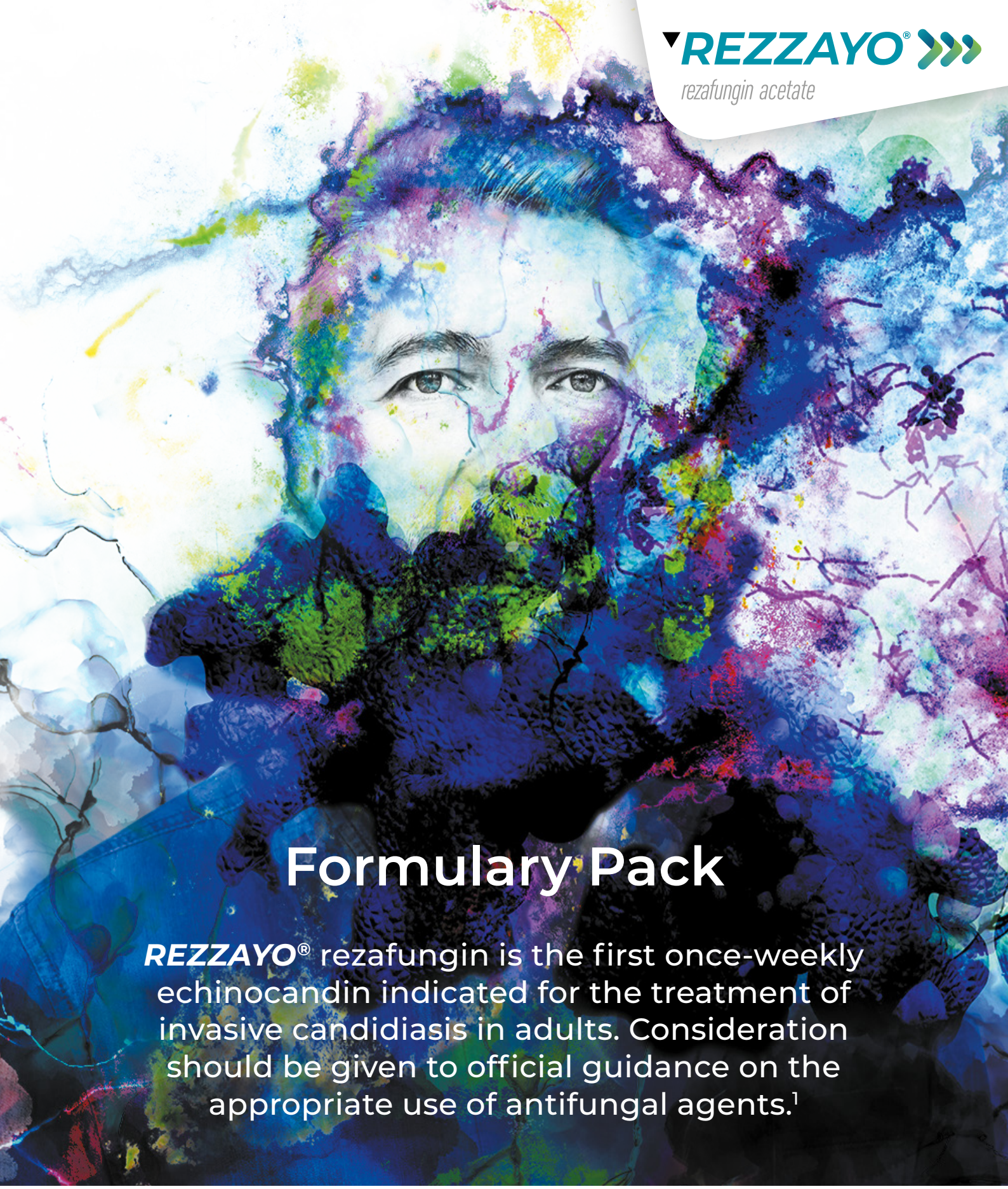
REZZAYO®
rezafungin acetate



# Formulary Pack

***REZZAYO***® rezafungin is the first once-weekly echinocandin indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents.[1]

**This information is intended for UK healthcare professionals only.**

**Prescribing information for Great Britain (GB) and for Northern Ireland (NI) can be found at the end of this material.**

**Reporting adverse events**

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/**

Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444 or **drugsafetyukandROI@mundipharma.com**

NAPP mundi pharma


Job Code: UK-RZF-2400027 | Prepared: April 2024

REZZAYO®

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# Executive summary

## Efficacy

- In the ReSTORE pivotal phase III trial, once-weekly ***REZZAYO®*** demonstrated efficacy in global response at day 14 compared to the once-daily caspofungin group (with optional step-down to oral fluconazole after 3 days or more), primary efficacy outcome met[2]*

*Global response rates at day 14 in the mITT population: ***REZZAYO®***, 55/93 adult patients (59%); caspofungin, 57/94 adult patients (61%). Weighted treatment difference -1.1%; 95% CI -14.9 to 12.7. Consisted of clinical cure as assessed by the investigator, radiological cure (for patients with invasive candidiasis documented by radiological or imaging evidence at baseline), and mycological eradication, as confirmed by an independent data review committee.[2]

## Safety and tolerability

Generally **well tolerated** in the clinical trial programmes[2,3]

## Spectrum of activity

**Demonstrated activity across a broad range of *Candida* species**, including some harder-to-treat species, such as *C. glabrata* and *C. parapsilosis*[3–5]

## Indication for use

***REZZAYO®*** is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents.[1]

## Pharmacokinetics and dosing

**Need for dose adjustments is considered unlikely when co-administered with other medicinal products** and not currently required for special populations[1,6]

***REZZAYO®*** had no or minimal effects on the exposure of probe substrates for the following enzymes/transporter proteins: CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-glycoprotein (P-gp) (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1 and MATE-2 (metformin); organic anion transporting polypeptides (OATP) (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin).[1,6]

The drug–drug interaction potential of ***REZZAYO®*** has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax.[1]

No dose adjustments for patients with hepatic or renal impairment, or elderly (≥65 years) or obese (body mass index ≥30) patients, and can be administered independently of the timing of haemodialysis.[1]

**Phototoxicity**
Rezafungin may cause increased risk of phototoxicity. Patients should be advised to avoid sun exposure and other sources of UV radiation without adequate protection during treatment and for 7 days after the last administration of rezafungin.[1]

**Hepatic effects**
In clinical trials, elevations in liver enzymes have been seen in some patients treated with rezafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with rezafungin, clinically significant hepatic dysfunction has occurred; a causal relationship to rezafungin has not been established. Patients who develop elevations in liver enzymes during rezafungin therapy should be monitored and the risk/benefit of continuing rezafungin therapy should be re-evaluated.[1]

## Treatment settings

***REZZAYO®*** rezafungin is the first **once-weekly echinocandin** indicated for the treatment of invasive candidiasis in adults,[1,2] which could enable use across intensive care unit **(ICU), ward and outpatient** healthcare settings

## One IV infusion, once weekly for approximately 1 hour[1]

Supplied as a single-dose vial containing 200 mg of rezafungin

400mg is the loading dose of rezafungin

## Storage

An unopened vial of ***REZZAYO®*** has a 3-year shelf life. Do not store above 25°C.[1]

Unopened vials: do not store above 25°C. Keep the vial in the outer carton in order to prevent exposure to light.

**For further information please see the *REZZAYO®* Summary of Product Characteristics.**

REZZAYO®
rezafungin acetate

# Contents

**This document contains key data for how *REZZAYO*®, as the first once-weekly echinocandin, can potentially support the treatment of invasive candidiasis**


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Learn more about the benefits of ***REZZAYO***® from clinical experts or download resources for use with your patients. Visit:
***www.napphcp.co.uk/medicines/rezzayo***

# Unmet needs

Invasive candidiasis is a severe, life-threatening systemic fungal infection characterised by bloodstream infection with *Candida* spp. (candidaemia) and/or deep-seated infection in the organs and tissues[7]


Invasive candidiasis, an increased burden linked to advances in medical technology, is widely recognised as a major cause of morbidity and mortality[7]


of all invasive fungal infections are caused by *Candida*[9]

**_Candida_ is the most common cause of life-threatening fungal infection, accounting for 70% to 90% of all invasive fungal infections[9]**

There are five *Candida* species that account for more than 90% of all invasive candidiasis diagnoses: *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*[10]

## Invasive candidiasis contributes to a significant healthcare burden[11,12]

Despite current antifungal treatments, mortality rates for invasive candidiasis range from 20% to 50% globally[11]

As a median, an invasive candidiasis patient will **stay in hospital for 17–51 days[13–19]**


Invasive candidiasis patients are likely to spend a median of **4–33 days in the intensive care unit (ICU)[20–23]**

**16%** (100/621) of patients suffering with candidaemia experienced a prolonged hospital stay, which was attributed to the need for parenteral antifungal treatment (a study conducted by the European Confederation of Medical Mycology (ECMM) with data from 20 different countries)[12]

# The treatment of invasive candidiasis needs to evolve

## Epidemiological shift

- Globally, **non-*albicans* species are on the rise** and responsible for **at least 50% of invasive candidiasis cases**[24,25]
- Among the non-*albicans* species that cause disease, ***C. glabrata*** ranks second as the causative agent of nosocomial systemic *Candida* infections, with an associated **30-day mortality rate of 30–60%**[26]

## Increasing azole resistance

- **The widespread use of fluconazole** has been linked to a **rise in fluconazole-resistant strains**, affecting both *C. albicans* and other *Candida* species[27,28]
- An analysis of 20,788 invasive *Candida* isolates, sourced from the global SENTRY programme between 1997 and 2016, highlighted an **increase in resistance to fluconazole across multiple *Candida* strains**[28]
- **In one study, the overall rate of fluconazole resistance in *C. glabrata* was ~10% (n=49)**[27]
- The same study also showed that **33% of *C. parapsilosis* strains were resistant to fluconazole (n=194)**[27]

## Increasingly complex patients

- Many antifungals used to treat invasive candidiasis are frequently linked with DDIs, including cytochrome P450 (CYP)-mediated interactions with drugs such as venetoclax, idelalisib, ruxolitinib, cyclosporine and rifampicin[7,29–32]
- Over the last decade, an increase in DDIs – due to the emergence of targeted therapies for haematological malignancies – has further increased treatment challenges[32]
- Most of these targeted therapies for haematological malignancies are metabolised by the CYP enzymes in the liver. This predisposes these drugs to potentially severe DDIs, especially when used in conjunction with triazoles that are moderate-to-strong inhibitors of CYP3A4[32]

# Introducing the benefits of *REZZAYO*® – the first once-weekly echinocandin

## Providing continuity of care for invasive candidiasis

### *REZZAYO*® is different from other echinocandins

Distinct structural features of rezafungin confer greater stability, leading to a prolonged half-life (5–6 days) that allows for once-weekly dosing[1,29,30,33,34]

### *REZZAYO*® allows for once-weekly IV administration

A single 400 mg loading dose on day 1, followed by 200 mg on day 8 and once weekly thereafter[1]

### Dose adjustments are considered unlikely*

The need for dose adjustments of rezafungin is considered unlikely when coadministered with other medicinal products[1,7†]

### Demonstrated activity across a broad range of *Candida* species[3]

Including harder-to-treat species such as *C. glabrata* and *C. parapsilosis*[4,5]

### Benefits of a once-weekly therapeutic without compromising efficacy[1,2]

*No dose adjustments for patients with hepatic or renal impairment, or elderly (≥65 years) or obese (body mass index ≥30) patients, and can be administered independently of the timing of haemodialysis.[1]

†Assessed in healthy adults, ***REZZAYO***® had no or minimal effects on the exposure of probe substrates for the following enzymes/transporter proteins: CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-glycoprotein (P-gp) (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1 and MATE-2 (metformin); organic anion transporting polypeptides (OATP) (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin). The drug–drug interaction potential of ***REZZAYO***® has also been assessed clinically. The need for dose adjustments is considered unlikely for: tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax. The drug–drug interaction potential of ***REZZAYO***® has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax.[1,6]

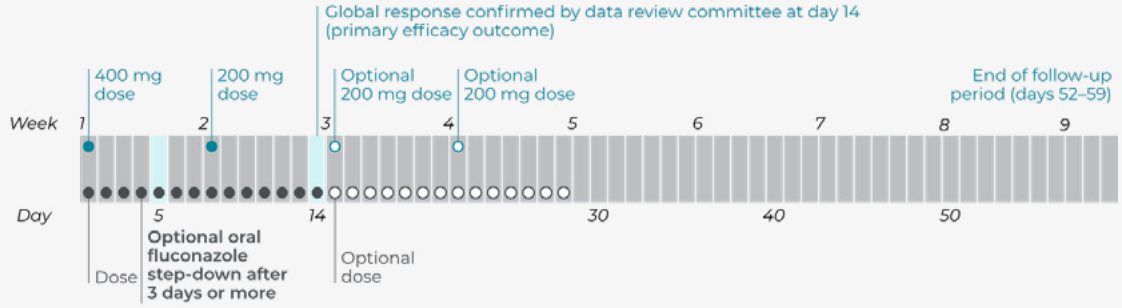
# *REZZAYO*®: randomised clinical trial evidence

## ReSTORE: pivotal phase III

ReSTORE was a prospective, double blind, randomised, non-inferiority phase III trial of once-weekly intravenous ***REZZAYO***® vs daily caspofungin (with an optional step-down to fluconazole after 3 days or more) for the treatment of invasive candidiasis in adults, conducted at 66 tertiary care centres in 15 countries. 199 patients meeting inclusion criteria of being 18 or older and having systemic signs and mycological confirmation of candidaemia or invasive candidiasis were randomised 1:1. Randomisation was stratified based on diagnosis, modified APACHE II score and absolute neutrophil count[2]

## ReSTORE study design[2]

mITT N=187




*Dose may be adjusted for hepatic impaired and obese patients.

| Primary efficacy outcome[2] | Secondary efficacy outcomes[2] | Exploratory outcomes[2,35] |
|---|---|---|
| Global response at day 14 | All-cause mortality at day 30<br><br>Global response at day 5, day 30, end of treatment and follow-up visits<br><br>Mycological eradication, clinical response as assessed by an investigator, and radiological response for invasive candidiasis at day 5, day 30, end of treatment and follow-up visits<br><br>*Secondary endpoints not controlled for multiplicity* | Time to the first negative blood culture[2]<br><br>Hospital and ICU length of stay[35] |

Efficacy outcomes assessed by a data review committee

### Key point

- The ***REZZAYO***® group was non-inferior to the caspofungin group in the treatment of invasive candidiasis, as shown in the ReSTORE phase III trial.[2] Its efficacy was further supported in a pre-specified pooled analysis of phase II and III data[3]

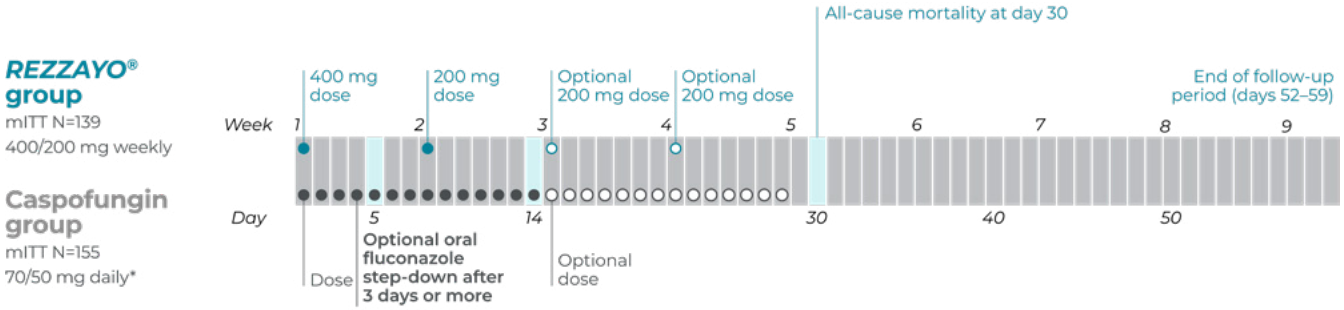
# *REZZAYO*®: randomised clinical trial evidence

## Pooled analysis of ReSTORE (phase III) and STRIVE (phase II) trials[1]

ReSTORE (phase III) and STRIVE (phase II) were international, multicentre, double-blind, randomised controlled trials conducted in adults with IC/C. The studies were similarly designed allowing for a pre-planned analysis of the pooled data, which included 294 adult patients meeting inclusion criteria of having systemic signs of IC/C plus mycological evidence obtained from blood or a normally sterile sampling site within 96 hours before randomisation.[1]

## Pooled analysis dosing and design[6]

pooled mITT N=294




*Dose may be adjusted for hepatic impaired and obese patients.

| Endpoints analysed[3,35] |
|---|
| All-cause mortality at day 30[3] |
| Mycological eradication at day 5 and at day 14[3] |
| Time to the first negative blood culture[3] |
| Hospital and ICU length of stay (*post hoc* analysis)[35] |

*The primary endpoint of global response at day 14 could not be pooled due to difference in definitions between the two studies*

### Key point

- The ***REZZAYO***® group was non-inferior to the caspofungin group (not controlled for multiplicity) in the treatment of invasive candidiasis, as shown in the ReSTORE phase III trial.[2] Its efficacy was further supported in a pre-specified pooled analysis of phase II and III data[2]

# Once-weekly *REZZAYO*®: efficacious echinocandin

Primary endpoint

## Once-weekly *REZZAYO*® met its primary endpoint of global response at day 14[2]

In the ReSTORE pivotal phase III trial, once-weekly ***REZZAYO***® demonstrated non-inferiority in global response* at day 14 compared to caspofungin[2†]

| | *REZZAYO*® group (n=93) | Caspofungin group (n=94) | Treatment difference (95% CI) |
|---|---|---|---|
| **Global response at day 14 as assessed by DRC (primary endpoint)** | | | |
| Cure | 55 (59.9%) | 57 (60.6%) | −1·1 (−14·9 to 12·7) |
| Failure | 28 (30%) | 29 (31%) | .. |
| Indeterminate | 10 (11%) | 8 (9%) | .. |

Adapted from Thompson GR III, *et al*. 2023.[2]

*Data Review Committee-assessed global response consisted of clinical cure as assessed by the investigator, radiological cure (for patients with invasive candidiasis documented by radiological or imaging evidence at baseline), and mycological eradication.
†Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

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# Once-weekly *REZZAYO®* secondary efficacy outcome: all-cause mortality at day 30

Secondary endpoints

## All-cause mortality at day 30: the ReSTORE phase III trial (mITT population)[2]

| | *REZZAYO®* group (n=93) | Caspofungin group (n=94) | Treatment difference (95% CI) |
|---|---|---|---|
| **All-cause mortality at day 30** | | | |
| Died | 22 (24%) | 20 (21%) | 2·4 (−9·7 to 14·4) |
| Known to have died | 19 (20%) | 17 (18%) | .. |
| Unknown survival | 3 (3%) | 3 (3%) | .. |
| **All-cause mortality at day 30 by diagnosis** | | | |
| Candidaemia only | 18/64 (28%) | 17/67 (25%) | 2.8 (-12.5 to 18.0) |
| Invasive candidiasis | 4/29 (14%) | 3/27 (11%) | 2.7 (-16.7 to 21.7) |

Adapted from Thompson GR III, *et al.* 2023.[2]

## Global response at day 5 and 14: the ReSTORE phase III trial

Secondary endpoint: 56% of patients (52/93) in the ***REZZAYO®*** group achieved global response within 5 days (mITT population)[2]

| | *REZZAYO®* group (n=93) | Caspofungin group (n=94) | Treatment difference (95% CI) |
|---|---|---|---|
| **Outcomes at the day 5 visit** | | | |
| Global response as assessed by DRC | 52 (56%) | 49 (52%) | 3.8 (−10·5 to 17.9) |
| **Outcomes at the day 14 visit** | | | |
| Mycological eradication | 63 (68%) | 62 (66%) | 1·8 (−11·7 to 15·2) |
| Patients with candidaemia only | 46/64 (72%) | 47/67 (70%) | 1·7 (−13·9 to 17·2) |
| Investigator assessment of clinical cure | 62 (67%) | 63 (67%) | −0·4 (−13·8 to 13·1) |

Adapted from Thompson GR III, *et al.* 2023.[2]

**Interpret with caution. Study was not designed to infer results of secondary endpoints to a wider population.**

# Once-weekly *REZZAYO*®: mycological response

Secondary endpoints

## Mycological eradication at day 5 and day 14: the ReSTORE phase III trial

Secondary endpoint: mycological eradication at day 5 was 69% (64/93) and at day 14 was 68% (63/93) for the ***REZZAYO***® group (mITT population)[2*]

| Outcomes at the day 5 visit | *REZZAYO*® group (n=93) | Caspofungin group (n=94) | Treatment difference (95% CI) |
|---|---|---|---|
| At day 5 | 64 (69%) | 58 (62%) | 7.1 (-6.6 to 20.6) |
| At day 14 | 63 (68%) | 62 (66%) | 1.8 (-11.7 to 15.2) |

Adapted from Thompson GR III, *et al*. 2023.[2]

*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

## Mycological eradication at day 5 and at day 14: pooled analysis

In a pre-planned pooled analysis of ReSTORE and STRIVE, mycological eradication at day 5 was 73% (102/139) and at day 14 was 72% (100/139) for the ***REZZAYO***® group (mITT population[3]

| Mycological eradication, n (%) | *REZZAYO*® group (n=139) | Caspofungin group (n=155) | Treatment difference in eradication rate (95% CI) |
|---|---|---|---|
| At day 5 | 102 (73%) | 100 (65%) | 10.0 (-0.3 to 20.4) |
| At day 14 | 100 (72%) | 106 (68%) | 4.3 (-6.2 to 14.7) |

Adapted from Thompson GR III, *et al*. 2023.[3]

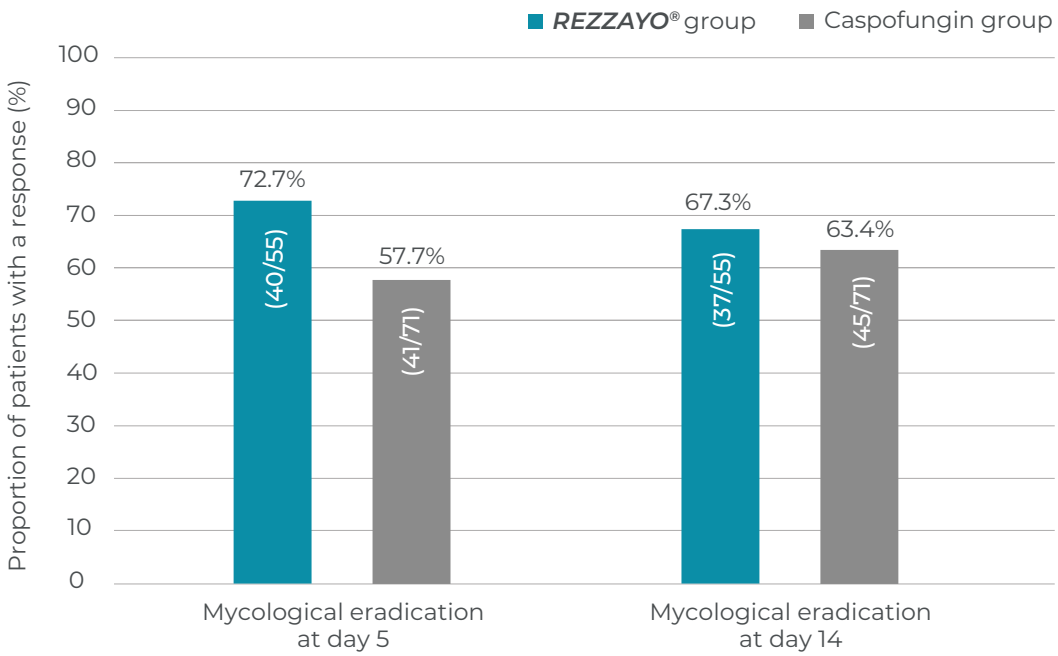
**Interpret with caution. Study was not designed to infer results of secondary endpoints to a wider population.**

# Once-weekly *REZZAYO*®: mycological response

*Post hoc* endpoints

## Mycological eradication at day 5 and day 14 in the ICU subgroup

ICU subgroup *post hoc* analysis of the pooled data: mycological eradication at day 5 was 72.7% (40/55) and at day 14 was 67.3% (37/55) for the ***REZZAYO***® group[36]*




Adapted from Honoré PM, *et al.* 2023.[36]

ICU subgroup post hoc analysis of the pooled data: all-cause mortality at day 30 with ***REZZAYO***® was 36.4% (20/55) with 7.3% (4/55) deaths attributable to invasive candidiasis. In the caspofungin arm all-cause mortality was 26.8% (19/71) and 8.5% (6/71) respectively.[36]

**Interpret with caution. This analysis was not powered to detect significant differences, and further investigation is required to confirm the *post hoc* results.**

*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

Of the 294 patients in the pooled analysis, the ICU population (patients treated in the ICU at any time) was n=126 (n=55, ***REZZAYO***®; n=71, caspofungin [with optional oral fluconazole step down after 3 days or more]). n=37/126 of patients had impaired renal function (baseline creatine clearance <50 mL/min: n=18, ***REZZAYO***®; n=19, caspofungin). Baseline patient characteristics were similar between the arms, except for the proportion of patients undergoing mechanical ventilation: 29.1% (16/55) with ***REZZAYO***® and 46.5% (33/71) with caspofungin. Proportion of patients with APACHE II score ≥20 was 32.1% (17/53) with ***REZZAYO***® and 29.6% (21/71) with caspofungin.

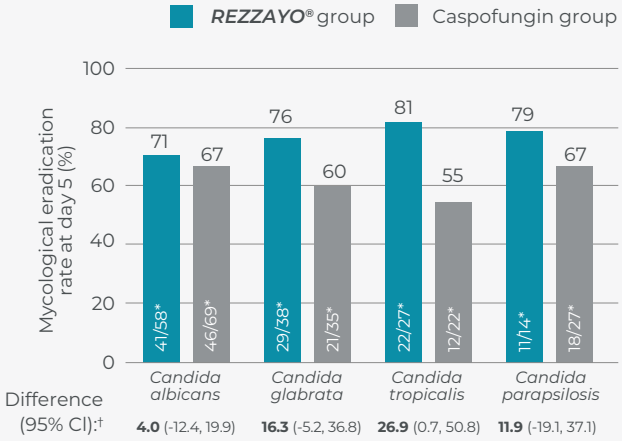
# Spectrum of activity

## *REZZAYO*® demonstrated activity across a broad range of *Candida* species, including some harder-to-treat species, such as *C. glabrata* and *C. parapsilosis*

## Mycological eradication at day 14 in patients with *C. glabrata* infection

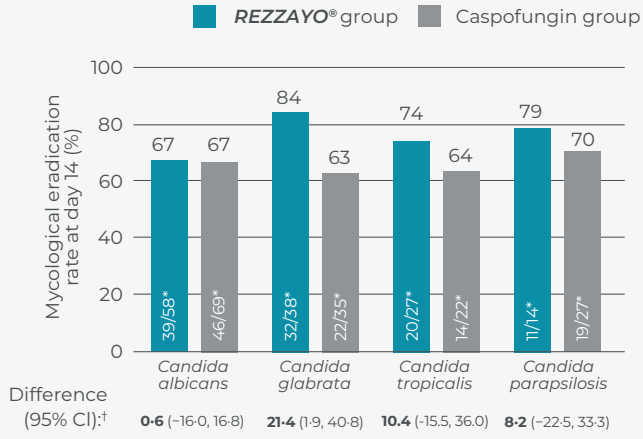
In a pre-planned pooled analysis, mycological eradication in patients infected with *C. glabrata* at day 14 was 32/38 (84%) with ***REZZAYO***® and 22/35 (63%) in the caspofungin group; difference 21.4% (95% CI 1.9–40.8); **study not designed to infer differences between group**†

### Mycological eradication at day 5, according to baseline *Candida* species in the pooled analysis (mITT population)[3†]




Adapted from Thompson GR III, *et al.* 2023.[3]

### Mycological eradication at day 14, according to baseline *Candida* species in the pooled analysis (mITT) population[3†]

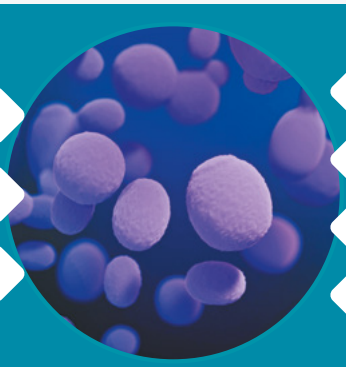



Adapted from Thompson GR III, *et al.* 2023.[3]

**This analysis was not powered to address differences between treatments. Interpret with caution, not controlled for inferential statistics.**

***In vitro* activity against a broad range of clinically relevant *Candida* species, including:**

- *C. albicans*[37]
- *C. glabrata*[37]
- *C. dubliniensis*[37]



- *C. krusei*[37]
- *C. parapsilosis*[37]
- *C. tropicalis*[37]
- *C. auris*[38‡]

**Efficacy of *REZZAYO*® in treating infections caused by *C. auris* has not been established in clinical trials. *In vitro* data does not imply clinical efficacy.**

*n/N = number of subjects with *Candida* species demonstrating mycological eradication/total number of subjects with the corresponding species at baseline.
†Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.
‡*In vitro* data demonstrate that ***REZZAYO***® is active against some *C. auris* isolates. Efficacy of ***REZZAYO***® in treating infections caused by these isolates has not been established in clinical trials. For species with low n number, descriptive statistics were provided. For *Candida krusei*, 2/5 patients in the ***REZZAYO***® group and 2/3 in the caspofungin group achieved mycological eradication at day 5. At day 14, 2/5 patients in the rezafungin group and 3/3 patients in the caspofungin group achieved mycological eradication. For *Candida metapsilosis*, 3/3 patients in the ***REZZAYO***® group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with *Candida metapsilosis*. For *Candida dubliniensis*, 3/3 patients in the ***REZZAYO***® group and 2/2 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. For *Candida guilliermondii*, 1/2 patients in the ***REZZAYO***® group achieved mycological eradication at day 5 and day 14. No patients in the caspofungin group were infected with *Candida guilliermondii*. For *Candida kefyr*, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the ***REZZAYO***® group were infected with *Candida kefyr*. For *Candida nivariensis*, 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14. No patients in the ***REZZAYO***® group were infected with *Candida nivariensis*. For *Candida lusitaniae*, 1/1 patients in the ***REZZAYO***® group and 1/1 patients in the caspofungin group achieved mycological eradication at day 5 and day 14.[3]

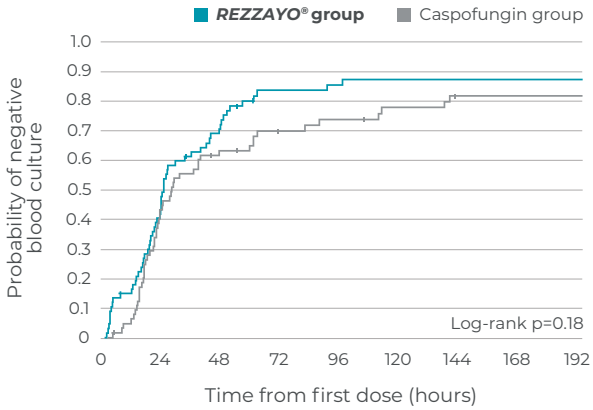
# Once-weekly *REZZAYO*®: exploratory endpoint

Blood cultures for efficacy following the first dose of study drug were performed until the first negative blood culture result for *Candida* spp. with no subsequent positive culture. Blood samples for cultures were drawn daily when possible although may have been drawn every other day.

## ReSTORE trial:

Patients with negative blood culture—at 24 hours: 54% (36/67) with ***REZZAYO***® and 46% (30/65) with caspofungin; at 48 hours: 74% (49/66) with ***REZZAYO***® and 64% (41/64) with caspofungin[2]

Median time to a negative blood culture was 23.9 hours for the ***REZZAYO***® group and 27.0 hours for the caspofungin group in patients enrolled with a positive blood culture (mITT population)[2]*



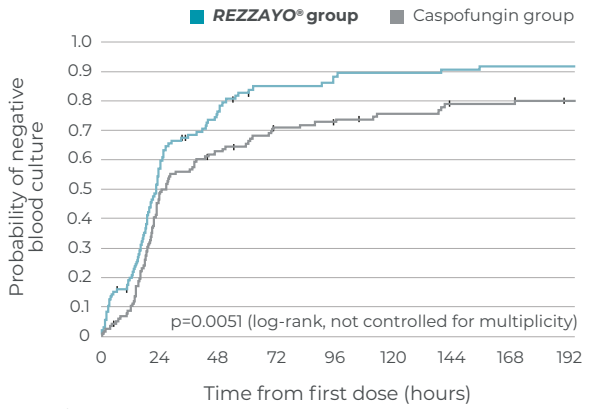

**Number at risk (number censored)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***REZZAYO***® | 69(0) | 31(2) | 17(1) | 9(2) | 8(0) | 7(0) | 7(0) | 7(0) | 7(0) |
| Caspofungin group | 69(0) | 35(4) | 23(1) | 16(3) | 14(0) | 11(1) | 8(1) | 8(0) | 8(0) |

Adapted from Thompson GR III, *et al.* 2023.[2]

## Pre-planned pooled analysis:

In a pre-planned pooled analysis of ReSTORE and STRIVE, at 24 hours, 60% (63/105) of patients in the ***REZZAYO***® group and 49% (57/116) in the caspofungin group had a negative blood culture. At 48 hours, this was 78% (80/103) and 64% (73/115), respectively.[4]*




**Number at risk (number censored)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***REZZAYO***® | 109(0) | 42(2) | 23(4) | 13(6) | 10(6) | 9(6) | 8(6) | 7(6) | 7(6) |
| Caspofungin group | 122(0) | 59(3) | 42(4) | 30(7) | 27(8) | 23(9) | 19(10) | 19(10) | 16(12) |

Adapted from Thompson GR III, *et al.* 2023.[4]

Clinical relevance of numerical differences between efficacy outcomes between the arms cannot be determined due to small sample size. Denominator is patients in the mITT population with a positive culture at baseline. **This analysis was not powered to detect significant differences. Interpret with caution, *post hoc* analysis of secondary efficacy outcome. Not controlled for inferential statistics.**

No MCID available for this endpoint.

*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

## Which patients are at risk of invasive candidiasis?

The risk of invasive candidiasis is increased for critically ill and immunocompromised patients, such as those being treated for cancer or undergoing transplants[39,40]

Other risk factors associated with invasive candidiasis include[39–41]

**Renal impairment**

**Use of mechanical ventilation**

**Long hospital and ICU stays**

**Central venous catheterisation**

**Sepsis**

**Total parenteral nutrition**

**Use of broad-spectrum antibiotics**

**Increased age**

**Rare *Candida* spp. as causative pathogens**

**Abdominal surgery**

# Safety and tolerability

## *REZZAYO*® was generally well tolerated in the clinical trial programme[2,3]

| Adverse reaction | Frequency |
|---|---|
| **Gastrointestinal disorders** | |
| Diarrhoea | Very common |
| Vomiting | Common |
| Nausea | Common |
| Abdominal pain | Common |
| Constipation | Common |
| **Metabolism and nutrition disorders** | |
| Hypokalaemia | Very common |
| Hypomagnesaemia | Common |
| Hypophosphataemia | Common |
| Hyperphosphataemia | Uncommon |
| Hyponatraemia | Uncommon |
| **Blood and lymphatic disorders** | |
| Anaemia | Common |
| **Vascular disorders** | |
| Hypotension | Common |
| **Investigations** | |
| Blood alkaline phosphatase increased | Common |
| Hepatic enzymes increased | Common |
| Alanine aminotransferase increased | Common |
| Aspartate aminotransferase increased | Common |
| Blood bilirubin increased | Common |
| Eosinophil count increased | Uncommon |
| **Injury, poisoning and procedural complications** | |
| Infusion-related reactions | Common |
| **Respiratory, thoracic and mediastinal disorders** | |
| Wheezing | Common |
| **Skin and subcutaneous tissue disorders** | |
| Erythema | Common |
| Rash | Common |
| Phototoxicity | Uncommon |
| Urticaria | Not known |
| **Musculoskeletal and connective tissue disorders** | |
| Tremor | Uncommon |
| **General disorders and administration site conditions** | |
| Pyrexia | Very common |

Adapted from ***REZZAYO***® Summary of Product Characteristics (SmPC).[1]

**Please read the *REZZAYO*® Summary of Product Characteristics in full before prescribing.**

# Additional safety considerations[1]

### Infusion-related reactions

- Transient infusion-related reactions have occurred with ***REZZAYO***® (common: ≥1/100 to <1/10), characterised by flushing, sensation of warmth, nausea and chest tightness
- In clinical trials, infusion reactions resolved within minutes, some without interruption or discontinuation of infusion. For those that require stoppage of the infusion, consideration may be given to restarting the infusion at a slower rate after the symptoms have resolved
- Monitor for infusion reactions and reduce the rate of infusion if deemed medically necessary (see section 4.2 of the SmPC)

### Phototoxicity

- ***REZZAYO***® may cause increased risk of phototoxicity
- Patients should be advised to avoid sun exposure and other sources of ultraviolet radiation without adequate protection during treatment and for 7 days after the last administration of ***REZZAYO***®

### Hepatic effects

- Elevations in liver enzymes occurred in some patients treated with ***REZZAYO***® in clinical trials
- In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with ***REZZAYO***®, clinically significant hepatic dysfunction has occurred
- No causal relationship has been established
- Patients who develop elevations in liver enzymes should be monitored and the risk/benefit re-evaluated

### Other precautions for use

- The efficacy of ***REZZAYO***® has only been evaluated in a limited number of neutropenic patients
- The Safety and Efficacy of ***REZZAYO***® have only been assessed up to 4 weeks (28 days).

**Please read the *REZZAYO*® Summary of Product Characteristics in full before prescribing.**

# Safety and tolerability in ReSTORE

## In the phase III trial, ReSTORE, *REZZAYO*® was generally well tolerated[2]*

- The once-weekly dosing of ***REZZAYO***® did not have any additional safety outcomes compared to once-daily caspofungin[2]

## Treatment-emergent (TEAE) and serious adverse events (SAE)

| Adverse event, n (%) | *REZZAYO*® group (n=98) | Caspofungin group (n=98) |
|---|---|---|
| **≥1 TEAE**<br>Study-drug–related | 89 (91%)<br>16 (16%) | 83 (85%)<br>9 (9%) |
| **SAE**<br>Study-drug–related | 55 (56%)<br>2 (2%) | 52 (53%)<br>3 (3%) |

Adapted from Thompson GR III, *et al.* 2023.[2]

Safety population included all subjects who had received ≥1 dose of study drug.

## Breakdown of TEAEs in the ReSTORE phase III clinical trial[2]*

| | *REZZAYO*® group (n=98), n (%) | Caspofungin group (n=98), n (%) |
|---|---|---|
| Pyrexia | 14 (14) | 5 (5) |
| Hypokalaemia | 13 (13) | 9 (9) |
| Pneumonia | 10 (10) | 3 (3) |
| Septic shock | 10 (10) | 9 (9) |
| Anaemia | 9 (9) | 9 (9) |
| Hypomagnesaemia | 7 (7) | 3 (3) |
| Diarrhoea | 6 (6) | 7 (7) |
| Sepsis | 6 (6) | 4 (4) |
| Vomiting | 6 (6) | 2 (2) |
| Abdominal pain | 5 (5) | 4 (4) |
| Bacteraemia | 5 (5) | 3 (3) |
| Constipation | 5 (5) | 3 (3) |
| Hypophosphataemia | 5 (5) | 4 (4) |
| Hypotension | 5 (5) | 6 (6) |
| Multiple organ dysfunction syndrome | 5 (5) | 2 (2) |
| Nausea | 5 (5) | 2 (2) |
| Urinary tract infection | 4 (4) | 6 (6) |
| Acute kidney injury | 3 (3) | 8 (8) |
| Hyperkalaemia | 2 (2) | 6 (6) |

Adapted from Thompson GR III, *et al.* 2023.[2]

**Please read the *REZZAYO*® Summary of Product Characteristics in full before prescribing.**

*Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

# Safety and tolerability in pooled data

## Most commonly occurring TEAEs reported in ≥5% of adults in either pooled treatment in the safety population[3]*

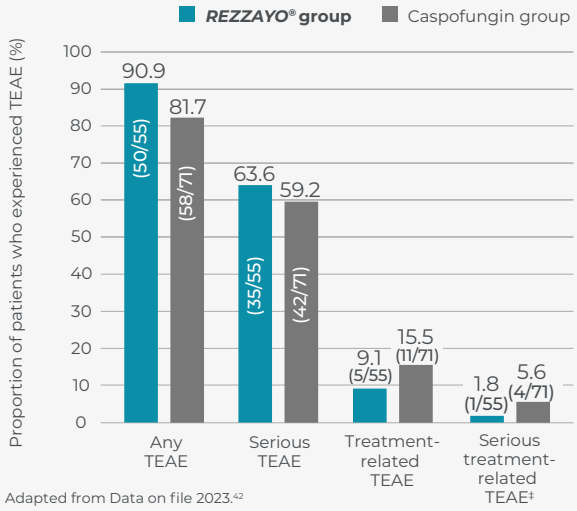
| TEAE | ***REZZAYO*® group** (n=151), n (%) | Caspofungin group† (n=166), n (%) |
|---|---|---|
| Hypokalaemia | 22 (15) | 17 (10) |
| Pyrexia | 18 (12) | 11 (7) |
| Diarrhoea | 17 (11) | 17 (10) |
| Anaemia | 15 (10) | 13 (8) |
| Vomiting | 14 (9) | 7 (4) |
| Nausea | 13 (9) | 8 (5) |
| Hypomagnesaemia | 12 (8) | 5 (3) |
| Pneumonia | 12 (8) | 7 (4) |
| Abdominal pain | 11 (7) | 9 (5) |
| Septic shock | 11 (7) | 12 (7) |
| Sepsis | 10 (7) | 8 (5) |
| Constipation | 8 (5) | 8 (5) |
| Hypophosphataemia | 8 (5) | 5 (3) |
| Hypotension | 7 (5) | 10 (6) |
| Acute kidney injury | 6 (4) | 11 (7) |
| Urinary tract infection | 5 (3) | 9 (5) |
| Hyperkalaemia | 3 (2) | 9 (5) |
| Pleural effusion | 3 (2) | 10 (6) |

Adapted from Thompson GR III, *et al.* 2023.[3]

*A statistical analysis using Fisher's exact test was performed evaluating differences between the ***REZZAYO***® and caspofungin groups. A difference was noted between rezafungin and caspofungin for the category of ≥1 AEs (rezafungin: 92%; caspofungin: 83%; p=0.018) and ≥1 TEAEs (rezafungin: 91%; caspofungin: 83%; p=0.0304). No significant differences were identified for study-drug–related TEAEs, severe or grade ≥3 TEAEs, SAEs, study-drug–related SAEs or any TEAEs leading to interruption or discontinuation of study drug or study. **Conclusions of difference or similarities between groups cannot be inferred as the study wasn't designed to look at this.**

## TEAEs in the ICU subgroup[42]

- ICU subgroup *post hoc* analysis of the pooled data: the rates of TEAEs with ***REZZAYO***® and caspofungin[42†]




Adapted from Data on file 2023.[42]

**Interpret with caution. This analysis was not powered to detect significant differences, and further investigation is required to confirm the *post hoc* results.**

**Please read the *REZZAYO*® Summary of Product Characteristics in full before prescribing.**

Of the 294 patients in the pooled analysis, the ICU population (patients treated in the ICU at any time) was n=126 (n=55, ***REZZAYO***®; n=71, caspofungin). n=37/126 of patients had impaired renal function (baseline creatine clearance <50 mL/min: n=18, ***REZZAYO***®; n=19, caspofungin). Baseline patient characteristics were similar between the arms, except for the proportion of patients undergoing mechanical ventilation: 29.1% (16/55) with ***REZZAYO***® and 46.5% (33/71) with caspofungin. Proportion of patients with APACHE II score ≥20 was 32.1% (17/53) with ***REZZAYO***® and 29.6% (21/71) with caspofungin.

†Stable patients in the caspofungin group who met relevant criteria could step down to fluconazole after 3 days or more.

‡Due to infusion-related reaction in the ***REZZAYO***® arm, and anaphylactic shock, hypertransaminasaemia, rectal haemorrhage and ventricular tachycardia in the caspofungin arm.

# Dosing considerations[1,6]

## The need for dose adjustments of *REZZAYO®* is considered unlikely when co-administered with other medicinal products* and not currently required for special populations[1,7]**

- ***REZZAYO®*** had no or minimal effects on the exposure of probe substrates for the following enzymes/transporter proteins:
  - CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-glycoprotein (P-gp) (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1, and MATE-2 (metformin); organic anion transporting polypeptides (OATP) (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin). The need for dose adjustments is considered unlikely for medicinal products that are substrates of these[6]
- The drug–drug interaction potential of ***REZZAYO®*** has also been assessed clinically. The need for dose adjustments is considered unlikely for: tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax[1]

## *REZZAYO®* is unlikely to require dose adjustment for special populations:[1]

Patients with **hepatic impairment**

Patients with **renal impairment**

**Elderly patients** ≥65 years

**Clinically obese patients** (BMI ≥30)

- Can be administered independently of the timing of haemodialysis[1]

*Based on currently available data, the need for dose adjustments is considered unlikely for medicinal products that are substrates for the CYP2C8, CYP3A4, CYP1A2, and CYP2B6 enzymes and P-gp, BCRP, OATP, OCT1, OCT2, MATE1, and MATE2 transporter proteins, when administered with ***REZZAYO®***. The drug-drug interaction potential of ***REZZAYO®*** with a number of co-administered medicinal products has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax when administered with ***REZZAYO®***.[1]

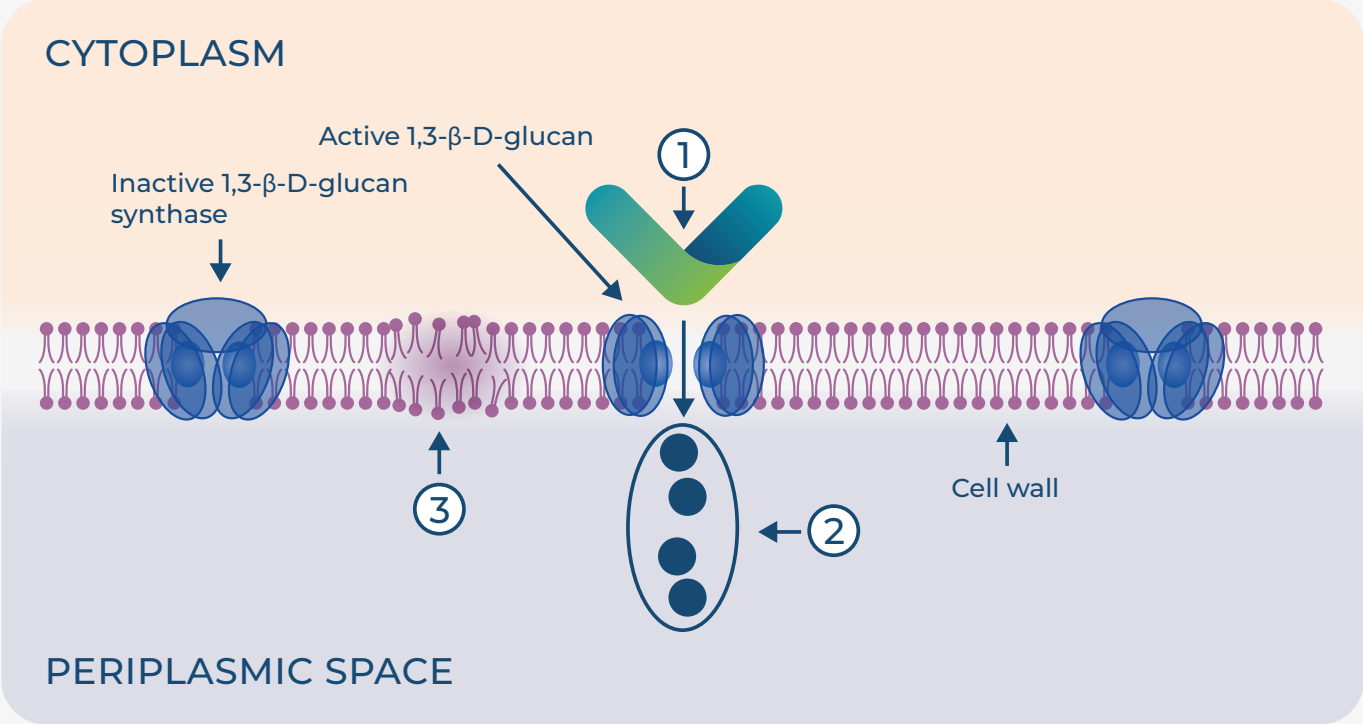
**Based on currently available data, patients with hepatic or renal impairment, elderly (≥65 years) or obese (BMI ≥30) patients, and can be administered independently of the timing of haemodialysis.[1]

# *REZZAYO*® is the longest-acting echinocandin[1,29,30,34,43]

***REZZAYO***® is different from other echinocandins because of the combination of its front-loaded dosing and distinct structural features that confer greater stability, leading to a prolonged half-life (5-6 days) that allows for once-weekly dosing[1,30,31,34,43]

## Mechanism of action

***REZZAYO***® has a known mechanism of action: it inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall[44]




Adapted from Ong V, *et al*, 2016 and Patil A and Majumdar S, 2017.[44,45]

**1.** Enzyme identification and inhibition

**2.** 1,3-β-D-glucan chain production depletion leading to cell wall disruption

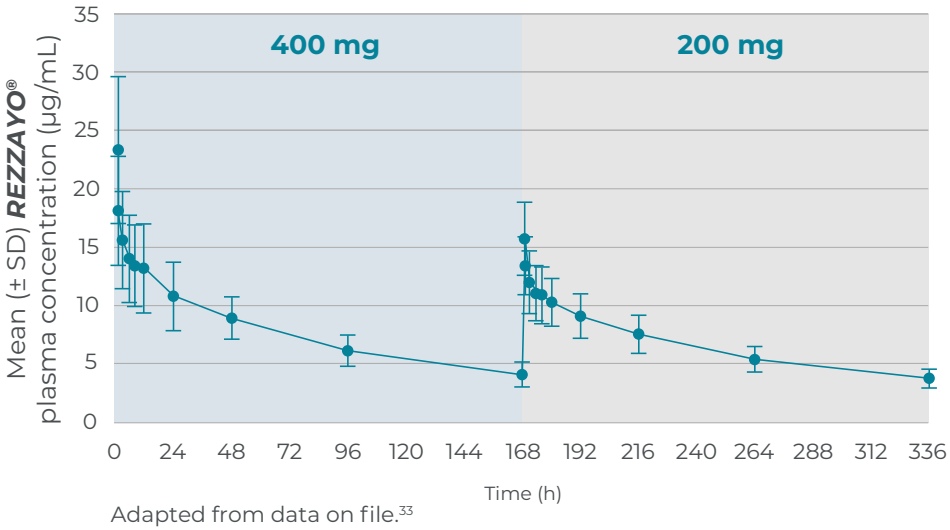
**3.** Cell wall disruption and osmotic instability leading to fungal cell death or inhibition[44,46]

# *REZZAYO*® is the longest-acting echinocandin[1,29,30,34,43]

## High plasma concentration early in therapy[33,47]

- The first dose (400 mg) of ***REZZAYO***® yields high plasma drug concentrations early in therapy
- Steady state is achieved with the first loading dose[1]
- The area under the concentration-time curve divided by the minimum inhibitory concentration (AUC/MIC) values were maintained throughout the dosing interval[52]*

**A phase I, single-centre, open-label, cross-over inpatient study of *REZZAYO*® in healthy adults (N=24)[33]**

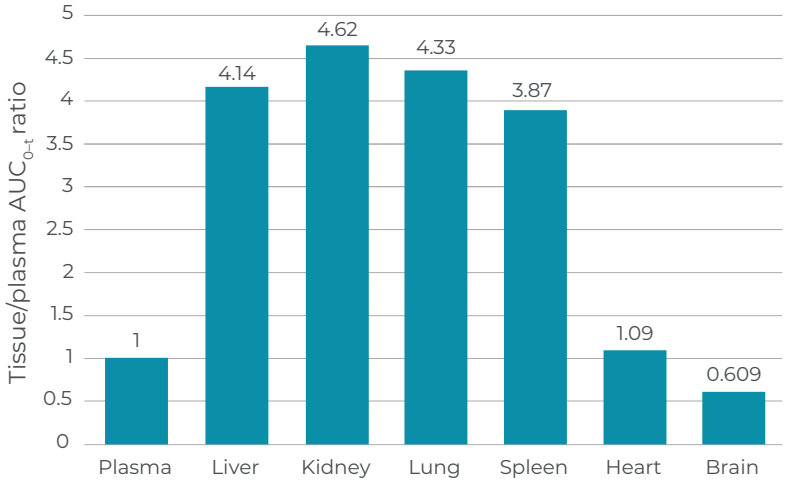



Adapted from data on file.[33]

## Extensive tissue distribution[46]

Non-clinical studies have demonstrated that ***REZZAYO***® provides extensive tissue distribution, with concentrations within some major organs approximately 4-fold higher compared with plasma[46]

**Comparable tissue and plasma AUC exposures for *REZZAYO*® (data from rats)[46]**




Adapted from Ong V, *et al.* 2017.[46]

***Assessed in preclinical model; no human data is available.**

# Dosing and administration

## One IV infusion, once weekly for 1 hour[1]

**Time-effective dosing**

(supplied as a single-dose vial containing 200 mg of rezafungin):[1]

**400 mg**
**loading dose**

**200 mg**
**once weekly thereafter**

One infusion takes approximately **1 hour** to complete[1]

- An infusion may be slowed, or paused and restarted at a lower rate if infusion-related reactions occur[1]
- The safety information on ***REZZAYO®*** treatment durations longer than 4 weeks is limited[1]
- The duration of treatment should be based upon the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture[1]

## Storage

An unopened vial of ***REZZAYO®*** has a 3-year shelf life. Do not store above 25°C.[1]

Unopened vials: do not store above 25°C. Keep the vial in the outer carton in order to prevent exposure to light.

# International guidelines recommend echinocandins as first-line treatment for invasive candidiasis[39,48–51]

## Current European and international guidelines recommend the use of echinocandins for:

- Initial treatment of invasive candidiasis in non-neutropenic and neutropenic patient groups[39,48]
- The strength of recommendation is the same (strongly recommended) for anidulafungin, caspofungin and micafungin and is also the same for the overall and the haematologic populations[39,48–51] (although the quality of evidence is lower for haematologic patients compared to the overall population as the number of neutropenic patients recruited in the clinical trials was low). **Please note that rezafungin data was not used to create these guidelines**

| Organisation/ task force | Guideline | Echinocandin use for treatment |
|---|---|---|
| ESCMID[48] | Diagnosis and management of *Candida* diseases in non-neutropenic adult patients | Strongly recommended for targeted antifungal treatment of candidaemia in non-neutropenic adult patients |
| ESCMID[49] | Diagnosis and management of *Candida* diseases in adults with haematological malignancies and after haematopoietic stem cell transplant (HSCT) | Recommended for empirical treatment of *Candida* disease in adults with haematological malignancies and after HSCT causing severe and prolonged neutropenia |
| ESICM/ESCMID[50] | Practical management of invasive candidiasis in critically ill patients | First-line therapy of choice for critically ill patients with septic shock and multiple organ failure with invasive candidiasis |
| ECIL-6[51] | Treatment of invasive candidiasis, aspergillosis and mucormycosis in leukaemia and HSCT patients | Strongly recommended for the initial treatment of candidaemia |
| IDSA[39] | Clinical practice guideline for the management of candidiasis: 2016 update | First-line treatment of invasive candidiasis in non-neutropenic and neutropenic patients |

REZZAYO®
rezafungin acetate

# Once-weekly *REZZAYO*® in the antifungal care pathway

## International guidelines recommend echinocandins as first-line treatment for invasive candidiasis

### In ward

As the only once-weekly echinocandin,[1,30,31,34] ***REZZAYO***® has:

- The need for dose adjustments of rezafungin is considered unlikely when coadministered with other medicinal products[1,6]*
- No therapeutic drug monitoring requirement (monitoring of medication levels in the blood) during treatment

### In ICU

- The need for dose adjustments of rezafungin is considered unlikely when coadministered with other medicinal products[1,2]*
- No dose adjustments are required for:
  - Patients with hepatic impairment
  - Patients with renal impairment
  - Elderly patients (≥≥65 years old)
  - Clinically obese patients (BMI (≥30)
- Broad activity across a range of *Candida* species including some harder-to-treat species[3–5]
- Front-loaded dosing leads to high plasma drug concentration early in therapy, with AUC/MIC values maintained throughout the dosing interval[33,47,52,†]
- Non-clinical data supporting extensive tissue distribution[46]
- No therapeutic drug monitoring requirement (monitoring of medication levels in the blood during treatment)

### Outpatient

- Once-weekly infusions

AUC, area under the curve; DDIs, drug–drug interactions; ICU, intensive care unit; LoS, length of stay; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; OPAT, outpatient parenteral antimicrobial therapy; SAP, statistical analysis plan; SD, standard deviation.

*No dose adjustments for patients with hepatic or renal impairment, elderly (≥65 years) or obese (body mass index ≥30) patients, and can be administered independently of the timing of haemodialysis.[1]

†***REZZAYO***® had no or minimal effects on the exposure of probe substrates for the following enzymes/transporter proteins: CYP2B6 (efavirenz); CYP3A4 (midazolam and tacrolimus); CYP1A2 (caffeine); CYP2C8 (repaglinide); P-glycoprotein (P-gp) (digoxin and tacrolimus); OCT-1, OCT-2, MATE-1, and MATE-2 (metformin); organic anion transporting polypeptides (OATP) (pitavastatin, rosuvastatin and repaglinide); and BCRP (rosuvastatin).[7] The drug–drug interaction potential of ***REZZAYO***® has also been assessed clinically. The need for dose adjustments is considered unlikely for: tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax.[1,6]

# Invasive candidiasis (IC) contributes to a significant healthcare burden[11,12]

Despite current antifungal treatment, **mortality rates for invasive candidiasis range from 20% to 50% globally**[11]

Invasive candidiasis is one of the **most frequent** invasive fungal infections in the hospital setting[12]

A study conducted by the ECMM in 20 European countries showed that **16% of patients with candidaemia had a prolonged hospital stay due to parenteral antifungal treatment** (n=100/621)[12]

# References

## Abbreviations

AE, adverse event; AUC, area under the curve; BCRP, breast cancer resistance protein; BMI, body mass index; CI, confidence interval; CL, confidence limit; CYP, cytochrome P450; DDI, drug–drug interaction; DRC, data review committee; ECIL, European Conference on Infections in Leukemia; ECMM, European Confederation of Medical Mycology; EMA, European Medicines Agency; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESICM, European Society of Intensive Care Medicine; FDA, Food and Drug Administration; HCP, healthcare professional; HSCT, haematopoietic stem cell transplant; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IV, intravenous; LOS, length of stay; MATE, multidrug and toxin extrusion; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; NIHR, National Institute for Health Research; OATP, organic anion transporting polypeptides; OPAT, outpatients or via treatment at home; OCT, organic cation transporter; P-gp, P-glycoprotein; SAE, serious adverse event; SAP, statistical analysis plan; SD, standard deviation; SmPC, summary of product characteristics; TEAE, treatment-emergent adverse event; TTNBC, time to negative blood culture.

## References


1. ***REZZAYO***® (rezafungin). Summary of Product Characteristics. Mundipharma 2023.
2. Thompson GR III, et al. Lancet. 2023;401(10370):49–59.
3. Thompson GR III, et al. Lancet ID. 2023; https://doi.org/10.1016/S1473-3099(23)00551-0.
4. Fioriti S, et al. J Fungi (Basel). 2022;8(10):1077.
5. Govrins M and Lass-Flörl C. Nat Rev Microbiol. 2023 Sep 6.
6. Flanagan S, et al. Microbiol Spectr. 2023;11(3):e0133923.
7. Pappas PG, et al. Nat Rev Dis Primers. 2018;4:18026.
8. Brown GD, et al. Med Mycology. 2012;4(165)1–9.
9. Delaloye J, Calandra T. Virulence. 2014;5(1):161–169.
10. Antinori S, et al. Eur J Intern Med. 2016;34:21–28.
11. World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action, 2022. https://www.who.int/publications/i/item/9789240060241. Accessed April 2024.
12. Hoenigl M, et al. Lancet Infect Dis. 2023;23(6):751–761.
13. Choi H, et al. Int J Infect Dis. 2019;83:49–55.
14. Ha YE, et al. Antimicrob Agents Chemother. 2012;56(7):3950–3956.
15. Aldardeer NF, et al. BMC Infect Dis. 2020;20(1):55.
16. Kofteridis DP, et al. Mycopathologia. 2017;182(7–8):665–672.
17. Liu F, et al. Infect Drug Resist. 2021;14:3233–3246.
18. Menichetti F, et al. J Chemother. 2018;30(5):304–309.
19. Zhong L, et al. BMC Infect Dis. 2020;20(1):810.
20. Ylipalosaari P, et al. Crit Care. 2012;16(2):R62.
21. Bloos F, et al. J Crit Care. 2013;28(1):2–8.
22. Cui N, et al. BMC Infect Dis. 2017;17(1):93.
23. Baronia A et al. Indian J Crit Care Med. 2017;21(1):40–5.
24. Arendrup MC, et al. J Infect. 2023;87(5):428–437.
25. McCarty TP, et al. Infect Dis Clin North Am. 2021;35(2):389–413.
26. Gupta A, et al. Indian J Crit Care Med. 2015;19(3):151–154.
27. Mesini A, et al. Mycoses. 2020;63(4):361–368.
28. Pfaller MA, et al. Open Forum Infect Dis. 2019;6(Suppl 1):S79–S94.
29. Caspofungin. Summary of Product Characteristics.
30. Micafungin. Summary of Product Characteristics.
31. Amphotericin B. Summary of Product Characteristics.
32. Brüggemann RJ, et al. Lancet Haematol. 2022;9(1):e58–e72.
33. Data on file, Mundipharma, REF-16722.
34. Anidulafungin. Summary of Product Characteristics.
35. Data on file, Mundipharma, REF-16629.
36. Honoré PM, et al. Critical Care. 2023, 27(S1): P164.
37. Zhao Y, et al. Cell Microbiol. 2016;18:1308–1316.
38. Berkow EL and Lockhart SR. Diagn Microbiol Infect Dis. 2018;90(3) :196–197.
39. Pappas PG, et al. Clin Infect Dis. 2016;62(4):e1–e50.
40. Kullberg BJ and Arendrup MC. N Engl J Med. 2015;373(15):1445–1456.
41. Ghrenassia E, et al. Ann Intensive Care. 2019;9(1):62.
42. Data on file, Mundipharma, REF-16628.
43. Krishnan BR, et al. J Antibiot. 2017;70(2):130–135.
44. Ong V, et al. Antimicrob Agents Chemother. 2016;60(11):6872–6879.
45. Patil A and Majumdar S. J Pharm Pharmacol. 2017;69(12):1635–1660.
46. Ong V, et al. Antimicrob Agents Chemother. 2017;61(4):e01626–16.
47. Sandison T, et al. Antimicrob Agents Chemother. 2017;61 (2):e01627–16.
48. Cornely OA, et al. Clin Microbiol Infect. 2012;18(Suppl 7):19–37.
49. Ullmann AJ, et al. Clin Microbiol and Infect. 2012;18(Suppl 7):53–67.
50. Martin-Loeches I, et al. Intensive Care Med. 2019;45(6):789–805.
51. Tissot F, et al. Haematologica. 2017;102(3):433–44.
52. Lepak AJ, et al. Antimicrob Agents Chemother. 2018;62(2):e02154–17.

# Prescribing information

**▼REZZAYO (rezafungin) 200 mg powder for concentrate for solution for infusion GB PRESCRIBING INFORMATION**

**Refer to Summary of Product Characteristics (SmPC) before prescribing.**

**Presentation:** Each vial contains 200 mg rezafungin (as acetate). Powder for concentrate for solution for infusion. White to pale yellow cake or powder. **Indication:** REZZAYO is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents. **Dosage and administration:** A single 400 mg loading dose on Day 1, followed by 200 mg on Day 8 and once weekly thereafter. The duration of treatment should be based upon the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. During clinical trials patients were treated with rezafungin for up to 28 days. The safety information on rezafungin treatment durations longer than 4 weeks is limited. For intravenous use only. After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour, infusion time may be increased up to 180 minutes to manage any evolving symptoms of infusion-related reaction. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to other medicinal products of the echinocandin class. **Warnings and precautions:** The efficacy of rezafungin has only been evaluated in a limited number of neutropenic patients. Hepatic effects: In clinical trials, elevations in liver enzymes have been seen in some patients treated with rezafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with rezafungin, clinically significant hepatic dysfunction has occurred; a causal relationship to rezafungin has not been established. Patients who develop elevations in liver enzymes during rezafungin therapy should be monitored and the risk/benefit of continuing rezafungin therapy should be re-evaluated. Infusion-related reactions: Transient infusion-related reactions have occurred with rezafungin, characterised by flushing, sensation of warmth, nausea, and chest tightness. In clinical trials, infusion reactions resolved within minutes, some without interruption or discontinuation of the infusion. Patients should be monitored during the infusion. If the infusion is stopped due to a reaction, consideration may be given to restarting the infusion at a slower rate after the symptoms have resolved. Phototoxicity: Rezafungin may cause increased risk of phototoxicity. Patients should be advised to avoid sun exposure and other sources of UV radiation without adequate protection during treatment and for 7 days after the last administration of rezafungin. **Interactions:** The drug-drug interaction potential of rezafungin with a number of probe substrates of cytochrome P450 enzymes and/or transporter proteins has been assessed clinically. The need for dose adjustments is considered unlikely for medicinal products that are substrates for the CYP2C8, CYP3A4, CYP1A2, and CYP2B6 enzymes and P-gp, BCRP, OATP, OCT1, OCT2, MATE1, and MATE2 transporter proteins, when administered with rezafungin. The drug-drug interaction potential of rezafungin with a number of co-administered medicinal products has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax when administered with rezafungin. In vitro, rezafungin is metabolically stable and was found not to be a substrate for BCRP, P-gp, MRP2, OATP1B1, OATP1B3, OCT1, OCTN1, and OCTN2 transporter proteins. Therefore, the need for dose adjustments of rezafungin is considered unlikely when rezafungin is co-administered with other medicinal products. **Fertility, pregnancy and lactation:** There are no data from the use of rezafungin in pregnant women. Studies in animals did not show reproductive or developmental toxicity. Rezafungin has been shown to cross the placental barrier in animal studies. The potential risk for humans is unknown. Rezafungin is not recommended to be used during pregnancy and in women of childbearing potential not using contraception unless the benefit outweighs the potential risk to the foetus. There are no data from the use of rezafungin in lactating women. It is unknown whether rezafungin or its metabolites are excreted in human milk. Rezafungin excretion into milk was observed in rats. No data on the effect of rezafungin on human fertility are available. Rezafungin did not affect fertility in female rats or reproductive performance in male rats, despite reversible testicular effects in male rats. **Side effects:** Based on clinical trial experience, the most frequently reported adverse reactions for rezafungin were hypokalaemia, pyrexia, and diarrhoea (very common adverse reactions(≥ 1/10)). Common adverse reactions (≥ 1/100 to < 1/10 ) were: anaemia, hypomagnesaemia, hypophosphataemia, hypotension, wheezing, vomiting, nausea, abdominal pain, constipation, erythema, rash, blood alkaline phosphatase increased, hepatic enzymes increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased. Transient infusion-related reactions have occurred with rezafungin, characterised by flushing, sensation of warmth, nausea, and chest tightness. Uncommon (≥ 1/1 000 to < 1/100) were: hyperphosphataemia, hyponatraemia, phototoxicity, tremor, increased eosinophil count. Unknown incidence: urticaria.
**Refer to the SmPC for details on full side effect profile and interactions.**

**UK Basic NHS Price:** £1,999.95 per 1 200 mg vial.
**Classification:** POM **Marketing authorisation (MA):** PLGB 16950/0390 **Name and address of MA holder:** Napp Pharmaceuticals Ltd., Cambridge Science Park, Milton Road, Cambridge CB40AB UK. Tel: 01223424444. For medical information enquiries, please contact medicalinformationuk@napp.co.uk.

Adverse event reporting: Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444

**PI approval code: UK-RZF-2400013**

**Date of preparation: January 2024**

# Prescribing information

REZZAYO® rezafungin acetate

**▼ REZZAYO (rezafungin) 200 mg powder for concentrate for solution for infusion NI PRESCRIBING INFORMATION**

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**Presentation:** Each vial contains 200 mg rezafungin (as acetate). Powder for concentrate for solution for infusion. White to pale yellow cake or powder. **Indication:** REZZAYO is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents. **Dosage and administration:** A single 400 mg loading dose on Day 1, followed by 200 mg on Day 8 and once weekly thereafter. The duration of treatment should be based upon the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. During clinical trials patients were treated with rezafungin for up to 28 days. The safety information on rezafungin treatment durations longer than 4 weeks is limited. For intravenous use only. After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour, infusion time may be increased up to 180 minutes to manage any evolving symptoms of infusion-related reaction. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to other medicinal products of the echinocandin class. **Warnings and precautions:** The efficacy of rezafungin has only been evaluated in a limited number of neutropenic patients. Hepatic effects: In clinical trials, elevations in liver enzymes have been seen in some patients treated with rezafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with rezafungin, clinically significant hepatic dysfunction has occurred; a causal relationship to rezafungin has not been established. Patients who develop elevations in liver enzymes during rezafungin therapy should be monitored and the risk/benefit of continuing rezafungin therapy should be re-evaluated. Infusion-related reactions: Transient infusion-related reactions have occurred with rezafungin, characterised by flushing, sensation of warmth, nausea, and chest tightness. In clinical trials, infusion reactions resolved within minutes, some without interruption or discontinuation of the infusion. Patients should be monitored during the infusion. If the infusion is stopped due to a reaction, consideration may be given to restarting the infusion at a slower rate after the symptoms have resolved. Phototoxicity: Rezafungin may cause increased risk of phototoxicity. Patients should be advised to avoid sun exposure and other sources of UV radiation without adequate protection during treatment and for 7 days after the last administration of rezafungin. **Interactions:** The drug-drug interaction potential of rezafungin with a number of probe substrates of cytochrome P450 enzymes and/or transporter proteins has been assessed clinically. The need for dose adjustments is considered unlikely for medicinal products that are substrates for the CYP2C8, CYP3A4, CYP1A2, and CYP2B6 enzymes and P-gp, BCRP, OATP, OCT1, OCT2, MATE1, and MATE2 transporter proteins, when administered with rezafungin. The drug-drug interaction potential of rezafungin with a number of co-administered medicinal products has also been assessed clinically. The need for dose adjustments is considered unlikely for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax when administered with rezafungin. In vitro, rezafungin is metabolically stable and was found not to be a substrate for BCRP, P-gp, MRP2, OATP1B1, OATP1B3, OCT1, OCTN1, and OCTN2 transporter proteins. Therefore, the need for dose adjustments of rezafungin is considered unlikely when rezafungin is co-administered with other medicinal products. **Fertility, pregnancy and lactation:** There are no data from the use of rezafungin in pregnant women. Studies in animals did not show reproductive or developmental toxicity. Rezafungin has been shown to cross the placental barrier in animal studies. The potential risk for humans is unknown. Rezafungin is not recommended to be used during pregnancy and in women of childbearing potential not using contraception unless the benefit outweighs the potential risk to the foetus. There are no data from the use of rezafungin in lactating women. It is unknown whether rezafungin or its metabolites are excreted in human milk. Rezafungin excretion into milk was observed in rats. 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Uncommon (≥ 1/1 000 to < 1/100) were: hyperphosphataemia, hyponatraemia, phototoxicity, tremor, increased eosinophil count. Unknown incidence: urticaria.
**Refer to the SmPC for details on full side effect profile and interactions.**

**UK Basic NHS Price:** £1,999.95 per 1 200 mg vial. **Classification:** POM **Marketing authorisation (MA):** EU/1/23/1775/001 **Name and address of MA holder:** Mundipharma GmbH, De-Saint-Exupery-Strasse 10, Frankfurt Am Main, 60549, Germany. Tel: 01223424444. For medical information enquiries, please contact medicalinformationuk@napp.co.uk.

Adverse event reporting: Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444

**PI approval code: UK-RZF-2300065**

**Date of preparation: January 2024**

**Reporting adverse events**
Adverse events should be reported. Reporting forms and information can be found at
**https://yellowcard.mhra.gov.uk/**
Adverse events should also be reported to Napp Pharmaceuticals on 01223 424444 or **drugsafetyukandROI@mundipharma.com**

Learn more about the benefits of ***REZZAYO®*** from clinical experts or download resources for use with your patients. Visit:
www.napphcp.co.uk/medicines/rezzayo

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