REF UM-CID-040

Instructions for Use

UMIC Cefiderocol

For *in vitro* diagnostic use

CE IVD

Language: en

Revision A (May 2022)

Legal and regulatory notices

Read this section before proceeding to the rest of the sections.

Document history

Title:	Instructions for Use UMIC Cefiderocol
Revision:	Revision A (May 2022)
First revision:	May 2022

The following table describes important changes from the previous revision of this document.

Section	**Changes**
–	No changes: first revision

Table of contents

1 Intended purpose

The UMIC Cefiderocol is an *in vitro* diagnostic medical device for the quantitative susceptibility testing of clinically relevant fast-growing aerobic Gram-negative bacteria (Enterobacterales, *Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*) against cefiderocol using Iron-depleted CAMHB. Susceptibility is detected by determining minimum inhibitory concentration according to EUCAST or CLSI guidelines. Only pure cultures obtained from human test material can be used.

The test is not automated. The device is intended for laboratory professional use only. The results of the test are intended solely as an aid to diagnosis for targeted antibacterial therapy and must not be used as single source for diagnosis, treatment or patient management decision.

2 Precautions and warnings

2.1 General precautions

- UMIC Cefiderocol is for single use only. Do not re-use!
- Inspect the product on arrival and do not use in case of damage. If the primary packaging (aluminum composite foil pouch) is damaged, check the integrity of the sealing foil on the UMIC Cefiderocol. If the sealing foil is undamaged, the UMIC Cefiderocol can be used. If the sealing foil is damaged, discard the UMIC Cefiderocol.
- Wear protective clothing and observe federal, state and local regulations.
- The Instructions for Use must be strictly adhered to; any deviation can affect the quality of the results.
- The test results should be interpreted by trained staff with experience in microbiology. Clinical background, sample origin, colony and microscopic morphology, and the identification result need to be considered when interpreting the results.

2.2 Precautions for handling the product

- Do not use for other purposes than the intended use.
- Do not pipette reagents by mouth.
- Carefully cut the sealing foil without damaging the sealing foil of the adjacent strips. Strips with damaged sealing foil should not be used later, because there could be a loss of drug activity.

2.3 Precautions for handling specimens

Samples, bacterial cultures, and inoculated UMIC Cefiderocol should be treated as potentially biohazardous and should be handled properly by appropriately qualified and trained staff while observing all relevant precautions. Use aseptic technique throughout the whole test procedure. For more information, see the current version of “BioSafety in Microbiological and Biomedical Laboratories, HHS publication (CDC)” or the relevant national regulations. After reading and evaluating the test results, all samples and inoculated or contaminated items should be autoclaved, incinerated, or treated with a bactericidal disinfectant solution before disposal.

Dispose of transport and secondary packaging of the UMIC Cefiderocol according to the local waste disposal regulations.

3 Product description

3.1 Summary and explanation

Cefiderocol is a cephalosporin antibiotic that uses a siderophore sidechain to force entry into bacterial cells. At low iron concentrations in the surrounding medium, bacteria use siderophores to effectively capture iron and transport it into their cells. In case of cefiderocol, this mechanism is used to push the whole molecule including the antibiotic into the cell. To provide low iron concentrations when testing susceptibility against cefiderocol, it is vital that Iron-depleted CAMHB is used. Iron-depleted CAMHB is Mueller Hinton Broth (MHB) from which cations have been removed, leading to low concentrations of Fe^{3+}, Ca^{2+}, Mg^{2+} and Zn^{2+}. The UMIC Cefiderocol should be used with cation-adjusted MHB (CAMHB) that has been reconstituted to contain 20-25 mg/L of Ca^{2+}, 10-12.5 mg/L of Mg^{2+} and 0.5-1 mg/L Zn^{2+}. Iron concentrations will be ≤ 0,03 mg/L.

Cefiderocol is indicated for the treatment of infections caused by Gram-negative multi-drug resistant bacteria, see section 1. It retains activity against bacteria producing serine carbapenemases, metallo-beta lactamases and extended-spectrum beta lactamases. It thus provides a treatment option for complicated urinary tract infections and bacterial pneumonia caused by Gram-negative multi-drug resistant bacteria.

3.2 Test principle

The UMIC Cefiderocol is a test system that is used for the determination of minimum inhibitory concentration (MIC). The MIC is defined as the lowest concentration of an antibiotic that inhibits visible bacterial growth. MIC determination with the UMIC Cefiderocol is based on broth microdilution (BMD) which allows for a quantitative test result regarding susceptibility against cefiderocol for the tested isolate. Cefiderocol is vacuum-dried in 12-well-strips. Eleven wells contain antibiotic, while the twelfth well is the growth control. Cefiderocol is rehydrated by the addition of Iron-depleted CAMHB, inoculated with the bacteria to be tested. After inoculation, strips are incubated for 18-24 hours at 35-37 °C and results are read visually for MIC determination.

3.3 Kit contents

Each pack is sufficient for 40 susceptibility tests and contains:

- 5 UMIC Cefiderocol plates, each containing 8 test strips with 12 wells. Each strip contains cefiderocol for final concentrations ranging from 0.03 to 32 mg/L.
- Lid and frame
- Certificate of Analysis
- Instructions for Use
- Results Sheet

3.4 Materials required but not included

- Iron-depleted CAMHB (E2-333-020); manufacturer: Bruker Daltonics GmbH & Co. KG

Note *Determination of valid MIC values using the UMIC Cefiderocol test system requires the usage of the Iron-depleted CAMHB manufactured by Bruker Daltonics GmbH & Co. KG.*

Note *The exact composition of Iron-depleted CAMHB is confidential.*

Media	**Ingredients**
Iron-depleted CAMHB	Beef extract Acid hydrolysate of casein Starch

- Blood agar without additives

Note *Use of agar media other than blood agar without additives requires validation by the user.*

- NaCl 0.9%, pH 5.5 to 6.5
- Adjustable pipette, e. g. 20-200 µL, incl. pipette tips
- McFarland standard 0.5 or densitometer
- Incubator
- Inoculation loops
- Marker pen

Optional: UMIC Box Cefiderocol

4 Quality control

Strips and reagents are subjected to several quality inspections, systematically executed during various production stages. Bacteriological quality control can be performed using the following strains:

Strains	**ATCC[1] No.**	**DSMZ[2] No.**
Escherichia coli	ATCC 25922	DSM 1103
Pseudomonas aeruginosa	ATCC 27853	DSM 1117

MIC results of the control strains should fall within the quality control ranges of the respective drug tested as specified in the relevant standard.

[1] *ATCC=American Type Culture Collection*

[2] *DSMZ=Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (German Collection of Microorganisms and Cell Cultures Ltd.)*

5 Specimen requirements

Use axenic cultures from blood agar without additives that are not older than 24 hours.

6 Test procedure

This section describes all the steps that are necessary for using the UMIC strips.

6.1 Preparing the inoculum

Provide a tube with 2-5 mL NaCl 0.9%, pH 5.5-6.5.

Provide a tube with 5 mL Iron-depleted CAMHB.

1. Pick several single colonies from an 18-24-hour-old pure culture from blood agar without additives.
2. Homogenize the colonies well in 2-5 mL NaCl 0.9% until the turbidity matches to a McFarland standard of 0.5.
3. Pipette 25 µL of the bacterial suspension into 5 mL Iron-depleted CAMHB and homogenize well.

6.2 Inoculating the strips

Remove the UMIC Cefiderocol test strips from their resealable packaging max. 30 minutes before use.

1. Cut the sealing foil and remove the strips from the frame.
2. Put the remaining strips back in the resealable packaging immediately and seal the packaging tightly.
3. Insert the strips into the empty frame that is supplied with the pack. The printed marking “CID” on each strip must be on the left side of the frame.
4. Remove the sealing foil and note the sample number on the respective strip to prevent mixing up of samples.
5. Inoculate each well of each test strip with 100 µL of the prepared suspension.

6.3 Sealing and incubation

1. After inoculation, seal the strips by placing the lid on the frame.
2. Incubate the test strips at 35-37 °C under aerobic conditions for 18-24 hours in humid atmosphere (e. g. UMIC Box Cefiderocol).

6.4 Reading

1. Remove the lid.
2. Wipe the bottom of the strips.
3. Visually read the strips and document the results. Growth is indicated either by turbidity or by cell deposit at the bottom of the wells. To read MIC results in accordance with EUCAST and/or CLSI, consult the relevant standards and guidance documents, see section 11.

Note *Growth must be visible in the growth control, otherwise the test must be repeated.*

6.5 Analysis

Document the results on the product-specific Results Sheet and interpret the MIC values according to the currently valid international CLSI or EUCAST standards. The Results Sheet is not part of this Instructions for Use.

7 Evaluating results

Occasionally, skipped wells can occur within a test strip. A skipped well is characterized by lack of growth in one or more wells of an antibiotic serial dilution while the wells of the next lower/higher concentration show growth. The reasons for skipped wells are diverse: heteroresistance, inhomogeneous inoculum or inhomogeneous inoculation of the wells, etc.

For UMIC Cefiderocol test strips, a single skipped well in a serial dilution can be ignored. The concentration of the well after which no more visible growth is detectable can be read as the MIC value. If several skipped wells occur in a serial dilution, the sample and test preparation must be repeated.

8 Troubleshooting

Issue	Recommendation
MIC values of quality control strains are out of range	Make sure that Iron-depleted CAMHB manufactured by Bruker Daltonics GmbH & Co. KG was used. Ensure that the test strips are aligned correctly when inserting them into the frame. The printed marking “CID” on each strip must be on the left side of the frame. Pre-heat the Iron-depleted CAMHB before use. Incubate at 35-37 °C for 1 hour.
Skipped wells	Take care that no drops of bacterial suspension remain at the edges of the wells after you have inoculated the test strips. Drops at the edges of the wells may not have contact with the antibiotic.
Insufficient growth in the positive control	Make sure to adjust the NaCl suspension exactly to McFarland standard 0.5. Homogenize the prepared suspension sufficiently. If stock cultures are being used, freshly inoculate a blood agar plate without additives and use after incubation at 35-37 °C for no more than 24 hours. The incubation time of the UMIC Cefiderocol must not be less than 18 hours.
Suspected contamination	Inoculate a blood agar plate without additives with the bacterial suspension for purity control.
Wells dry out	Incubate in a humidity chamber.

9 Limitations of the method

Cefiderocol concentrations 0.03 µg/ml, 0.06 µg/ml, and 0.125 µg/ml are for quality control strains only, see section 4. Results for clinical isolates in this range are reported as ≤0.25 µg/ml. MIC values that are smaller than 0.03 µg/ml or larger than 32 µg/ml cannot be measured.

10 Performance characteristics

The general requirements of ISO 20776-1, ISO 20776-2 and/or EUCAST or CLSI apply.

For clinical performance, an Essential Agreement of 90.8 % and bias of -9.9 % were determined. All parameters also fulfill the requirements of ISO 20776-2:2021.

Analytical performance was shown to fulfill all requirements. In detail, repeatability was 100 %. Reproducibility (day-to-day, site-to-site, and operator-to-operator) was 97.6 % and run-to-run reproducibility was 95.5 %. Lot-to-lot reproducibility was 100 %. All parameters fulfill the ≥ 95 % requirement.

UMIC Cefiderocol used in conjunction with Iron-depleted CAMHB shows no cross-reactivity or interference with other substances, which means that analytical specificity is not applicable. Analytical sensitivity is also not applicable, as the product is read visually.

11 References

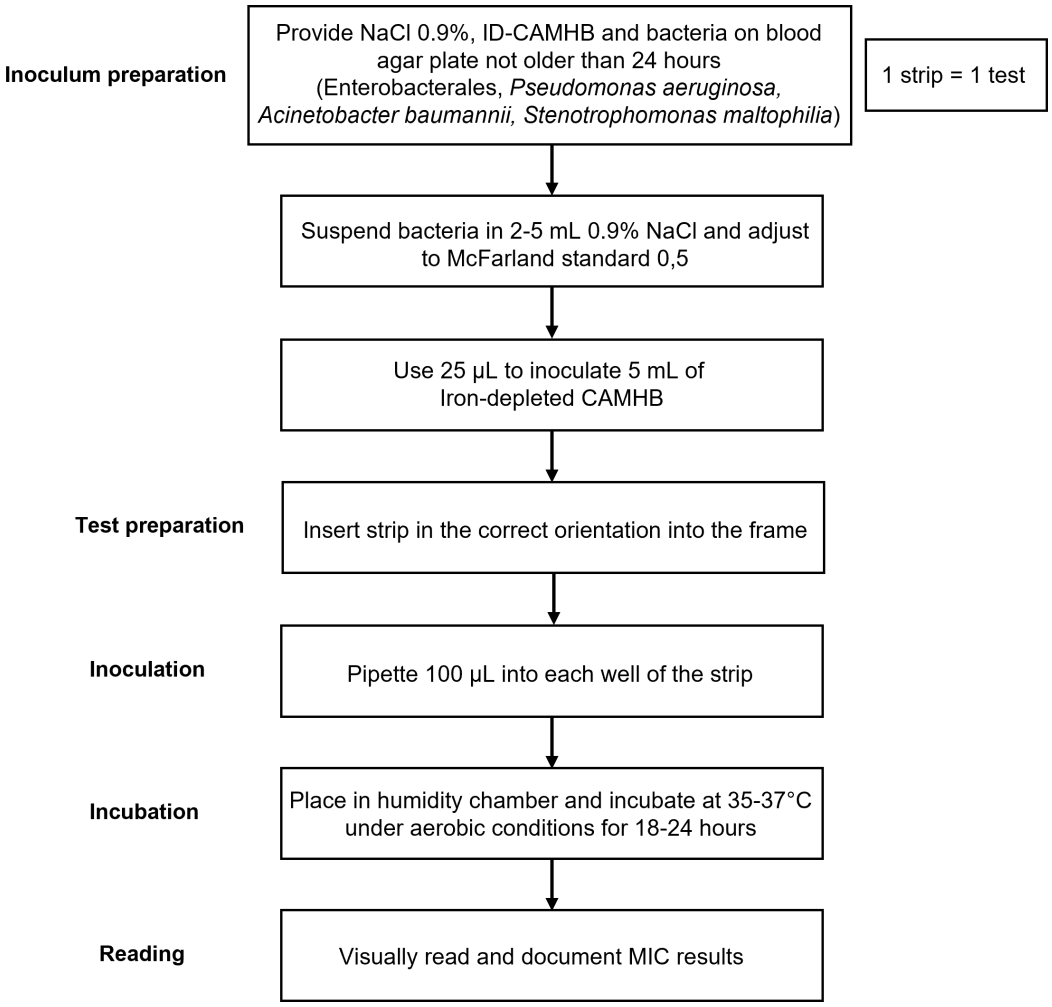
Note *The standards and guidance documents listed below are subject to update.*

- Ito A., Nishikawa T., Matsumoto S., et al. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against Pseudomonas aeruginosa. Antimicrobial Agents Chemotherapy. 2016; 60(12): 7396-7401
- Zhanel G. G., Golden A. R., Zelenistky S., et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli. Drugs. 2019; 79(3): 271-289
- ISO 20776-1 — Clinical laboratory testing and in vitro diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices — Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases.
- ISO 20776-2 — Clinical laboratory testing and in vitro diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices — Part 2: Evaluation of performance of antimicrobial susceptibility test devices.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST), Breakpoint tables for interpretation of MICs and zone diameters.
- European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusions as recommended by EUCAST.
- European Committee on Antimicrobial Susceptibility Testing. Guidance document on broth microdilution testing of cefiderocol.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance.
- Performance Standards for Antimicrobial Susceptibility Testing; CLSI Document M100.

12 Abbreviations

ATCC	American Type Culture Collection
BMD	Broth Microdilution
CLSI	Clinical and Laboratory Standards Institute
DSMZ	Deutsche Sammlung von Mikroorganismen und Zellkulturen
EUCAST	European Committee on antimicrobial susceptibility testing
CID	Cefiderocol
Iron-depleted CAMHB	Iron-depleted Mueller Hinton Broth, cation-adjusted
IFU	Instructions for use
ISO	International Organization for standardization
MIC	Minimum inhibitory concentration
N/A	Not applicable
NaCl	Sodium chloride

13 UMIC Cefiderocol short instruction



14 Symbols

Symbol	Description
	Do not re-use
	Contains sufficient for <n> tests
	Temperature limit
	Consult Instructions for Use
	Caution
	Use-by date
	Batch code
	*In vitro* diagnostic medical device
	Catalog number
	Global Trade Item Number
	Manufacturer

15 Manufacturer

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Descriptions and specifications supersede all previous information.