated urinary tract infections, including acute pyelonephritis	11	*P. aeruginosa, K. pneumoniae*
Complicated intra-abdominal infections	5	*P. aeruginosa, K. pneumoniae*
Osteomyelitis	15	*P. aeruginosa, A. baumannii, K. pneumoniae, Serratia marcescens*
Bloodstream infection	5	*P. aeruginosa, A. baumannii, E. coli*
Meningitis	2	*P. aeruginosa, A. baumannii*
Acute bacterial skin and skin structure infections (ABSSSI)	2	*P. aeruginosa*
Empyema	1	*P. aeruginosa*
Endocarditis	1	*P. aeruginosa*

*Certain patients may have multiple sites of infection

Table 14: MIC Distribution among the Carbapenem-Resistant Gram-Negative Pathogens Isolated from 44 Patients Treated with ZAYNICH

Pathogens (all carbapenem-resistant)	Number of isolates	MIC (mg/L) range
P. aeruginosa	36	2 – 64
K. pneumoniae	5	0.5 – 64
A. baumannii	4	16 – 64
E. coli	1	0.25
S. marcescens	1	4

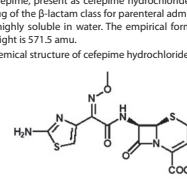
Considering serious patients from the Phase 2 trial and the compassionate use, a total of 22 patients with HABP/VABP, 17 patients with cIAI and 44 patients with cUTI, all infected by carbapenem-resistant Gram-negative pathogens were successfully treated by ZAYNICH. Fifteen patients with osteomyelitis were also successfully treated with ZAYNICH under compassionate use. The MIC data clearly demonstrate that ZAYNICH can treat patients with Gram-negative infections up to the MIC of 64 mg/L. This is also supported by the global Phase 3 cUTI trial, where ZAYNICH showed superior efficacy compared to meropenem, despite pathogens being susceptible to meropenem.

8. DESCRIPTION

ZAYNICH (zidebactam and cefepime) is an antibacterial combination product that contains zidebactam, a novel synthetic β-lactam enhancer and cefepime, a semisynthetic fourth-generation cephalosporin for intravenous administration.

Zidebactam, present as zidebactam dihydrate, is a white crystalline powder. It is a non-β-lactam with a diazabicyclo acyl hydrazide pharmacophore. It is highly soluble in water. The chemical name of zidebactam dihydrate is (2S, 5R)-7-Oxo-6-sulphooxy-2-[N'-((R)-piperidin-3-carbonyl) -hydrazinocarbonyl]-1,6-diaza-bicyclo[3.2.1] octane dihydrate, empirical formula is $C_{13}H_{21}N_5O_9S.2H_2O$ and the molecular weight is 427 amu.

Chemical structure of zidebactam dihydrate



Cefepime, present as cefepime hydrochloride monohydrate, is a broad-spectrum antibacterial drug of the β-lactam class for parenteral administration. It is a white to pale yellow powder and is highly soluble in water. The empirical formula is $C_{19}H_{25}N_6O_5S_2Cl.HCl.H_2O$ and the molecular weight is 571.5 amu.

Chemical structure of cefepime hydrochloride monohydrate

9. PHARMACEUTICAL PARTICULARS

9.1 Incompatibilities

Compatibility of ZAYNICH with other medicines has not been established. ZAYNICH should not be mixed with or physically added to solutions containing other medicinal products.

There is a physical-chemical incompatibility with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate. Should concomitant therapy be indicated, such agents must be administered separately.

9.2 Shelf-Life

Expiry date is indicated on the pack.

9.3 Packaging Information

ZAYNICH for Injection is supplied as a white to pale yellow sterile powder for reconstitution. It is packed in a 50 mL clear USP Type I glass vial with a rubber stopper and flip-off seal. It is supplied as single-use vial in a monocarton.

9.4 Storage and Handling Instructions

Store refrigerated at 2°C to 8°C (36°F to 46°F); excursions are permitted to 25°C (77°F). Retain the vial in the outer carton prior to and after reconstitution to protect it from light.

Storage conditions for reconstituted and diluted solutions of ZAYNICH are described in another section of labelling (see section 4.2).

10. REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Tenth Edition. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-seventh Informational Supplement, CLSI document M100-S27, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2017.
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard-Twelfth Edition. CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

11. PATIENT COUNSELLING INFORMATION

Serious Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment. Ask the patient about any previous hypersensitivity reactions to ZAYNICH, other β-lactams (including cephalosporins) or other allergens (see section 4.4).

Neurotoxicity

Advise patients of neurological adverse reactions that could occur with the use of ZAYNICH. Instruct patients or their caregivers to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia (disturbance of speaking and understanding spoken and written language), myoclonus, seizures and non-convulsive status epilepticus (see section 4.4).

Potentially Serious Diarrhoea

Diarrhoea is a common problem caused by antibacterial drugs, including ZAYNICH, which usually ends when the antibacterial drug is discontinued. Inform the patient that they may develop watery and bloody stools (with or without stomach cramps and fever) during treatment and as late as two or more months after having taken the last dose of the antibacterial drug. Inform patients that they should contact their physician as soon as possible if this occurs (see section 4.4).

Antibacterial Resistance

Counsel patients that antibacterial drugs, including ZAYNICH, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed (see section 4.4).

PATENTED

12. DETAILS OF MANUFACTURER

MANUFACTURED BY:

Wockhardt Limited, At: plot No. B3, B4, B5 (Pt), B6(Pt), B11-B18, SIPCOT Industrial Park, Irungattukottai, 1st Cross, 4th main road, village 602117, Sriperumbudur, Kancheepuram, Tamil Nadu, India

MARKETED BY:

Wockhardt Limited, Plot No. C-2, Wockhardt Towers Bandra Kurla Complex, Bandra (East) Mumbai, Maharashtra (India)-400051

IMPORTANT: REPORTING OF SIDE EFFECTS

If you experience any side effects, talk to your doctor, pharmacist, or nurse. You can also report side effects directly to:

Wockhardt Pharmacovigilance Department

Toll-Free Helpline: 1800-258-8127 (Business Hours: Mon–Fri, 08:00–18:00 IST)

Email: pvsafety@wockhardt.com

Landline Number: 022-71596770 (Business Hours: Mon–Fri, 08:00–18:00 IST)

13. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

DCGI permission no. MF/IND/26/000001 dated 25 August 2026

Mfg. Lic. No.: TN/28A/00387

14. DATE OF REVISION

10/2026

® Registered Trademark of Wockhardt

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WOCKHARDT | LiFE WiNS

WOCKHARDT Creative Unit

Brand Name	Zaynich 3g/vial
Division	Wockhardt Research
Dosage Form	Vial
Dimensions	Open 128 x 600 mm, Folded size 128 x 30 mm
L.I. No.	W-151
SAP Code/Item Code	229639
FG Code	–
Barcode	N.A.
Pharma Code	N.A.
Component Type	Pack Insert (PI)
Artwork Type	Sale
Business Type	Inhouse
Mfg. Location	Gland Chemicals - Tamil Nadu
Artwork Preparation/ Revision/Modification	1st PDF - 06/10/2026, 2nd PDF - 08/10/2026 3rd PDF - 09/10/2026, 4th PDF - 12/10/2026
Changes	New Product
Colors	Pantone 199 C, Pantone 7690 C, Pantone 2602 C, Black