Truenat®

EBV

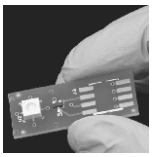
Chip-based Real Time PCR Test for Epstein-Barr Virus

1. INTENDED USE

Truenat® EBV (REF 601600005 / 601600020 / 601600025 / 601600050 / 601600100 / 601600200) an automated point-of-care or near patient Chip-based Real Time Polymerase Chain Reaction (PCR) test for the quantitative detection of Epstein-Barr virus in human blood/serum/plasma and CSF specimens and aids in diagnosis of EBV infection. **Truenat® EBV** runs on the **Truelab®** Real Time Quantitative micro PCR Analyzers. **Truenat® EBV** is a single use *in vitro* diagnostics test meant for professional use in near-patient, laboratory or any healthcare settings, by healthcare professionals or any user appropriately trained by a representative of Molbio Diagnostics.

2. INTRODUCTION

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. EBV is a large dsDNA virus and is the most common human virus that infects people of all ages. EBV causes infectious mononucleosis, also called mono or kissing disease, and is associated with a variety of other illnesses including several types of cancer. Symptoms of EBV infection can include fatigue, fever and inflamed throat, swollen lymph nodes in the neck, enlarged spleen, swollen liver and rash. EBV infections in children usually do not cause symptoms, or the symptoms are not distinguishable from other mild, brief childhood illnesses. People, who get symptoms from EBV infection, usually teenagers or adults, get better in two to four weeks. However, some people may feel fatigued for several weeks or even months. Once a person gets an EBV infection, the virus becomes latent (inactive) in the body. In some cases, the virus may reactivate. This does not always cause symptoms, but people with weakened immune systems are more likely to develop symptoms if EBV reactivates. EBV spreads most commonly through bodily fluids, especially saliva. However, EBV can also spread through blood and semen during sexual contact, blood transfusions, and organ transplantations. Serum testing for EBV antibodies such as the indirect fluorescent antibody (IFA)test and nucleic acid amplification tests such as PCR are the commonly used diagnostic tests with real time PCR being more sensitive and specific. Viral Load analysis for EBV through Real Time polymerase chain reaction is the best tool to measure viral load. However, nucleic acid based molecular tests such as real time PCR have so far been restricted to centralized reference laboratories as they require skilled manpower and elaborate infrastructure. Also, the turnaround time for results could take a few days to weeks leading to high losses to follow-up.



The **Truelab®** Real Time micro PCR System enables decentralization and near patient diagnosis and treatment monitoring of EBV infection by making real time PCR technology rapid, simple, robust and user friendly and offering "sample to result" capability even at resource limited settings. This is achieved through a combination of lightweight, portable, mains / battery operated **Truelab®** Real Time micro PCR Analyzer and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and room temperature stable **Truenat®** micro PCR chips and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kits so that even the peripheral laboratories with minimal infrastructure and minimally trained technician can easily perform these tests routinely in their facilities and report PCR results in less than an hour. Moreover, with these devices PCR testing can also be initiated in the field level, on site.

Truenat® EBV is a disposable, room temperature stable, chip-based Real Time PCR test with dried $MgCl_2$ in reaction well and freeze dried PCR reagents in microtube for performing Real Time PCR test for detection and diagnosis of Epstein-Barr virus (EBV) and runs on the **Truelab®** Real Time micro PCR Analyzer. It requires only six (6) µL of purified DNA to be added to the reaction well for the analysis. The intelligent chip also carries test and batch related information including standard values for quantitation. The **Truenat® EBV** chip also stores information of used test to prevent any accidental re-use of the test.

NOTE: Truelab® / Truenat® / Trueprep® / Truepet® are all trademarks of Molbio Diagnostics Private Limited.

The Truelab® Real Time micro PCR Analyzer is protected by the following patents and patents granted: IN 2313/CHE/2007 (Patent No. 281573), WO2009/047804 and corresponding claims of any foreign counterpart(s) thereof.

The Truenat® micro PCR chip is protected by the following patents and patents pending: IN 2312/CHE/2007, WO 2009/047805 and corresponding claims of any foreign counterpart(s) thereof.

3. PRINCIPLE OF THE TEST

Truenat® EBV works on the principle of Real Time Polymerase Chain Reaction based on Taqman chemistry. The DNA from the patient sample is first extracted using **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit. The **Truenat® EBV** chip is placed on the chip tray of the **Truelab®** Real Time micro PCR Analyzer. Six (6) µL of the purified DNA is then dispensed using the provided micropipette and tip into the microtube containing freeze dried PCR reagents and allowed to stand for 30-60 seconds to get a clear solution. ⚠ No mixing by tapping, shaking or by reverse pipetting should be done. Six (6) µL of this clear solution is then pipetted out using the same pipette and tip and dispensed into the reaction well of the **Truenat® EBV** chip and the test is started. A positive amplification causes the dual labeled fluorescent probe in the **Truenat® EBV** chip to release the fluorophores in an exponential manner which is then captured by the built-in opto-electronic sensor and displayed as amplification curve on the analyzer screen, on a real time basis during the test run. The Cycle threshold (Ct) is defined as the number of amplification cycles required for the fluorescent signal to cross the threshold (i.e. exceed the background signal). Ct levels are inversely proportional to the amount of target nucleic acid in the sample. (i.e. the lower the Ct level the greater is the amount of target nucleic acid in the sample). In the case of negative samples, amplification does not occur and a horizontal amplification curve is displayed on the screen during the test run. At the end of the test run, EBV "DETECTED" or "NOT DETECTED" result is displayed and in positive cases, Ct values and viral loads in copies per milliliter (copies/mL) is also displayed on the screen. Based on the detection of the internal positive control (IPC), the validity of the test run is also displayed. The IPC is a full process control that undergoes all the processes the specimen undergoes - from extraction to amplification thereby validating the test run from sample to result. Absence of or shift of IPC Ct beyond a pre-set range in case of negative samples invalidates the test run. While IPC will co-amplify in most positive cases also, in some specimen having a high target load, the IPC may not amplify, however the test run is still considered valid. The results can be printed using the **Truelab®** micro PCR printer or transferred to the lab computer/or any remote computer via Wifi network or 3G/GPRS network. Upto 20000 results in **Truelab® Uno Dx/Duo/Quattro** can be stored on the analyzer for future recall and reference.

4. TARGET SELECTION

The gene target sequence for the assay is LMP2 gene of Epstein-Barr virus genome.

5. CONTENTS OF THE Truenat® EBV KIT

A. Individually sealed pouches
B. Package Insert

Each individually sealed pouch contains:

1. **Truenat® EBV** micro PCR chip (1 Nos.)
2. Microtube with freeze dried PCR reagents (1 Nos.)
3. DNase & RNase free pipette tip (1 Nos.)
4. Desiccant pouch (1 Nos.)

REF	601600005	601600020	601600025	601600050	601600100	601600200
Σ	5T	20T	25T	50T	100T	200T

6. CONTENTS OF THE Trueprep® AUTO Universal Sample Pre-treatment Pack

A. Lysis buffer
B. Disposable transfer pipette (graduated)
C. Package Insert

REF	60205AB05	60205AB20	60205AB25	60205AB50	60205AB100	60205AB200
Σ	5T	20T	25T	50T	100T	200T

7. STORAGE AND STABILITY

Truenat® EBV is stable for two (2) years from the date of manufacture if stored between 2-30°C. It is also stable for one (1) month at temperatures up to 45°C. Avoid exposure to light or elevated temperatures (above recommended levels). Do not freeze.

Trueprep® AUTO Universal Sample Pre-treatment Pack is stable for two (2) years from the date of manufacture if stored between 2-40°C. It is also stable for one (1) month at temperatures upto 45°C. Do not freeze.

8. MATERIALS REQUIRED BUT NOT PROVIDED WITH THE KIT

Truelab® Real Time micro PCR Workstation (REF623010001 / 633010001/ 643010001 / 653010001) consisting of,

1. **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device (REF 603041001 / 603042001)
2. **Truelab® Uno Dx / Truelab® Duo / Truelab® Quattro** Real Time micro PCR Analyzer (REF 603021001 / 603022001 / 603023001).
3. **Truelab®** micro PCR Printer (REF 603050001).
4. **Truepet®** SPA fixed volume precision micropipette - 6 µl (REF 604070006).
5. **Truelab®** Microtube Stand (REF 603070001).

Also required additionally are: **Trueprep® AUTO** Universal Sample Pre-treatment Pack (REF 60205AB05 / 60205AB20 / 60205AB25 / 60205AB50 / 60205AB100 / 60205AB200), **Trueprep® AUTO** Universal Cartridge Based Sample Prep Kit (REF 60203AR05 / 60203AR25 / 60203AR50 / 60203AR100 / 60203AR200) or **Trueprep® AUTO v2** Universal Cartridge Based Sample Prep Kit (REF 60207AR05 / 60207AR25 / 60207AR50 / 60207AR100 / 60207AR200), Powder free disposable gloves, waste disposal container with lid.

9. SPECIMEN PREPARATION FOR EXTRACTION WITH Trueprep® AUTO/AUTO v2

Truenat EBV® requires purified nucleic acids from whole blood, plasma, serum and CSF. Whole blood or plasma should be collected in EDTA anticoagulant. The respective specimen is extracted using the **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit. Sample must be pre-treated using **Trueprep® AUTO** Universal Sample Pre-treatment Pack. Transfer 250 µl of whole blood or 500 µl of plasma/serum/CSF specimen using the transfer pipette provided into the lysis buffer tube provided and mix well. Use the entire content of lysis buffer tube containing the specimen for further procedure with the **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit (Refer to the User Manual of **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and the package insert of **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit for details).

Sample Storage and Transportation:

Sample pre-treatment decontaminates the specimen and makes it ready for storage / transportation / extraction. The specimen in this form is stable for up to 3 days at 40ºC and 1 week at 30ºC.

Nucleic acid extraction: Use entire content from the lysis Buffer tube containing specimen for further procedure with the **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit. (Refer to the User Manual of **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Device and the package insert of **Trueprep® AUTO/AUTO v2** Universal Cartridge Based Sample Prep Kit for details). ⚠ Dispose off lysis buffer tube and transfer pipette after use, as per the section on "Disposal and Destruction" (Section 17).

10. SAFETY PRECAUTIONS

1. For *in vitro* diagnostic use only.
2. Bring all reagents and specimen to room temperature (20-30°C) before use.
3. Do not use kit beyond expiry date.
4. Carefully read the User Manuals, package inserts and Material Safety Data Sheets (MSDS) of all the components of the **Truelab® Real Time micro PCR System** before use.
5. All materials of human origin should be handled as though potentially infectious.
6. Do not pipette any material by mouth.
7. Do not eat, drink, smoke, apply cosmetics or handle contact lenses in the area where testing is done.
8. Use protective clothing and wear disposable gloves when handling samples and while performing sample extraction.

11. PROCEDURAL PRECAUTIONS

1. Check all packages before using the kit. Damage to the packaging does not prevent the contents of the kit from being used. However, if the outer packaging is damaged the user must confirm that individual components of the kit are intact before using them.
2. Do not perform the test in the presence of reactive vapours (e.g., from sodium hypochlorite, acids, alkalis or aldehydes) or dust.
3. While retrieving the **Truenat® EBV** micro PCR chip, microtube and the DNase & RNase free pipette tip from the pouch, ensure that neither bare hands nor gloves that have been used for previous tests run are used.
4. Ensure that the colour of the desiccant pouch is orange after opening a sealed **Truenat®** chip pouch. If the colour of the desiccant pouch changes from orange to white due to the absorption of moisture, do not use the contents of the **Truenat®** chip pouch.

12. PROCEDURAL LIMITATIONS

1. Optimal performance of this test requires appropriate specimen collection, handling, storage and transport to the test site.
2. Though very rare, mutations within the highly conserved regions of the target genome where the **Truenat®** assay primers and/or probe bind may result in the under-quantitation of or a failure to detect the presence of the concerned pathogen.
3. The instruments and assay procedures are designed to minimize the risk of contamination by PCR amplification products. However, it is essential to follow good laboratory practices and ensure careful adherence the procedures specified in this package insert for avoiding nucleic acid contamination from previous amplifications, positive controls, or specimens.
4. A specimen for which the **Truenat®** assay reports "Not Detected" cannot be concluded to be negative for the concerned pathogen. As with any diagnostic test, results from the **Truenat®** assay should be interpreted in the context of other clinical and laboratory findings.

13. CLEANING AND DECONTAMINATION

1. Spills of potentially infectious material should be cleaned up immediately with absorbent paper tissue and the contaminated area should be decontaminated with disinfectants such as 0.5% freshly prepared sodium hypochlorite [10 times dilution of 5% sodium hypochlorite (household bleach) before continuing work].
2. Sodium hypochlorite should not be used on an acid-containing spill unless the spill-area is wiped dry first. Materials used to clean spills, including gloves, should be disposed off as potentially bio-hazardous waste e.g. in a biohazard waste container.

14. TEST PROCEDURE

(Please also refer the **Truelab®** Real Time micro PCR Analyzer user manual)

1. Switch on the **Truelab®** analyzer .
2. Select Username and enter password.
3. For **Truelab® Uno Dx**, select the test profile for "EBV" to be run from the Profiles Screen on the analyzer screen. For **Truelab® Duo/Quattro**, select the Bay (I/II) for **Duo** and (I/II/III/IV) for **Quattro** from the Status Screen to view the Profiles Screen. Select the test profile for "EBV" to be run from the Profiles Screen, on the analyzer screen.
4. Enter the patient details as prompted in the **Truelab®** analyzer screen.
5. Press Start Test.
6. For **Truelab® Uno Dx,** Press the eject button to open the chip tray. For **Truelab® Duo/Quattro**, the chip tray opens automatically on tapping the "Start Test" button.
7. Open a pouch of **Truenat® EBV** and retrieve the micro PCR chip, microtube and DNase & RNase free pipette tip. Do not open the pouch until ready to test.
8. Place the **Truenat® EBV** chip on the chip tray without touching the white reaction well. The reaction well should be facing up and away from the analyzer. Gently place the chip on the chip tray by aligning it in the slot provided.
9. Place the microtube containing freeze dried PCR reagents in the microtube stand provided along with the **Truelab®** Real Time micro PCR workstation after ensuring that white pellet of freeze dried PCR reagents remains at the bottom of the microtube. Remove the microtube cap and dispose it off as per the section on "Disposal and Destruction" (Section 17). Using the filter barrier tip provided in the pouch, pipette out six (6) µL of the purified DNA from the Elute Collection Tube into the microtube. Allow it to stand for 30-60 seconds (in-use time) to get a clear solution. ⚠ Do not mix it by tapping, shaking or by reverse pipetting. Using the same filter barrier tip, pipette out six (6) µL of this clear solution and dispense into the centre of the white reaction well of the **Truenat® EBV** chip. Take care not to scratch the internal well surface and not to spill elute on the outside of the well. Dispose off the microtip as per the section on "Disposal and Destruction" (Section 17).
10. For **Truelab® Uno Dx**, slide the chip tray containing the **Truenat® EBV** Chip-based Real Time PCR test loaded with the sample into the **Truelab®** analyzer. Press "YES" on the "Please Load Sample" prompt. For **Truelab® Duo/Quattro**, select "YES" at the "Please Load Sample" prompt. Chip tray will close automatically and the reaction will start. ⚠ Make sure to start the test promptly after 30-60 seconds of adding the elute to the microtube.
11. Read the result from the screen.
12. After the reaction is completed, for **Truelab® Uno Dx,** push the Eject button to eject the chip tray. For **Truelab® Duo/Quattro**, tap the "Open/Close Tray" button to eject the chip tray.
13. Take out the **Truenat® EBV** micro PCR chip at end of the test and dispose it off as per the section on "Disposal and Destruction" (Section 17).
14. Turn on **Truelab®** micro PCR printer and select print on the screen for printing out hard copy of the results. Test results are automatically stored and can be retrieved any time later. (Refer to **Truelab®** Analyzer manual).
15. Switch off the **Truelab®** Analyzer.

15. RESULTS & INTERPRETATIONS

Two amplification curves are displayed on the **Truelab®** Real Time micro PCR Analyzer screen when optical plot is selected to indicate the progress of the test. Both the target and the internal positive control (IPC) curves will take a steep, exponential path when the fluorescence crosses the threshold value in case of positive samples. The Cycle threshold (Ct) will depend on the number of target nucleic acids in the sample. The target curve will remain horizontal throughout the test duration and the IPC curve will take an exponential path in case of negative samples. In case the IPC curve remains horizontal in a negative sample, the test is considered as Invalid. At the end of the test run, the results screen will display "DETECTED" for Positive result or "NOT DETECTED" for Negative result. The result screen would also display the Ct value and the IU/ml for positive specimen. The result screen also displays the validity of the test run as "VALID" or "INVALID". Invalid samples have to be repeated with fresh specimen from the sample preparation stage. While IPC will co-amplify in most positive cases also, in some specimen having a high target load, the IPC may not amplify, however the test run is still considered valid.

16. QUALITY CONTROL PROCEDURES

To ensure that the **Truelab®** Real Time micro PCR Analyzer is working accurately, run known PCR positive and negative samples from time to time.

17. DISPOSAL AND DESTRUCTION

1. Submerge the used **Truenat® EBV** chip, microtube, microtube cap, transfer pipette, pipette tips, lysis buffer tube etc. in freshly prepared 0.5% sodium hypochlorite solution for 30 minutes before disposal as per the standard medical waste disposal guidelines.
2. Disinfect the solutions and/or solid waste containing biological samples before

discarding them according to local regulations.

3. Samples and reagents of human and animal origin, as well as contaminated materials, disposables, neutralized acids and other waste materials must be discarded according to local regulations after decontamination by immersion in a freshly prepared 0.5% of sodium hypochlorite for 30 minutes (1 volume of 5% Sodium hypochlorite for 10 volumes of water).
4. Do not autoclave materials or solutions containing Sodium hypochlorite.
5. Chemicals should be handled in accordance with Good Laboratory Practice and disposed off according to the local regulations.

19. SPECIFIC PERFORMANCE CHARACTERISTICS

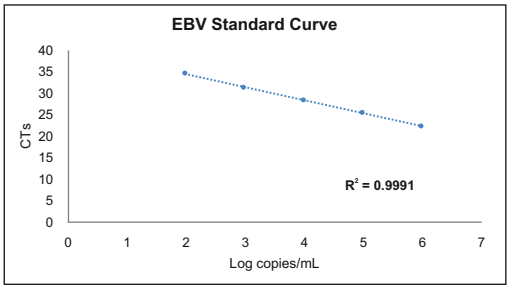
Analytical Exclusitivity (Primer specificity):

The following microorganisms were evaluated *in silico* from the NCBI database using the NCBI nucleotide blast and primer blast tools to determine potential cross-reactivity in the **Truenat® EBV** assay. No interference in the performance of the **Truenat® EBV** assay was observed with the listed group of organisms.

Organisms	Organisms
Human DNA	Vaccinia virus
Herpes Simplex Virus-1	Alphapapillomavirus 7
Herpes Simplex Virus-2	Alphapapillomavirus 9
SARS CoV-2	*E. coli*
Human immunodeficiency virus (1 & 2)	*Staphylococcus epidermidis*
Hepatitis B virus	*Mycobacterium tuberculosis*
Hepatitis C virus	*Mycobacterium gordonae*
Parvovirus	*Neisseria gonorrhoeae*
Adenovirus	*Chlamydia trachomatis*
Cytomegalovirus	*Candida albicans*
Influenza B Virus	*Staphylococcus aureus*
Human herpesvirus 3	*Enterobacter aerogenes*
Human herpesvirus 6	*Klebsiella pneumoniae*
Human herpesvirus 8	

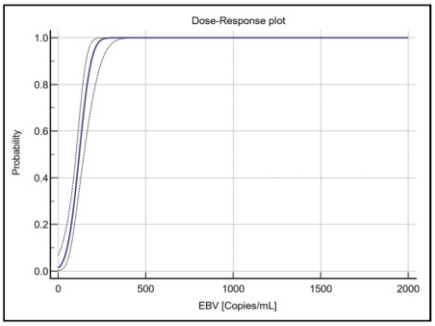
Linearity:

The linearity analysis was performed according to CLSI Guidelines. Serial dilutions of plasmid from 1.0E+06 to 1.0E+02 copies/mL were made and nucleic acids were extracted on **Trueprep® AUTO** Universal Cartridge Based Sample Prep Device in triplicates for each dilution followed by PCR on **Truelab®** Real Time micro PCR Analyzer. The assay is found to be linear over 5 orders of magnitude (from 1.0E+06 to 1.0E+02 copies/mL) for EBV plasmid clone sample.



Limit of detection (LoD):

The LoD was determined by making dilutions of cloned and quantified EBV plasmid sample and performing nucleic acid extractions on **Trueprep® AUTO** Universal Cartridge Based Sample Prep Device for each of the dilution 24 times followed by PCR on **Truelab®** Real Time micro PCR Analyzer. Probit analysis of the data was used to determine the concentration of the DNA with 95% probability of detection. The LoD was found to be 209 copies/mL for cloned and quantified EBV Plasmid sample .



LoD: 209.0 [95% CI: 174.36 - 279.83]

Robustness:

To determine whether the **Truenat® EBV** Chip-based Real Time PCR test showed any signs of carryover of PCR products between runs, alternating runs of positive samples and negatives samples were performed. The number of samples runs was 20 positives and 20 negatives. The **Truenat® EBV** test did not exhibit detectable carryover between positive and negative samples.

Reproducbility:

The purpose of this study is to compare the functional performance of the **Truenat® EBV** assay using three different titres of samples on **Truelab®** Real Time micro PCR Analyzer. High, medium and low titre samples were extracted on **Trueprep® AUTO** Universal Cartridge Based Sample Prep Device and tested among three different users (Inter user), on three different devices (Inter device) and on 5 consecutive days (Inter day) to check the variability. Mean %CV values for all titres has been calculated as Inter User (1.05), Inter day (1.35) and Inter Device (1.49) which were in the accepted range of ≤15% CV for **Truenat® EBV** assay.

Precision:

Precision was determined by performing DNA extractions and **Truenat® EBV** PCR for varying titres of samples over 5 consecutive days. The %CV values obtained for titre 1 (1.25), titre 2 (1.40) and titre 3 (1.91) were within the accepted range of ≤15% CV for **Truenat® EBV** assay.

Clinical validations:

A panel of 35 plasma samples comprising of 20 negative and 15 positive specimens were tested on three different manufacturing lots of **Truenat® EBV** assay at Microbiological Laboratory, Coimbatore against the reference CE marked kit.

		Reference CE marked kit		
		Positive	Negative	Total
Truenat® EBV	Positive	15	0	15
	Negative	0	20	20
	Total	15	20	35

Sensitivity: 100% (95% CI 78.2% to 100%)
Specificity: 100% (95% CI 83.16% to 100%)
Accuracy: 100% (95% CI 90.0% to 100%)

With the consideration of above data, **Truenat® EBV** assay performed consistently in this study with observed sensitivity of 100% and specificity of 100% in comparison with reference CE marked kit and the inter-lot variation data obtained was within the accepted range of ≤15% CV for **Truenat® EBV** assay.

20. REFERENCES

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SYMBOL KEYS

 Consult instruction for use.	 *In vitro* Diagnostic Medical Device. Not for medicinal use.	 Batch number/ Lot number.	 Catalogue number.	 Unique Device Identifier.	 This way up.	 Manufacturer.	 Caution.	 Non sterile.
 Contains sufficient for <n> tests	 Temperature limitations.	 Date of manufacture.	 Date of expiry.	 For single use only.	 Keep dry.	 Keep away from sunlight	 Device for near-patient testing	

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TNEBV/1023/V-01