DaraEx*plus*

These instructions for use are valid for all current batches of DaraEx*plus*.

Version 10.1_EN_CE, 2024-07-02

Σ	Up to 30 tests per sales unit (300 µl)
2°C 8°C	Store at 2...8°C

Important Notice! Any serious incident that has occurred in connection with this IVD shall be reported to the manufacturer and to the competent authority of the member state in which the user and/or the patient are established.

1. Introduction

1.1. Overview

These instructions for use describe the use of imusyn's

anti-CD38 antibody neutralizing agent (DaraEx*plus*)

to inhibit the agglutination effect of the anti-CD38 antibodies daratumumab, isatuximab, and felzartamab in the indirect anti-human globulin test (IAT).

Anti-CD38 antibodies interfere with the crossmatch, the antibody search, and the antibody identification in the IAT, resulting in false positive reactions. This interference can occur up to 6 months after the last administration of the drug[1].

1.2. Test Principle

DaraEx*plus* masks CD38 on the surface of red blood cells, thereby preventing the anti-CD38 antibodies daratumumab, isatuximab, and felzartamab from binding and inducing agglutination.

1.3. Intended Purpose

DaraEx*plus* is a diagnostic aid for eliminating the interference of therapeutic anti-CD38 antibodies (daratumumab, isatuximab, and felzartamab) in the determination of irregular antibodies in the IAT. DaraEx*plus* is intended for manual use with gel card systems. DaraEx*plus* is to be used by qualified personnel only in accordance with current local guidelines and is not intended for use by or on patients. DaraEx*plus* does not provide qualitative, semi-quantitative, or quantitative information about anti-CD38 antibodies in the patient specimen.

2. Materials and Equipment

2.1. Components

DaraEx*plus* DaraEx*plus* Fab fragment of an anti-CD38 antibody, 300 µl total volume per sales unit, protein concentration ≥ 5 mg/ml, conserved with 0.1% ProClin® 300

WARNING! May cause an allergic skin reaction (H317). Harmful to aquatic life with long lasting effects (H412). Wear protective gloves (P280). If skin irritation or rash occurs: Get medical advice/attention (P333+P313). Dispose of contents/container in accordance with local/regional/national/international regulations (P501).

Safety data sheet (SDS) available on imusyn.de/IFU.

2.2. Storage, Expiry Date, and Disposal

Store at 2…8°C. If the storage conditions are met, DaraEx*plus* can be used until the expiration date given on the label and the certificate of analysis. DaraEx*plus* and its containers must be disposed of properly according to local guidelines.

⚠ Do not freeze DaraEx*plus*! The reactivity of frozen or frozen and thawed DaraEx*plus* cannot be guaranteed. The according container has to be disposed of immediately!

2.3. Materials and Equipment Supplied by the User

Materials and Equipment	Supplier
- ID-Card LISS/Coombs - Test cell preparations for the ID System	Bio-Rad
- MTS™ Anti-IgG Card - Test cell preparations for the MTS System	Ortho Clinical Diagnostics
- Process control PC e.g. Dara-PC, or 0.5 mg/ml daratumumab in NaCl, or a known and otherwise non-reactive daratumumab-containing specimen	Not applicable / imusyn
If applicable - Reaction vessels, PP	Multiple suppliers
If applicable - NaCl	Multiple suppliers
- Centrifuge for gel cards or work station, matching the gel card system used	Bio-Rad / Ortho Clinical Diagnostics
- Incubator, 37°C	Multiple suppliers
- Pipettes and pipette tips	Multiple suppliers
- Tabletop centrifuge	Multiple suppliers

Note: All materials and devices indicated with a specific manufacturer have been validated for use with DaraEx*plus*.

3. Preparation and Usage

During all activities, care must be taken to avoid contaminations. The reagents used must be brought to room temperature before use.

DaraEx*plus* is a clear and colorless solution. Do not use DaraEx*plus* if its color has changed or if the solution is clouded!

⚠ Only use DaraEx*plus* in undamaged primary packaging! Damaged DaraEx*plus* containers must be disposed of.

3.1. Specimen Preparation

Do not use haemolytic or lipemic serum or plasma specimens. Plasma may be collected using the anticoagulants CPD-A, citrate, or EDTA. Particles, aggregates, or residual fibrin must be removed prior to testing to avoid non-specific results. Prepare and store red blood cells and serum or plasma specimens according to the manufacturers' instructions or local policies and/or national guidelines. The gel card manufacturer's restrictions on specimen material must also be observed.

⚠ Human specimens are potentially infectious. The specimens must be handled according to local guidelines and the appropriate protective measures must be taken.

3.2. Express Protocol

Use this protocol for 0.8% red blood cell preparations (e.g. test cell panels or preparations prepared from a red blood cell concentrate).

3.2.1. Test Cell Treatment

To 1 volume of red blood cells (0.8%), add 0.2 volumes of DaraEx*plus*, e.g. to 50 µl of cells add 10 µl of DaraEx*plus*. The cells can be used immediately; the addition can be done directly in the gel card or in a separate reaction vessel.

⚠ The test cell concentration is critical! Cells that are concentrated above 0.8% need higher volumes of DaraEx*plus* (see section 3.3)!

3.2.2. Test Procedure

Use the DaraEx*plus*-treated cells in the IAT system according to the manufacturer's instructions for use.

In addition to the specimens, a process control PC should be included. If a cell is still agglutinated by a specimen after DaraEx*plus* treatment, it is mandatory to test the affected cell with the PC or to repeat the test with the specimen in the alternative protocol (section 3.3). Use the PC like a specimen. The test with the PC is successful if no agglutination with DaraEx*plus*-treated cells occurs.

⚠ The sequence of pipetting is a critical factor! The treatment of the cells with DaraEx*plus* (section 3.2.1) must take place before addition of the specimen or PC to the IAT (section 3.2.2)!

3.3. Alternative Protocol

Use this protocol directly or if the express protocol did not provide satisfactory results. It is only applicable with 1.6% red blood cell preparations.

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3.3.1. Test Cell Preparation

Prepare 1.6% red blood cells according to local instructions for the preparation of red blood cells. For example, centrifuge 50 µl of 0.8% red blood cells for 5 min at 1,000xg and remove 25 µl of the supernatant. The resuspended cells have a concentration of 1.6%.

3.3.2. Test Cell Treatment

To 1 volume of red blood cells (1.6%), add the same volume of DaraEx*plus* (final cell concentration 0.8%), e.g. to 25 µl cells add 25 µl of DaraEx*plus*. The cells can be used immediately; the addition can be done directly in the gel card or in a separate reaction vessel.

3.3.3. Test Procedure

Use the DaraEx*plus*-treated cells in the IAT system according to the manufacturer's instructions for use.

In addition to the specimens, a process control PC should be included. If a cell is still agglutinated by a specimen after DaraEx*plus* treatment, it is mandatory to test the affected cell with the PC. Use the PC like a specimen. The test with the PC is successful if no agglutination with DaraEx*plus*-treated cells occurs.

⚠ The sequence of pipetting is a critical factor! The treatment of the cells with DaraEx*plus* (section 3.3.2) must take place before addition of the specimen or PC in the IAT (section 3.3.3)!

4. Analysis and Troubleshooting

4.1. Analysis

Treatment of the test cells with DaraEx*plus* should in most cases completely inhibit the agglutination caused by anti-CD38 antibodies. The IAT can be evaluated as if no anti-CD38 antibody was present in the specimen.

DaraEx*plus*-treated cells should not react with PC. If the cells agglutinate with both the PC and the specimen, the test result is invalid and cannot be used.

4.2. Troubleshooting

Problem	Possible cause	Solution
DaraEx*plus*-treated cells are agglutinated by the specimen, but not by the PC.	Incomplete inhibition of agglutination mediated by therapeutic anti-CD38 antibodies.	If the procedure was performed according to section 3.2, adjust the cell concentration to 1.6% and repeat the test according to section 3.3.
	Irregular antibodies in the specimen.	Evaluate the IAT as if no anti-CD38 antibody was present in the specimen (section 4.1).
	Anti-CD38 antibody concentration in the specimen is too high.	See section 5.1 Limitations.
DaraEx*plus*-treated cells are agglutinated by both the PC and the specimen.	Wrong sequence of pipetting (addition of DaraEx*plus* after or together with the addition of PC or specimen to cells).	Ensure that the PC and specimen are added after the treatment of the cells with DaraEx*plus*.
	Incomplete inhibition of agglutination mediated by therapeutic anti-CD38 antibodies.	Ensure that the procedure has been followed according to instructions and repeat the test if necessary.
		If the procedure was performed according to section 3.2, adjust the cell concentration to 1.6% and repeat the test according to section 3.3.
	CD38 expression on the cells used is too high.	If possible, repeat the test using other test cells.

Please also observe the instructions of the gel card manufacturer on error handling and the limits of the procedure! For technical support, you may also contact the manufacturer (contact see below).

5. Limitations and Specific Characterization

5.1. Limitations

DaraEx*plus* was tested with the standard volumes in the indicated gel card systems. The use of volumes other than those specified in the gel card manufacturers' instructions for use, especially the use of higher specimen volumes, may lead to incomplete inhibition of anti-CD38 antibody interference. The use of gel card systems or IAT methods other than those listed in section 2.3 may cause false results and must thus be validated by the user beforehand.

Specimens from patients with high levels of free anti-CD38 antibody, e.g. patients recently treated with therapeutic anti-CD38 antibodies, or cells with high CD38 expression may not be fully inhibited.

DaraEx*plus* has only been validated with respect to inhibition of agglutination by anti-CD38 antibodies listed in section 1.1. Inhibition of other antibodies, including other anti-CD38 antibodies, by DaraEx*plus* has not been tested.

Failure to follow these instructions for use may lead to false results. In particular, the use of more cells or cells of a higher concentration may cause incomplete inhibition of anti-CD38 interference. Prolonged incubation of cells with DaraEx*plus*, e.g. by storing treated cells, may also lead to false results.

The treatment of the test cells according to section 3.2 leads to a slight dilution of the specimen in the test system (usually about 12%). It cannot be excluded that this may result in a reduction of the reaction strength of low-titer antibodies.

Treatment of test cells with DaraEx*plus* may lead to a specific enhancement of agglutination by anti-M or anti-N antibodies by up to one reaction strength.

Contamination of reagents or specimens, use of reagents beyond their expiration date, and use of non-recommended reagents and equipment may cause false results.

5.2. Interfering Substances

The preservative ProClin® 300 contained in the storage buffer of DaraEx*plus* was found not to interfere with the reactions in the IAT.

5.3. Specific Characterization

Clinical performance data show better performance (complete elimination of daratumumab-mediated interference) of DaraEx*plus* than DTT treatment (as described[2]).

Treatment	Performance	$n_{inhibited}$ / n_{total}
DaraEx*plus*	86.5%*	128 / 148
DTT	68.2%	101 / 148

* For performance evaluation, the tests were first performed according to section 3.2 (express protocol). If inhibition was incomplete (62), the test was repeated according to section 3.3 (alternative protocol). For performance evaluation, tests were counted in which either the express protocol (86/148) or the repetition of the test in the alternative protocol (42/62) completely abolished the anti-CD38 antibody-mediated interference.

6. References

1. Oostendorp M, Lammerts van Bueren JJ, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion. 2015;55(6 Pt 2):1555-1562.
2. Empfehlung zum Vorgehen bei Störungen der serologischen Diagnostik durch Daratumumab und andere therapeutische monoklonale Antikörper gegen CD38, Version 2 vom 01.07.2019, Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI), Sektion V: Immunhämatologie und Immungenetik.

7. International Contacts

Switzerland	CH REP	Best Care Consulting GmbH Kehlhofrain 12a CH-6043 Adligenswil ar@ch-rep.com
United Kingdom	UKRP	Sussex Biologicals Ltd Unit H7/H8 Swallow Enterprise Park, Lower Dicker, East Sussex, BN27 4EL +44 1323 849944 info@sussexbiologicals.co.uk

8. Definition of Symbols and Abbreviations

NaCl	0.9% sodium chloride solution

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LOT	Batch code
REF	Catalogue number
⚠	Caution
📖	Consult instructions for use
DaraEx*plus*	DaraEx*plus*
⌛	Use by date (YYYY-MM)
◇!	Exclamation mark (GHS07) – Warning
IVD	*In vitro* diagnostic medical device (IVD)
🏭	Manufacturer
Σ	Contains sufficient for <n> tests

PC	Process control (see also section 2.3)
🌡	Temperature limit
CH REP	Swiss authorised representative
UKRP	UK Responsible Person

Patent EP3548898B1.

⚠ Please check imusyn.de/IFU regularly for updates to these instructions for use.

Changes to the previous version are highlighted.

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