# SUMMARY OF SAFETY AND PERFORMANCE (SSP)
# KarbaDia Rapid Test

## 1. Introduction

The Summary of Safety and Performance (SSP) is one of the requirements of the new Regulation (IVDR 2017/746), specific for class C and D devices, to enhance transparency and adequate access to information. It intends to provide public access to summarised data on the safety and performance of class C and class D IVD devices to all intended users – professionals and lay persons. GaDia is also providing this information for class B devices.

## 2. Summary of Safety and Performance (SSP)

| Requirements based on IVDR Article 29 | Potential regulatory sources |
|---|---|
| **Device identification and general information** | |
| Name or trade name including any model number or version | KarbaDia Rapid Test |
| Manufacturer (name and address) | GaDia SA<br>Route de l'Ile-au-Bois 1A<br>1870 Monthey<br>Switzerland |
| Manufacturers single registration number (SRN), if available | CH-MF-000031123 |
| Basic UDI-DI | 7649990065KARMM |
| **Intended purpose of the device** | |
| Intended purpose and indications | KarbaDiag is a non-automated rapid immunochromatographic test intended to be used for the qualitative detection of KPC-type, NDM-type, IMP-type, VIM-type and OXA-48-type carbapenemase in bacterial colonies. The assay is for professional use only and can aid in the diagnosis of KPC-type, NDM-type, IMP-type, VIM-type and OXA-48-type carbapenemase resistant strains. The test should be used in conjunction with other diagnostic procedures, such as genetic analysis, susceptibility testing and other microbial analysis. |
| Target populations | Bacterial colonies on agar plate suspected to be Carbapenem resistance Enterobacteriaceae. Bacteria can be isolated from human body fluids or other sources. |

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| Contraindications (limitations) | 1. The test procedure, precautions and interpretation of results for this test must be followed strictly when testing.<br>2. The test is for professional use only and not for home-testing or near- patient testing.<br>3. The product is only used for the detection of Candida antibody in serum, plasma and BAL samples.<br>4. The test results of this kit are for reference only and should not be used as the only basis for clinical diagnosis and treatment. The clinical management of patients should be comprehensively considered in conjunction with their symptoms, medical history, other laboratory tests and treatment responses.<br>5. The sample treatment solution must be clear and without turbidity. |
| **Device description** | |
| Device description | KarbaDia is a sandwich immunochromatographic assay. The test has 5 pre-coated test lines (K N I V O) on nitrocellulose membrane and one Control line (C) per test. If KPC-type, NDM-type, IMP-type, VIM-type or OXA-48-type carbapenemase are present in the specimen, it will bind to the gold-conjugated anti-KPC, anti-NDM, anti-IMP, anti-VIM or anti-OXA-48 antibodies, respectively, pre-dried on conjugate pad. The gold-conjugated antibody-antigen complex moves upward on the membrane by capillary action where it will react with the test lines. The immobilized anti-KPC, anti-NDM, anti-IMP, anti-VIM or anti-OXA-48 monoclonal antibodies on test lines will capture the gold-conjugated antibody-antigen complex and form red line(s). Whether the sample is positive or not, the nanoparticle complex continues to move across the membrane where immobilized goat anti-chicken IgY antibodies (control line) will bind the gold-conjugated chicken IgY antibodies and form a visible red control line. Positive test results form one |

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| | or more red line(s) in test area. Negative test results form only a control line (C line). The quality control line (C line) is an internal quality control that serve as (1) verification that sufficient volume is added, (2) that proper flow is obtained and (3) an internal control for the reagents. The control line must always appear. |
| Reference to previous generation(s) or variants of the device (as applicable) and a description of the differences | N/A |
| Description of accessories intended to be used in combination with the device (as applicable) | N/A |
| Description of other devices and products intended to be used in combination with the device (as applicable) | Materials Required but Not Supplied<br>1. Timer<br>2. Inoculation loop (5 µl)<br>3. Optional: Pipettes and sterile tips<br>4. Optional: Disposable sterile micro-centrifuge tubes (1.5 ml) |
| **Standards Reference** | |
| Harmonised standards and Common Specifications (CS) applied | IVDD 98/79/EC<br>EN ISO 13485:2016<br>EN ISO 15223-1:2021<br>EN ISO 17511:2021<br>ISO 14971:2019<br>ISO 18113-1:2009<br>ISO 18113-2:2009<br>ISO 20417:2021<br>ISO 13975:2003<br>ISO 13612:2002<br>ISO 23640:2011<br>ISO 20916:2019<br>IEC 62366-1:2015+A1:2020 |
| **Summary of the Performance Evaluation** | |
| A total of 212 clinical isolates were collected from European hospitals (81%) and American hospitals (15%) in 2019 and 2020, including 19 carbapenemase- negative isolates (9%) and 193 (91%) carbapenem-resistant Enterobacterales (CRE) with various carbapenemase types. These were collected from various infection sources including respiratory, urinary tract, intra-abdominal and chorionic villus sampling. Molecular analysis was performed on all isolates and MIC determination on discordant results. The isolates were cultivated on | |

blood agar for 24h at 37°C and analysed with KarbaDia rapid test. The primary end point was to assess the diagnostic performance of KarbaDia Rapid test (GaDia SA, Monthey, Switzerland) using cultivated bacterial colonies. The second end point was to assess the capacity of the test to detect specific variants and non-fermenter isolates. The usability of the test and feedbacks from user are also collected for the usability study. Vassarstats online tool (www.vassarstats.net) was used to calculate sensitivity (SE), specificity (SP), positive and negative predictive values (PPV, NPV), 95% confidence intervals, median, and Interquartile range (IQR); while significance (p-values) was calculated using student t test for independent samples with equal variances. Statistical significance was defined as $p < 0.05$.

| | |
|---|---|
| Total Isolates | 203 |
| Carbapenemase negative isolates | 19 |
| **KPC isolates** | **32** |
| KPC-2 | 20 (63%) |
| KPC-3 | 8 (25%) |
| KPC-4 | 3 (9%) |
| KPC-27 | 1 (3%) |
| **OXA isolates** | **61** |
| OXA-48-TYPE(u) | 2 (3%) |
| OXA-48(c) | 31 (51%) |
| OXA-181(c) | 11 (18%) |
| OXA-232(c) | 16 (26%) |
| OXA-244(c) | 1 (2%) |
| **NDM isolates** | **69** |
| NDM-1 | 49 (71%) |
| NDM-2 | 7 (10%) |
| NDM-5 | 10 (14%) |
| NDM-6 | 1 (1%) |
| NDM-7 | 1 (1%) |
| NDM-Type | 1 (1%) |
| **IMP isolates** | **13** |
| IMP-1 | 3 (23%) |
| IMP-4 | 2 (15%) |
| IMP-8 | 4 (31%) |
| IMP-26 | 1 (8%) |
| IMP Multicopy | 2 (15%) |
| IMP-Type | 1 (8%) |
| **VIM isolates** | **29** |
| VIM-1 | 24 (83%) |
| VIM-2 | 4 (14%) |
| VIM-Type | 1 (3%) |

| **Carbapenemase negative (n=19)** | | **Carbapenemase positive (n=184)** | |
|---|---|---|---|
| Europe | 12 (63%) | Europe | 149 (81%) |
| America | 7 (37%) | America | 27 (15%) |
| Asia | 0 (0%) | Asia | 6 (3%) |
| Pacific | 0 (0%) | Pacific | 2 (1%) |
| Enterobacteriaceae | 19 (100%) | Enterobacteriaceae | 139 (76%) |
| Age (average) | 64 | Age (average) | 56 |
| Female | 8 (42%) | Female | 62 (34%) |
| CVS isolation | 5 (26%) | CVS isolation | 45 (24%) |
| UTI isolation | 2 (11%) | UTI isolation | 35 (19%) |
| RTI isolation | 6 (32%) | RTI isolation | 69 (38%) |
| IAI isolation | 6 (32%) | IAI isolation | 34 (18%) |

| | | | | | |
|---|---|---|---|---|---|
| **KPC** | + | - | **Sensitivity** | **100%** | (CI95%: 87-100%) |
| + | 32 | 0 | **Specificity** | **100%** | (CI95%: 97-100%) |
| - | 0 | 180 | **PPV** | **100%** | (CI95%: 87-100%) |
| | | | **NPV** | **100%** | (CI95%: 97-100%) |
| **OXA** | + | - | **Sensitivity** | **98%** | (CI95%: 90-100%) |
| + | 58 | 2 | **Specificity** | **99%** | (CI95%: 95-100%) |
| - | 1 | 149 | **PPV** | **97%** | (CI95%: 87-99%) |
| | | | **NPV** | **99%** | (CI95%: 96-100%) |
| **NDM** | + | - | **Sensitivity** | **97%** | (CI95%: 89-99%) |
| + | 65 | 1 | **Specificity** | **99%** | (CI95%: 95-100%) |
| - | 2 | 139 | **PPV** | **98%** | (CI95%: 91-100%) |
| | | | **NPV** | **99%** | (CI95%: 94-100%) |
| **IMP** | + | - | **Sensitivity** | **93%** | (CI95%: 66-100%) |
| + | 14 | 0 | **Specificity** | **100%** | (CI95%: 98-100%) |
| - | 1 | 190 | **PPV** | **100%** | (CI95%: 73-100%) |
| | | | **NPV** | **99%** | (CI95%: 97-100%) |
| **VIM** | + | - | **Sensitivity** | **100%** | (CI95%: 85-100%) |
| + | 29 | 0 | **Specificity** | **100%** | (CI95%: 97-100%) |
| - | 0 | 183 | **PPV** | **100%** | (CI95%: 85-100%) |
| | | | **NPV** | **100%** | (CI95%: 97-100%) |

| Carbapenemase Type | Variants detected (previous study) | Variants detected (this study) |
|---|---|---|
| KPC | KPC-1, KPC-2, KPC-3, KPC-74 | KPC-2, KPC-3, KPC-4, KPC-27 |
| OXA | OXA-23<br>OXA-163, OXA-181, OXA-232 | OXA-48(c), OXA-48 Type(u)<br>OXA-181(c), OXA-232(c)<br>OXA-244(c) |
| NDM | NDM-1, NDM-5, NDM-7 | NDM-1, NDM-2, NDM-5, NDM-6, NDM-7 |
| IMP | IMP-1, IMP-3, IMP-4, IMP-6, IMP-10, IMP-25, IMP-26, IMP-30, IMP-34, IMP-38, IMP-40, IMP-42 | IMP-1, IMP-4, IMP-6, IMP-7, IMP-10, IMP-26 |
| VIM | VIM-1, VIM-2, VIM-4, VIM-5, VIM-9, VIM-10 | VIM-1, VIM-2 |

The main finding of this evaluation study, using an unmatched case control design including 91% (184/203) carbapenemase positive isolates is that the diagnostic performance of KarbaDia RDT on bacterial isolates is high and depend of the carbapenemase type detected. The sensitivity varied between 93% and 100% with lower sensitivity with IMP type, when comparing with genetic and MIC assay. In term of specificity, the diagnostic specificity is beween 99% and 100%, similar to other rapid tests.

In conclusion, KarbaDia gives valuable information in only 15 minutes to start the treatment earlier with the right antibiotic. Perfromance compared to genetic and MIC methods, longer and requiring laboratory equipment, has substancial agreement. Confirmation with laboratory methods should be conducted.

## Summary of the Post-Market Performance Follow-Up

Two published studies use the same device and bring important information about performance of the test. Findings of these 2 studies are summarized below.

*Sadek et al. Diagnostic Microbiology and Infectious diseases*

The Rapid carbapenemase test is a novel immunochromatographic test for detection of the 5 major carbapenemases (KPC, NDM, IMP, VIM, and OXA-48-like). This test is rapid, easy

to perform, and shows a good sensitivity and specificity (96.8% and 100%, respectively), being suitable for microbiology laboratories together with biochemical rapid tests.

The study tested different variants of carbapenemase that need to be included in the table in IFU and in Performance evaluation report. The following table indicates the additional variants detected in the study of Sadek et al. 2022)

| Carbapenemase type | Variant detected (Sadek et al) |
|---|---|
| KPC | KPC-2, KPC-3 |
| NDM | NDM-1, NDM-5, NDM-6, NDM-7, NDM-9, NDM-24 |
| VIM | VIM-1, VIM-2 VIM-4, VIM-19, VIM-53 |
| IMP | IMP-1, IMP-4, IMP-5, IMP-10, IMP-11, IMP-15, IMP-29 |
| OXA | OXA-48, OXA-162, OXA-181, OXA-204, OXA-244 |

*Zhang et al. antibiotics MDPI*

Rapid and accurate detection can help optimize patient treatment and improve infection control against nosocomial carbapenemase-producing organisms (CPO). In this study, a total of 217 routine clinical isolates (Enterobacterales and A. baumannii), including 178 CPOs and 39 non- CPOs, were tested to evaluate the performance of six phenotypic carbapenemase detection and classification assays, i.e., BD Phoenix CPO detect panel, Rapidec Carba-NP, O.K.N detection kit, and three carbapenem inactivation methods (CIMs; mCIM, eCIM, sCIM).

**Table 2.** Overall sensitivity and specificity of phenotype diagnostic assays.

| Diagnostic Assays | | Sensitivity | | Specificity | |
|---|---|---|---|---|---|
| | | % | 95% CI | % | 95% CI |
| BD Phoenix CPO detect panel | P/N test | 98.78 | 95.21–99.79 | 79.49 | 63.06–90.13 |
| | Ambler test | 56.71 | 48.75–64.34 | 94.87 | 81.37–99.11 |
| CPO detection tests | Rapidec Carba-NP | 91.93 | 86.30–95.45 | 100 | 88.83–100 |
| | mCIM | 98.06 | 94.00–99.50 | 97.44 | 84.92–99.87 |
| | sCIM | 96.89 | 92.52–98.85 | 94.87 | 81.37–99.11 |
| CPO classification tests | O.K.N Detection kit | 99.28 | 95.43–99.96 | 100 | 88.83–100 |
| | mCIM + eCIM | 92.90 | 87.35–96.23 | 97.44 | 84.92–99.87 |

**Table 4.** Performance of other carbapenemase detection and classification diagnostic assays.

| Ambler Class | Carbapenemase | CPO Detection Tests | | | CPO Classification Tests | |
|---|---|---|---|---|---|---|
| | | Rapidec Carba-NP | mCIM | sCIM | O.K.N Detection Kit | mCIM + eCIM |
| ClassA | | | | | | |
| | KPC ($n$ = 59) | 59 | 59 | 58 | 59 | 55 |
| ClassB | | | | | | |
| | NDM ($n$ = 52) | 52 | 52 | 52 | 51 | 52 |
| | IMP ($n$ = 15) | 15 | 15 | 15 | 0 | 12 |
| | VIM ($n$ = 1) | 1 | 1 | 1 | 0 | 1 |
| | SIM ($n$ = 1) | 1 | 1 | 1 | 0 | 1 |
| ClassD | | | | | | |
| | OXA-23 ($n$ = 5) | 5 | / | 1 | 0 | / |
| | OXA-58 ($n$ = 1) | 1 | / | 1 | 0 | / |
| | OXA-48-like ($n$ = 16) | 5 | 13 | 16 | 16 | 12 |
| Dual enzymes | | | | | | |
| Class A + B | KPC + NDM ($n$ = 4) | 4 | 4 | 4 | 4 | 4 |
| | KPC + IMP ($n$ = 2) | 0 | 2 | 2 | 2 | 2 |
| Class B + B | NDM + IMP ($n$ = 5) | 5 | 5 | 5 | 5 | 5 |
| non-CPO | ($n$ = 39) | 0 | 1 | 2 | 0 | 1 |

In this study, OXA-23 and OXA-58 were not detected as well as 1 strain with NDM variant (unknown variant).

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**PMPF Study 2023 – Cesena (Italy)**

This external evaluation was conducted at the Maurizio Bufalini Hospital, Cesena, Italy.

Samples prospectively collected between September and October 2023 were tested with KarbaDia rapid test and reference method (genetic analysis).

The results of the test were recorded and are available in the table below.

A total of 25 samples were used to evaluate the kit.

| N. | Sample ID | Born Date | Collection Date | Carba - Genetic | Tested Date | KarbaDiag RDT |
|---|---|---|---|---|---|---|
| 1 | 4074470501 | 20.11.33 | 01.10.23 | KPC | 06.10.23 | KPC |
| 2 | 3741189201 | 25.12.33 | 29.09.23 | KPC | 06.10.23 | KPC |
| 3 | 3741337101 | 26.01.63 | 03.10.23 | VIM | 06.10.23 | VIM |
| 4 | 3741346806 | 02.11.67 | 03.10.23 | OXA-48 | 06.10.23 | OXA-48 |
| 5 | 4074853904 | 15.05.38 | 04.10.23 | KPC | 09.10.23 | KPC |
| 6 | 4074678301 | 20.10.29 | 03.10.23 | KPC | 09.10.23 | KPC (weak pos NDM & OXA-48) |
| 7 | 4075299901 | 03.07.16 | 14.04.23 | KPC | 13.10.23 | KPC |
| 8 | 4070681704 | 24.06.58 | 23.08.23 | NDM | 13.10.23 | NDM |
| 9 | 4071467501 | 26.10.30 | 31.08.23 | NDM | 13.10.23 | NDM |
| 10 | 1848316801 | 04.03.31 | 03.09.23 | NDM | 13.10.23 | NDM |
| 11 | 4071655801 | 08.12.67 | 02.09.23 | NDM | 13.10.23 | NDM |
| 12 | 3739333001 | 12.01.67 | 06.09.23 | NDM | 13.10.23 | NDM |
| 13 | 4071940101 | 09.01.54 | 05.09.23 | OXA-48 | 13.10.23 | NDM e OXA-48 |
| 14 | 3740726901 | 09.03.45 | 24.09.23 | OXA-48 | 13.10.23 | OXA-48 |
| 15 | 4071940101 | 09.03.45 | 24.09.23 | OXA-48 | 13.10.23 | OXA-48 (weak pos NDM) |
| 16 | 3737742901 | 17.09.45 | 10.07.23 | OXA-48 | 13.10.23 | OXA-48 |
| 17 | 4074275601 | 07.09.71 | 29.09.23 | VIM | 13.10.23 | VIM |
| 18 | 3236408206 | 08.09.71 | 30.09.23 | VIM | 13.10.23 | VIM |
| 19 | 4074763002 | 05.01.48 | 04.10.23 | KPC + OXA-48 | 13.10.23 | VIM e OXA-48 e KPC |
| 20 | 4074348803 | 08.05.23 | 29.09.23 | VIM | 13.10.23 | VIM |
| 21 | 3740776801 | 26.08.60 | 25.09.23 | VIM | 13.10.23 | VIM |
| 22 | 3739877101 | 07.01.31 | 14.09.23 | NDM + KPC | 13.10.23 | NDM |
| 23 | 3736923702 | 09.02.31 | 09.08.23 | NDM + KPC | 13.10.23 | NDM |
| 24 | 3742078801 | 23.09.66 | 12.10.23 | KPC | 19.10.23 | KPC |
| 25 | 4076178001 | 16.04.43 | 18.10.23 | NDM | 19.10.23 | NDM |

Overall good agreement between Rapid test KarbaDia and reference methods. Samples 6 was also detected positive for NDM and OXA-48. Samples13 and 15 were also detected positive for NDM. Sample 19 was also positive for VIM. Samples 22 and 23 were only positive for NDM and not KPC.

The kit is Easy-to-use and contains test tubes ready for use for sample inoculation.

| **Metrological traceability** | |
|---|---|
| Metrological traceability of assigned values | N/A |
| **Users** | |
| User Profile | The tests can be performed in laboratories by health care workers or laboratory technicians with appropriate training in sample collection, biosafety and in the use of rapid tests. |
| User Training | Appropriate training in sample collection, biosafety and in the use of rapid tests. |
| **Device Risks Information** | |
| Residual risks and undesirable effects | - Contamination of the user by infected samples |

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| | - Wrong interpretation of the test results<br>- False negative |
| Warnings and precautions | 1. Read the instruction for use carefully before using the test.<br>2. Clearly identify the sample ID on the test cassettes.<br>3. This product is for in vitro diagnostic and professional use only.<br>4. Do not reuse the test<br>5. Do not use the test after expiry date<br>6. Read the test results within the specific time to avoid wrong interpretation.<br>7. Do not use the components from different batches or different types of reagents.<br>8. Properly dispose the specimen and used materials following the local biohazardous disposal regulation.<br>9. Use protective equipment when using the test and handling samples as they may contain infectious agents, human or animal components.<br>10. Sodium azide is used as preservative in the sample treatment solution. Dispose material according to relevant local regulations and avoid contact with eyes and skin.<br>11. Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established. |