ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

REZZAYO 200 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg rezafungin (as acetate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate)

White to pale yellow cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment with REZZAYO should be initiated by a physician experienced in the management of invasive fungal infections.

Posology

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.

If a scheduled dose is missed (not given on the assigned day) the missed dose should be administered as soon as possible.

- If the missed dose is administered within 3 days of the assigned day, the next weekly dose may be given on schedule.
- If the missed dose is administered more than 3 days after the assigned day, the dosing schedule should be revised to ensure there are at least 4 days before the next dose.
- If administration is restarted after at least 2 weeks of missed dosing, the dosing should be started again at the 400 mg loading dose.

Special populations

Elderly

No dose adjustment is required in elderly patients aged 65 years or more (see section 5.2).

Hepatic impairment

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

Renal impairment

No dose adjustment is required for patients with renal impairment. This medicinal product can be given without regard to the timing of haemodialysis (see section 5.2).

Other populations

No dose adjustment is required based on patients' weight (see section 5.2).

Paediatric population

The safety and efficacy of REZZAYO in children below 18 years have not yet been established. No data are available.

Method of administration

For intravenous use only.

After reconstitution and dilution (see section 6.6), 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 (see section 4.4).

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

4.3 Contraindications

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

Hypersensitivity to other medicinal products of the echinocandin class.

4.4 Special warnings and precautions for use

The efficacy of rezafungin has only been evaluated in a limited number of neutropenic patients (see section 5.1).

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.

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.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of rezafungin in pregnant women.
Studies in animals did not show reproductive or developmental toxicity (see section 5.3). 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.

Breast-feeding

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 (see section 5.3).

A risk to the breastfed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rezafungin therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Based on clinical trial experience, the most frequently reported adverse reactions for rezafungin were hypokalaemia, pyrexia, anaemia, and diarrhoea (very common adverse reactions).

Transient infusion-related reactions have occurred with rezafungin, characterised by flushing, sensation of warmth, nausea, and chest tightness (see section 4.4).

Tabulated list of adverse reactions

The following table includes adverse reactions from 173 subjects that received rezafungin 400/200 mg listed by system organ class (SOC) and MedDRA preferred terms with frequency corresponding to very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and from spontaneous reports with frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Table of adverse reactions

System organ class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**	**Not known**
Blood and lymphatic system disorders	Anaemia			
Metabolism and nutrition disorders	Hypokalaemia	Hypomagnesaemia, hypophosphataemia	Hyperphosphataemia, hyponatraemia	
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders		Wheezing		
Gastrointestinal disorders	Diarrhoea	Vomiting, nausea, abdominal pain, constipation		
Skin and subcutaneous tissue disorders		Erythema, rash	Phototoxicity	Urticaria

Musculoskeletal and connective tissue disorders			Tremor	
General disorders and administration site conditions	Pyrexia			
Investigations		Blood alkaline phosphatase increased, hepatic enzymes increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased	Eosinophil count increased	
Injury, poisoning and procedural complications		Infusion-related reactions		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, supportive care and symptomatic treatment is advised with maintenance of homeostasis and vital functions.

In a Phase 1 clinical trial, single doses of 600 mg and 1 400 mg were administered with no reported dose-limiting toxicity. Rezafungin doses of 400 mg once weekly for up to 4 weeks were administered in a Phase 2 clinical trial with no reported dose-limiting toxicity.

Rezafungin is highly protein-bound and not expected to be dialysable (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX08

Mechanism of action

Rezafungin selectively inhibits fungal 1,3-β-D-glucan synthase. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall which is not present in mammalian cells. Inhibition of 1,3-β-D-glucan synthesis results in rapid and concentration-dependent fungicidal activity in *Candida* species (spp.).

Activity *in vitro*

Rezafungin MIC_{90} values (obtained using a modified EUCAST methodology) are generally ≤ 0.016 mg/L across non-*parapsilosis Candida* spp. (*Candida parapsilosis* MIC_{90} = 2 mg/L).

When tested against a collection of clinical isolates of *Candida* spp. enriched for echinocandin-resistant and/or azole-resistant strains, rezafungin activity was similar to that of anidulafungin.

Resistance

Reduced susceptibility to echinocandins, including rezafungin, arises from mutations in glucan synthase catalytic subunit-encoding *FKS* genes (*FKS1* for most *Candida* spp.; *FKS1* and *FKS2* for *C. glabrata*).

Susceptibility testing interpretative criteria

MIC (minimum inhibitory concentration) interpretative criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for rezafungin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

A modified EUCAST broth microdilution MIC methodology has been used for testing the susceptibility of *Candida* spp. to rezafungin as well as to obtain the respective interpretative breakpoints.

Clinical efficacy

Candidaemia and invasive candidiasis in adult patients
The efficacy of rezafungin in the treatment of patients with candidaemia and/or invasive candidiasis (C/IC) was evaluated in a single Phase 3 study.

The Phase 3 study was multicentre, prospective, randomised and double-blind. Patients with septic arthritis in a prosthetic joint, osteomyelitis, endocarditis or myocarditis, meningitis, endophthalmitis, chorioretinitis or any central nervous system infection, chronic disseminated candidiasis and urinary tract candidiasis secondary to obstruction or surgical instrumentation were excluded from the study. Subjects were randomised in a 1:1 ratio to receive rezafungin as a 400 mg loading dose on Day 1, followed by 200 mg on Day 8 and once weekly thereafter, for a total of 2 to 4 weeks or caspofungin as a single 70 mg intravenous loading dose on Day 1 followed by caspofungin 50 mg intravenous once daily for a total treatment of 14 days to 28 days.

For rezafungin and caspofungin treatment groups, 77.0 % and 74.2 % patients, respectively, had a final diagnosis of candidaemia only. Most of them had a modified APACHE II score < 20, representing 84.4 % and 81.5 % of rezafungin and caspofungin subjects, respectively. For rezafungin and caspofungin treatment groups, 88.5 % and 91.1 % patients, respectively, had an ANC ≥ 500/mm^3 at baseline.

The primary efficacy outcome was global response (confirmed by the Data Review Committee [DRC]) at Day 14. Global response was determined from clinical response, mycological response, and radiologic response (for qualifying subjects with IC). Non-inferiority was to be concluded if the lower bound of the 95 % confidence interval (CI) for the difference in Day 14 cure rates (rezafungin - caspofungin) was > -20 %. Secondary efficacy outcomes included all-cause mortality at Day 30 [30-day ACM] and global response at Day 5. The results of these endpoints are shown in Table 2 for the mITT analysis set, defined as all subjects with a documented *Candida* infection based on Central Laboratory evaluation of a blood culture or a culture from a normally sterile site obtained ≤ 4 days (96 hours) before randomisation and who received ≥ 1 dose of investigational medicinal product.

Table 2. Summary of results from the phase 3 ReSTORE study (mITT analysis set)

	Rezafungin (R) (N = 115) n (%)	**Caspofungin (C) (N = 117) n (%)**	**Difference (R-C) (95 % CI)**
Global Response (Cure) [1]			
Day 5	60 (52.2)	57 (48.7)	3.5 (-9.4, 16.2)
Day 14	65 (56.5)	67 (57.3)	-1.0 (-13.5, 11.6)
Day 30 ACM (Deceased) [2, 3]	29 (25.2)	29 (24.8)	0.4 (-10.8, 11.6)

[1] Two-sided 95 % confidence intervals (CIs) for the observed differences in cure rates (rezafungin minus caspofungin) is calculated using the unadjusted methodology of Miettinen and Nurminen except for global cure at day 14 which is calculated adjusting for the two randomisation strata (diagnosis [candidaemia only; invasive candidiasis] and APACHE II score/ANC [APACHE II score ≥ 20 OR ANC < 500 cells/mm^3; APACHE II score < 20 AND ANC ≥ 500 cells/mm^3] at screening) using methodology of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights are used for the stratum weights.
[2] Two-sided 95 % confidence interval (CI) for the observed difference in death rates, rezafungin minus caspofungin treatment group, is calculated using the unadjusted methodology of Miettinen and Nurminen.
[3] Subjects who died on or before Day 30, or with unknown survival status.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with REZZAYO in one or more subsets of the paediatric population in treatment of invasive candidiasis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of rezafungin have been characterised in healthy subjects, special populations and patients. Rezafungin has a long half-life, allowing for once-weekly dosing. Steady state is achieved with the first loading dose (twice the weekly maintenance dose).

Distribution

Rezafungin is rapidly distributed with a volume of distribution approximately equal to body water (~ 40 L). Protein binding of rezafungin is high in humans (> 97 %).

Biotransformation

In vitro, rezafungin was stable across species after incubation with liver and intestinal microsomes and with hepatocytes.

In a single-dose clinical trial, radiolabelled (^{14}C) rezafungin (approximately 400 mg/200 µCi of radioactivity) was administered to healthy volunteers. The main circulating moiety was parent rezafungin; plasma AUC of rezafungin accounted for ~ 77 % of total radiocarbon AUC, with individual metabolites accounting for less than 10 % each.

Elimination

Following single doses of rezafungin (intravenous infusion over 1 hr; 50, 100, 200, and 400 mg), mean total body clearance of rezafungin was low (approximately 0.2 L/h) throughout the dose levels with a mean terminal half-life of 127 to 146 hours. The fraction of dose excreted in urine as unchanged

rezafungin was < 1 % at all dose levels, indicating minor contribution of renal clearance in rezafungin excretion.

In a single-dose clinical trial, radiolabelled (^{14}C) rezafungin (approximately 400 mg/200 µCi of radioactivity) was administered to healthy volunteers. Estimated, mean total recovery of radioactivity was 88.3 % at Day 60, based on interpolated data (from return visits to the clinical unit on Day 29 and Day 60). Approximately 74 % of the recovered radioactive dose was in faeces (primarily as unchanged rezafungin) and 26 % in urine (mainly as metabolites), indicating that elimination of rezafungin is primarily faecal excretion, as unchanged rezafungin.

Linearity

Following single dose intravenous infusion, the pharmacokinetics of rezafungin are linear over a dose range of 50 to 1 400 mg. Time to reach maximum plasma concentration (T_{max}) was observed at the end of infusion, as expected, for all doses and AUC increased in a dose proportional manner.

Special populations

Hepatic impairment
Rezafungin PK was examined in subjects with moderate (Child-Pugh B, n=8) and severe (Child-Pugh C, n = 8) hepatic impairment. Mean rezafungin exposure was reduced by approximately 30 % in subjects with moderate and severe hepatic impairment compared to matched subjects with normal hepatic function. Rezafungin PK was similar in subjects with moderate and severe hepatic impairment, and rezafungin exposure did not change with increasing degree of hepatic impairment. Hepatic impairment did not have a clinically meaningful effect on rezafungin PK.

Renal impairment
A population PK analysis, including data from Phase 1, Phase 2 and Phase 3 studies, showed that creatinine clearance was not a significant covariate of rezafungin PK.

Elderly
A population PK analysis, including data from Phase 1, Phase 2 and Phase 3 studies, showed that age was not a significant covariate of rezafungin PK.

Weight
A population PK analysis including data from Phase 1, Phase 2 and Phase 3 studies, showed that body surface area was a significant covariate of rezafungin PK. Simulation of exposure in clinically obese patients (body mass index (BMI) ≥ 30) showed that exposure was reduced in these subjects, but the reduction is not considered clinically meaningful.

Gender/Ethnicity
A population PK analysis including data from Phase 1, Phase 2 and Phase 3 studies showed that gender and ethinicity were not significant covariates of rezafungin PK.

5.3 Preclinical safety data

Rezafungin induced an acute histamine-release response in rats, but not in monkeys.

Rezafungin was negative for genotoxicity in the bacterial and mammalian cell *in vitro* studies, and in a rat micronucleus study.

During reproductive toxicology studies, rezafungin did not affect mating or fertility in male and female rats following intravenous (short bolus) administration once every 3 days at doses up to 45 mg/kg (6 times the clinical exposure, based on AUC determined in a separate rat study). During the male fertility study, decreased sperm motility was noted at ≥ 30 mg/kg and most males at 45 mg/kg showed mild/moderate hypospermia and had no detectable motile sperm. At rezafungin doses

≥ 30 mg/kg there was an increased incidence of sperm with abnormal morphology as well as mild to moderate degeneration of the seminiferous tubules.

In a 3-month toxicology study in rats, rezafungin was intravenously (short bolus) dosed once every 3 days. Males dosed at 45 mg/kg showed minimal tubular degeneration/atrophy in the testes and cellular debris in the epididymides at the end of 3 months. The incidence of this finding reduced by the end of a 4-week reversibility period.

By contrast, there were no testicular, epidydimal or spermatogenesis effects at 45 mg/kg (about 4.7 times the clinical dose based on AUC comparisons) in rats dosed intravenously (short bolus) once weekly for 6 months or after a 6-month recovery period.

Sperm concentration, production rate, morphology and motility were unaffected in adult monkeys dosed once weekly with rezafungin, up to 30 mg/kg (about 6 times the clinical dose based on AUC comparisons) for 11 or 22 weeks or after a 52-week recovery period.

No reproductive or developmental toxicity was observed with rezafungin following intravenous administration to pregnant rats and rabbits at ≥ 3.0-fold the predicted human AUC plasma concentration at steady state.

In a pre- and post-natal development study in rats administered up to 45 mg/kg rezafungin intravenously, there were no adverse effects on offspring growth, maturation, or measures of neurobehavioral or reproductive function. Rezafungin was measurable at low concentrations in the plasma of the foetuses of dosed animals (with concentrations in foetal plasma 2.0-3.6 % of those found in maternal plasma) and was excreted in maternal milk (with concentrations in milk 22-26 % of those found in maternal plasma).

Reversible intention tremors (defined as a tremor that is more pronounced when movements are initiated) were observed in one 3-month monkey study with administration once every 3 days and had higher incidence at ≥ 30 mg/kg. The no observed effect level (NOEL) for intention tremors is considered to be 10 mg/kg in this study (about 2.5 times the clinical dose based on AUC comparisons). Intention tremors were not observed in the 6-month monkey study, in which animals were dosed intravenously once a week with up to 30 mg/kg (about 5.8 times the clinical dose based on AUC comparisons) or in any rat studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Histidine
Polysorbate 80
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

Stability of the reconstituted solution in the vial and the diluted solution for infusion

Chemical and physical in-use stability, when reconstituted with water for injections, has been demonstrated for up to 24 hours at 25 °C and 2 to 8 °C.

Chemical and physical in-use stability of the diluted solution for infusion (immediately following reconstitution) has been demonstrated for 48 hours at 25 °C and 2 to 8 °C.

From a microbiological point of view, the reconstituted solution and the diluted solution for infusion should be used immediately. If not used immediately, in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C from first opening, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Glass vial with chlorobutyl rubber stopper and aluminium seal with plastic flip-off cap.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

REZZAYO should be administered as a single agent via intravenous infusion in sodium chloride 9 mg/mL (0.9 %) solution for injection, sodium chloride 4.5 mg/mL (0.45 %) solution for injection, or 5 % glucose.

INSTRUCTIONS FOR USE IN ADULT PATIENTS

REZZAYO must be reconstituted and diluted prior to administration.

From a microbiological point of view, the reconstituted solution and the diluted solution for infusion should be used immediately. If not used immediately, in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C from first opening, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Using aseptic techniques, reconstitute each vial with 9.5 mL water for injections. The concentration of the reconstituted vial will be 20 mg/mL. Do not use sterile sodium chloride 9 mg/mL (0.9 %) solution for injection to reconstitute the vial, only use water for injections.

To minimise foaming, do not shake or mix vigorously. The white to pale yellow powder will dissolve completely. Mix using a gentle swirling motion for up to 5 minutes until the reconstituted solution is a clear, colourless to pale yellow solution. The reconstituted solution should be visually inspected for particulate matter or discolouration. If irregularities are found, do not use the vial.

The vial is for single use only. Therefore, unused reconstituted concentrate must be discarded immediately.

For the 400 mg loading dose, the reconstitution step should be repeated for the additional vial of REZZAYO (refer to dosing table).

The infused total volume should be 250 mL, therefore, the volume of the intravenous infusion bag (or bottle) should be adjusted accordingly, as shown in the dosing table. Aseptically transfer 10 mL from each of the reconstituted vials into an intravenous infusion bag (or bottle) containing either sodium chloride 9 mg/mL (0.9 %) solution for injection, sodium chloride 4.5 mg/mL (0.45 %) solution for injection, or 5 % glucose. The total reconstituted volume to be added to the intravenous bag or bottle is shown in the dosing table. Mix the solution by gentle inversion of the intravenous bag (or bottle). Avoid excessive agitation.

After dilution, the solution is to be discarded if particulate matter or discolouration is identified.

DOSING TABLE - PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

Dose (mg)	**Number of vials**	**Volume to be removed from 250 mL intravenous bag/bottle (mL)**	**Volume of water for injections to be added to each vial (mL)**	**Total reconstituted volume to add to intravenous bag/bottle (mL)**	**Total infusion volume (mL)**	**Final infusion solution concentration (mg/mL)**
400	2	20	9.5	20*	250	1.6
200	1	10	9.5	10	250	0.8

* 10 mL from each of two vials totalling 20 mL.

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

7. MARKETING AUTHORISATION HOLDER

Mundipharma GmbH,
De-Saint-Exupery-Strasse 10,
Frankfurt Am Main,
60549
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1775/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 22 December 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Fareva Mirabel
Route de Marsat Riom
Clermont-Ferrand
63963
France

OR

Mundipharma DC B.V.
Leusderend 16
Leusden
Utrecht
3832 RC
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

REZZAYO 200 mg powder for concentrate for solution for infusion
rezafungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg rezafungin (as acetate)

3. LIST OF EXCIPIENTS

Also contains, mannitol, histidine, polysorbate 80, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mundipharma GmbH,
De-Saint-Exupery-Strasse 10,
Frankfurt Am Main,
60549
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1775/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

REZZAYO 200 mg powder for concentrate
rezafungin
IV use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

REZZAYO 200 mg powder for concentrate for solution for infusion
rezafungin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What REZZAYO is and what it is used for

What REZZAYO is
REZZAYO contains the active substance rezafungin, which is an antifungal. Rezafungin belongs to a group of medicines called echinocandins.

What REZZAYO is used for
This medicine is given to adults to treat invasive candidiasis, a serious fungal infection in your tissues or organs that is caused by a type of yeast called *Candida*.

How REZZAYO works
This medicine blocks the action of an enzyme (a type of protein) that is needed by fungal cells to make a molecule that strengthens their cell walls. This makes the fungal cells fragile and stops the fungus from growing. This stops the infection from spreading and gives the body's natural defences a chance to remove the infection.

2. What you need to know before you are given REZZAYO

REZZAYO must not be given
- if you are allergic to rezafungin, other echinocandins (such as caspofungin, anidulafungin), or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given REZZAYO.

Effects on the liver
Your doctor may decide to monitor you for liver function more closely if you develop liver problems during your treatment.

Infusion-related reactions
REZZAYO may cause infusion-related reactions, which could include reddening of the skin (flushing), sensation of warmth, nausea (feeling sick) and chest tightness. Your doctor may decide to monitor you during the infusion for signs of an infusion-related reaction. Your doctor may decide to slow down your infusion (drip) if an infusion-related reaction occurs.

Light sensitivity
REZZAYO may increase your risk of phototoxicity (condition in which the skin or eyes become very sensitive to sunlight or other forms of light). During your treatment, and for 7 days after you have been given the last dose of this medicine, you should avoid being out in the sun or using artificial sun tanning lights without protection (like sunscreen).

Other medicines and REZZAYO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
You should not use this medicine unless specifically told by your doctor. If you are pregnant or breast-feeding, or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. If you are a woman of childbearing potential, you may be advised by your doctor to use contraception during your therapy with REZZAYO.
The effect of REZZAYO in pregnant or breast-feeding women is not known.

Driving and using machines
This medicine is unlikely to have an effect on driving or using machines.

REZZAYO contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How REZZAYO is given

This medicine will be prepared and given to you by a doctor or a healthcare professional.

Recommended dose
Your treatment will start with a ‘loading dose' (an initial dose of a medicine which is higher than the maintenance dose) of 400 mg on the first day. This will be followed by a maintenance dose of 200 mg on day 8 of your treatment and once weekly thereafter.

REZZAYO should be given to you once a week, by infusion (a drip) into your vein. This will take at least 1 hour. Your doctor will determine how long the infusion time will be and may increase it to up to 3 hours to avoid infusion-related reactions.

Your doctor will determine how long you need to receive treatment based on your response to the medicine and your condition.

In general, your treatment will continue for at least 14 days after the last day *Candida* was found in your blood.

If symptoms of invasive candidiasis come back, tell your doctor or another healthcare professional immediately.

If you have been given more REZZAYO than you should
You should not receive this medicine more than once a week. If you are concerned that you may have been given too much REZZAYO, tell your doctor or another healthcare professional immediately.

If you miss a dose of REZZAYO
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, if you miss an appointment to receive this medicine, contact your doctor or another healthcare professional as soon as possible to schedule a new appointment.

If you stop using REZZAYO
Your doctor will monitor your response and condition to determine when to stop your treatment with this medicine. You should not experience any side effects after this.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects - tell your doctor or another healthcare professional immediately should you experience any of the following side effects:
- reddening of the skin, sensation of warmth, nausea (feeling sick), chest tightness – these may be signs you are having an infusion-related reaction (common – may affect up to 1 in 10 people).

Other side effects

Very common (may affect more than 1 in 10 people)
- low blood potassium level (hypokalaemia)
- diarrhoea
- fever (pyrexia)
- decreased red blood cells (anaemia)

Common (may affect up to 1 in 10 people)
- low blood magnesium level (hypomagnesaemia)
- low blood phosphate level (hypophosphataemia)
- low blood pressure (hypotension)
- wheezing
- vomiting
- feeling sick (nausea)
- stomach (abdominal) pain
- constipation
- redness of the skin (erythema)
- rash
- increased blood levels of alkaline phosphatase, an enzyme (protein) made in the liver, bones, kidney and gut
- increased levels of liver enzymes (including alanine aminotransferase and aspartate aminotransferase)
- increased blood levels of bilirubin, a breakdown product of red blood cells

Uncommon (may affect up to 1 in 100 people)
- high blood phosphate levels (hyperphosphataemia)
- low blood sodium level (hyponatraemia)
- skin or eyes become very sensitive to sunlight or other forms of light (phototoxicity)
- shaking (tremor)
- high blood levels of eosinophils (a type of white blood cell)

Not known (frequency cannot be estimated from the available data)
- Hives (urticaria)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store REZZAYO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Keep the vial in the outer carton in order to protect from light.

Only a trained healthcare professional who has read the complete directions can prepare this medicine for use. Once REZZAYO has been prepared, it should normally be used immediately. However, the reconstituted and diluted infusion solution may be stored up to 24 hours in a refrigerator.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What REZZAYO contains
- The active substance is rezafungin. Each vial contains 200 mg rezafungin (as acetate).
- The other ingredients are mannitol, histidine, polysorbate 80, hydrochloric acid, sodium hydroxide (see section 2 “REZZAYO contains sodium”).

What REZZAYO looks like and contents of the pack

REZZAYO is a powder for concentrate for solution for infusion (powder for concentrate) in a glass vial with a rubber stopper and an aluminium seal with plastic flip-off cap. It is a white to pale yellow cake or powder.
Each pack contains 1 vial.

Marketing Authorisation Holder
Mundipharma GmbH,
De-Saint-Exupery-Strasse 10,
Frankfurt Am Main,
60549
Germany
Tel: +49 69506029-000
Email: info@mundipharma.de

Manufacturer
Fareva Mirabel
Route de Marsat Riom
Clermont-Ferrand
63963
France

OR

Mundipharma DC B.V.
Leusderend 16
Leusden
Utrecht
3832 RC
Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

REZZAYO should be administered as a single agent via intravenous infusion in sodium chloride 9 mg/mL (0.9 %) solution for injection, sodium chloride 4.5 mg/mL (0.45 %) solution for injection, or 5 % glucose.

INSTRUCTIONS FOR USE IN ADULT PATIENTS

REZZAYO must be reconstituted and diluted prior to administration.

From a microbiological point of view, the reconstituted solution and the diluted solution for infusion should be used immediately. If not used immediately, in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C from first opening, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Using aseptic techniques, reconstitute each vial with 9.5 mL water for injections. The concentration of the reconstituted vial will be 20 mg/mL. Do not use sterile sodium chloride 9 mg/mL (0.9 %) solution for injection to reconstitute the vial, only use water for injections.

To minimise foaming, do not shake or mix vigorously. The white to pale yellow powder will dissolve completely. Mix using a gentle swirling motion for up to 5 minutes until the reconstituted solution is a clear, colourless to pale yellow solution. The reconstituted solution should be visually inspected for particulate matter or discolouration. If irregularities are found, do not use the vial.

The vial is for single use only. Therefore, unused reconstituted concentrate must be discarded immediately.

For the 400 mg loading dose, the reconstitution step should be repeated for the additional vial of REZZAYO (refer to dosing table).

The infused total volume should be 250 mL, therefore, the volume of the intravenous infusion bag (or bottle) should be adjusted accordingly, as shown in the dosing table. Aseptically transfer 10 mL from each of the reconstituted vials into an intravenous infusion bag (or bottle) containing either sodium chloride 9 mg/mL (0.9 %) solution for injection, sodium chloride 4.5 mg/mL (0.45 %) solution for injection, or 5 % glucose. The total reconstituted volume to be added to the intravenous bag or bottle is shown in the dosing table. Mix the solution by gentle inversion of the intravenous bag (or bottle). Avoid excessive agitation.

After dilution, the solution is to be discarded if particulate matter or discolouration is identified.

DOSING TABLE - PREPARATION OF THE SOLUTION FOR INFUSION IN ADULTS

Dose (mg)	**Number of vials**	**Volume to be removed from 250 mL intravenous bag/bottle (mL)**	**Volume of water for injections to be added to each vial (mL)**	**Total reconstituted volume to add to intravenous bag/bottle (mL)**	**Total infusion volume (mL)**	**Final infusion solution concentration (mg/mL)**
400	2	20	9.5	20*	250	1.6
200	1	10	9.5	10	250	0.8

* 10 mL from each of two vials totalling 20 mL.