**WARNING**

**THE ANALYSES MUST BE ONLY AND EXCLUSIVELY PERFORMED ON EX VIVO TISSUE IN NON-STERILE AREA**

**The use of this device requires user training**

## Users and training

The TempoCaps-ENT-Blue device must be handled by trained ENT surgeons. Training is provided to surgeons during initial use.

The device is not intended to be used by physicians of a specialty other than surgery, in particular pathologists.

## Intended Use

The TempoCaps-ENT-Blue is an In Vitro Diagnostic device of the reagent type, used in combination with the TempoTouch® (see User Manual TempoTouch®). It identifies significant relative over- or under-expression of membrane EGFR at the surface of a tissue during surgical excision of head and neck carcinomas. Based on that, it indicates qualitatively to the user if there is a high risk of cancer cells presence. It is used in the operating room by trained surgeons outside the sterile area, only on excised tissue/ex-vivo.

## Function

- Help the surgeons delimit -intraoperative- margins during the resection of epidermoid head and neck carcinomas
- To be clipped at the distal end of the TempoProbe, providing it with the ability to detect EGFR surface marker
- To emit a variable light signal depending on the presence of EGFR, in response to the laser emitted by the TempoTouch®
- To take a reference on healthy or tumorous tissue / To allow the measurement of relative expression levels compared to a reference tissue
- To monitor the surgeon's therapeutic actions during surgical margin assessment to ensure controlled resection

## Benefits

Using this technology should reduce the need for frozen section examination, thereby reducing the duration of the surgery. In case of uncertainty, the surgeon always has the option to perform frozen sections examination with the pathology department.

## Contra indications

In some cases, use of the device is contra-indicated:

- History of treatment with cetuximab or other anti-EGFR monoclonal antibodies
- Lack of EGFR expression by tumor cells previously demonstrated on biopsy
- Do not use in pregnant women or persons under 18 years old.
- The area to be tested was burned using an electric scalpel, laser or other device used during surgery
- Inability to identify with a reasonable degree of confidence an area of healthy or tumoral tissue that can be used as a reference

## Restrictions

- Utilization strictly prohibited in vivo. Do not use directly onto the patient.
- The device is not intended to perform a diagnostic or to replace the final post-operative analysis of the tumor performed by the anatomopathological department

## Residual risk

The user must exercise particular caution when selecting the tissue type to be used as a reference. If the reference does not correspond to the tissue type selected on the TempoTouch®, the results may be inconsistent.

## Analytical Performance

The analytical performance of the TempoCaps biosensor were established in vitro to establish its ability to detect EGFR in solution. The following indicators were obtained :

- C50 value : [EGFR]=3.97nM
- C10 value : [EGFR]=1.64nM
- C90 value : [EGFR]= 8.32nM

This results in the following performance when identifying presence of EGFR at a concentration above 10nM :

| Statistic | Value | 95% CI |
|---|---|---|
| **Sensitivity** | 85.71% | 76.81% to 92.17% |
| **Specificity** | 93.90% | 86.34% to 97.99% |
| **Accuracy** | 89.60% | 84.06% to 93.72% |
| **Positive Likelihood Ratio** | 14.06 | 5.99 to 33.00 |
| **Negative Likelihood Ratio** | 0.15 | 0.09 to 0.25 |

## Clinical Performance

Clinical performances of TempoCaps-ENT-Blue was evaluated during a multicentric non interventional clinical study assessment by measuring the accuracy of EGFR detection for identifying tissue containing tumoral cells:

| | |
|---|---|
| **Sensitivity** | 53% |
| **Specificity** | 60.7% |
| **Positive predictive Value (PPV)** | 21.84% |
| **Negative predictive Value (NPV)** | 86.07% |

Tumoral tissue at the periphery of the resected specimen is suggestive of a positive margin. By allowing identification of such tissues, TempoCaps-ENT-Blue can be used to identify the presence of positive margins and thus potentially prevent them, with the following performance measured during clinical performance study:

| | |
|---|---|
| **Sensitivity (of positive margin detection)** | 74.2% |
| **Specificity (of positive margin detection** | 40% |
| **Positive predictive Value (PPV)** | 52.27% |
| **Negative predictive Value (NPV)** | 63.64% |

## TempoCaps-ENT-Blue technical characteristic

| | |
|---|---|
| **Tumor Marker** | EGFR |
| **Type of device** | Single use |
| **In use stability** | 6 touches |
| **Shelf life** | 159 days |
| **Storage and transport conditions** | keep between +2 to +8°C |
| **Ambient temperature shelf life** (19-26°C) | 1h |

## Storage and stability in use

TempoCaps-ENT-Blue must remain moist throughout their lifetime.

They are packed in HEPES-NaCl to preserve their hydration.

TempoCaps-ENT-Blue have a shelf-life of 22 weeks in the refrigerator at 2°C to 8°C. The capsule must be used in the normal atmospheric conditions of an operating room between 19°C and 26°C.

## Composition of a box

Each box of TempoCaps-ENT-Blue contains 12 non-sterile capsules (4 bags of 3 capsules). Each TempoCaps-ENT-Blue is stored in an individual tube filled with saline buffer (HEPES-NaCl pH=7.4). This solution can be used to rehydrate or rinse the TempoCaps (see Rehydration / rinsing of the TempoCaps-ENT-Blue).

Liquid solution composition:

| Ingredient | Concentration |
|---|---|
| HEPES (CAS 7365-45-9) | 10 mM |
| NaCl ( CAS 7647-14-5) | 150 mM |

## Equipment and Material Required

The capsules TempoCaps-ENT-Blue required the use of Dyameo's IVD Class A instrument TempoTouch® and its accessory, the TempoProbe. TempoTouch® and TempoProbe are not included with the TempoCaps-ENT-Blue but can be bought separately.

## Quality Control

Before use, inspect the packaging and capsules for any visible damage, seal compromise, or changes in external appearance. Do not use the device if any such changes are observed, as this may affect performance and safety. The tube must contain a TempoCaps and an colorless solution sealed with a blue cap, the plastic bag must contain 3 tubes and be sealed.

Once a bag is opened, all capsules must be used within the nex hour. Any remaining capsules must be discarded, as storage after opening may compromise performance.

The TempoTouch® evaluates the performance of each new TempoCaps-ENT-Blue clipped on a TempoProbe by verifying the intensity of the two fluorophores present on the biosensor. If a capsule is not functional, the TempoTouch® will detect it and display a specific error message. If a TempoCaps-ENT-Blue remains unused for 5 minutes, TempoTouch® will

display a message telling you to soak it in a saline solution. After 15 minutes, the TempoTouch® will display a message forcing the user to change the TempoCaps.

## Safety precaution

----------**WARNING** ----------

- Respect use-by date
- Respect storage temperatures
- Do not reuse a capsule that has already been used its maximum number of time
- In case of uncertainty, the surgeon always has the option of performing intraoperative frozen section analysis with the pathology department.
- Do not use a dropped the capsule
- Do not expose the capsule directly under powerful artificial lights
- Do not use the capsule if the heat-sealed bag or the tube is damaged
- Do not use if the capsule is not stored in a liquid before opening
- Remove the capsule from the storage fridge as late as possible (maximum 1 hour before use)
- The device must be operated by a trained surgeon.
- The device must not come into contact with the patient
- No modifications of the device are authorized
- Only use accessories supplied by Dyameo
  - The device must only be used with dyameo's devices
  - The device is not intended to be used in the sterile field of the operating room.
  - Do not place the capsule near a source of heat
  - Do not use the capsule from the same sealed bags on different patients

## Symbols

| | | | |
|---|---|---|---|
| Σ | Sufficient content for « n » trials | | Keep dry |
| | Use-by date | | Keep away from sunlight |
| LOT | Batch code | | Do not use if package is damaged and consult instructions for use |
| | Storage temperature | | Consult the instructions for use |
| | Do not reuse | | Manufacturer |
| IVD | In Vitro Diagnostic Medical Device | NON STERILE | Non sterile device |
| | Near patient testing | CE | CE marking |

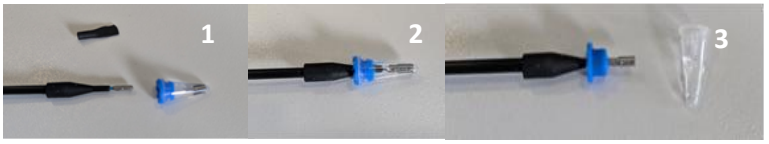
## Preparation for Use

### Specimen preparation

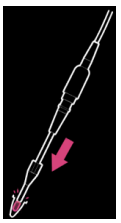
The specimen does not required preparation. If the specimen is soaked with blood or any external contaminant, it is preferable to rinse the specimen with a saline solution or water (not provided by dyameo). The specimen must be at least 2mm wide to be compatible with a TempoCaps-ENT-blue use.

### TempoCaps installation

This procedure is described in detail in the TempoTouch® user manual.
1-Check that the stainless-steel ferrule is clean and free of marks.
2-Pierce the lid containing the capsule with the probe or remove the blue cap and insert the end of the fiber into the capsule until it is clipped into place.
3-Remove the fiber along with the blue cap. OR remove the probe without the cap. In this case, make sure that the TempoCaps-ENT-Blue is still correctly attached to the end of the TempoProbe after passing through the cap.
4-Press the ENTER button
The TempoCaps-ENT-Blue is ready for the performance verification stage.




### TempoCaps-ENT-Blue verification stage



This stage checks the conformity of the capsule. It must be performed away from ambient light to ensure accurate collection of the emitted light signal.
1-Place the end of the probe and the capsule in the dark compartment on the top of the TempoTouch
2-Close the trapdoor and press the TempoTouch® footswitch to initiate the verification

### Rehydration / rinsing of the TempoCaps-ENT-Blue

If not used after 5 minutes (the TempoTouch has a built-in timer), the TempoCaps must be rehydrated with the solution contained in the primary packaging (HEPES NaCl). If the primary packaging (tube with the blue cap) is not accessible, a saline solution can be used instead. The saline solution is not provided by Dyameo. It is recommended to rinse each time after any contact with a tissue, whether with HEPES NaCl or saline solution indistinctly. TempoCaps-ENT-Blue must be changed and throw away after 15 minutes without any use.
The TempoCaps-ENT-Blue can either be rehydrated / rinse with the remaining HEPES NaCl solution still present inside the packaging tube or with a saline solution by simply soak the tip of the TempoCaps-ENT-Blue for at least one second.

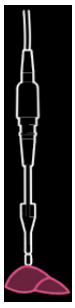
### Reference measurement

To make a comparison between healthy and tumor tissue, the device needs a reference measurement. According to the surgeon's choice and the surgical specimen, this reference measurement must be taken on the explanted specimen either:

- on tissue that has been visually identified as clearly healthy. This tissue must be similar to that in which the tumor developed. This is referred to as a 'HEALTHY' reference.
- on tissue that has been visually identified as clearly tumoral, budding and non-necrotic. This is referred to as 'TUMORAL' reference.

**Note:** *The device must not be used if it is impossible to identify with a reasonable degree of certainty a healthy or tumoral area that can be used as a reference.*

1-Use the left and right navigation keys to select the type of tissue you want to use as reference - HEALTHY' or 'TUMORAL' - and press 'ENTER'.
The device displays a screen so you can double-check the choice you have previously made



2-Position the TempoProbe with the TempoCaps-ENT-Blue on the tissue to be analyzed, keeping it as perpendicular as possible to the tissue
- Hold the probe in place for few seconds (3 seconds is sufficient)
- Press the footswitch to start a measurement
- While the measurement is being captured:
- The red light under the 'laser' logo is illuminated
- An audible signal is also emitted
- The display indicates a measurement in progress
- Hold the probe still on the tissue and keep the footswitch pressed until the sound of the buzzer stops

3-Once the reference measurement is complete, press the 'ENTER' button to save the reference measurement

- If the measurement is invalid (if the probe has been moved during the measurement, or if the surgeon identify afterward a more representative area of healthy or tumoral tissue usable as reference), press 'BACK' and repeat the reference measurement as described above.

- Each reference performed decreases the number of possible future measurements with the same capsule.

### Taking measurements

**Note:** *The analysis can be carried out either directly on the main resected tumoral specimen or on additionally sampled tissue (i.e. recut or biopsy sample)*

#### Processing and Interpretation of Results

During a measurement, TempoCaps emits a fluorescence signal from its biosensor in response to laser excitation, which is recorded as an optical spectrum that allow for evaluation of marker presence. This results is normalized to the reference to assess the amplitude of variation, which is then evaluated relative to a threshold to provide a qualitative result. The TempoTouch® additionally converts this fold change into a numerical score for display. Please note that only the qualitative result should guide surgical decisions. The score is only indicative of EGFR under/over expression level, any value under or above the threshold should be considered negative or positive, respectively.

#### Tissue measurement

Once the capsule has been checked and the reference measurement taken, the surgeon can proceed with the analysis of the explanted tissue

1-Place the probe in contact with the tissue you intend to analyze, in the same way as for the reference sample

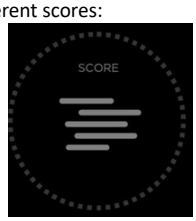
2-Start the measurement by pressing the footswitch until the end of the acoustic signal

#### Display of results

3 levels of results are possible:

- **0-25 :** The tissue is considered healthy (low level of EGFR)
  If the reference has been taken on a healthy tissue, when a score **below 5** is displayed, a warning concerning the nature of the reference is also displayed. The user can change the capsule to take another reference, or the user can keep using the same capsule if the surgeon was sure of the nature of the reference.
- **Inconclusive** : The tissue type cannot be determined with certainty. The surgeon therefore follows standard operating procedures (including frozen section analysis). This interval of uncertainty corresponds to a range around the decision threshold in which analytical variability and partial overlap of EGFR expression between negative and positive regions can result in ambiguous classification, preventing a definitive qualitative interpretation of the results.
- **70-999** The tissue is considered to have a high level of EGFR. If the reference has been taken on a tumoral tissue, when a score **over 130** is displayed, a warning concerning the nature of the reference is also displayed. The user can change the capsule to take another reference, or the user can keep using the same capsule if the surgeon was sure of the nature of the reference.

Example of the 3 different scores:




The presence of EGFR overexpressing cells at the surface of a tissue is highly indicative of the persistence of tumoral cells. The presence of such cells at the immediate periphery of the resected specimen suggest high risks of involved or close margin.

In few cases the results could also be incorrect.

For each analysis, the results are reported in the history in order of analysis. The last measurement is displayed on the main part of the screen.

To start a new measurement, reposition the probe on the tissue to be analyzed and press the footswitch.
When the capsules have reached their maximum number of analyses, a message appears prompting you to change capsules.
The same TempoCaps-ENT-Blue can be use on different specimen from the same patient (if there are some analysis left with this specific TempoCaps).

#### Replacing the capsule

After 5 analyses (or less if several reference measurements have been carried out), the capsule must be changed.
Remove the capsule from the TempoProbe using a pair of pliers or tweezer. Be sure to position it on the top of the capsule (towards the porthole) when removing it to avoid damaging the optical fiber.
Press the 'CAPSULE' button to start the replacement procedure. Follow the procedure described in §7.4.2 of the TempoTouch® IFU.

### Training

The training for the use of TempoCaps-ENT-blue is common and done at the same time as the TempoTouch® training. This training covers, in particular, the limit date of use, the shelf life in use, the specific type of cancer/patient/tissue it can be used on and why. The training covers all the potential dangers and misuse for the user, the patient and the surroundings. TempoCaps and TempoTouch® must be used by a trained user or under the supervision of a trained user.

### Disposal

The capsules are for single use only and must be treated after use as infectious risk waste (IRW) in accordance with operating theatre practices.

### Reporting serious incidents

Any serious incident related to the use of this device must be immediately reported to the manufacturer and to the competent authority of the Member State in which the user and/or patient is established.

For all request, contact:

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CE 2962

| Revision | Date | Description of change |
|---|---|---|
| V00.00 | 20/11/2024 | Creation |
| V01.00 | 23/09/2025 | addition of analytical and clinical performance |
| V02.00 | 09/02/2026 | CE Mark & ID of notify body<br>Data Matrix e-IFU link<br>General update |

This document and the instructions for use of the TempoTouch® can be found on Dyameo's website at the following URL, that can also be accessed through this QR code:

https://dyameo.com/usermanuals/

The Summary of Safety and Performance (SSP) is available on the Eudamed website.
https://ec.europa.eu/tools/eudamed/#/screen/home