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| Do. Tobell® Sect. 11 | **TECHNICAL DOSSIER** *"ANTIFUNGAL PLASTERS"* | | |
| | **Regulatory references and clinical data** | | |
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# REGULATORY REFERENCES

Italian Legislative Decree 46/97 transposing the European Directive 93/42/EEC (MDD, Medical Devices Directive), and its subsequent amendments, such as those provided for by the Italian Legislative Decree No. 37 of 25 January 2010, which transposes the European Directive 2007/47/EC.

Ministerial Decree 15.XI.2005 (Approval of templates of forms for reporting incidents or near-miss situations involving medical devices and in vitro diagnostic medical devices).

UNI EN ISO 9001:2015 (Quality management systems - Requirements).

UNI CEI EN ISO 13485:2016 (Medical devices - Quality management systems).

UNI CEI EN ISO 14971:2012 (Application of risk management to medical devices).

UNI CEI EN ISO 15223-1:2017 (Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements).

UNI CEI EN 1041:2013 (Information supplied by the manufacturer of medical devices).

UNI EN ISO 10993-1: 2010 (Biological evaluation of medical devices - Part 1: Evaluation and testing).

UNI EN ISO 10993-10:2013 (Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization).

UNI ISO 2859-1 (Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection).

CEI EN 62366:2008 (Medical devices – Application of usability engineering to medical devices).

***General information***

The clinical evaluation is required by the legislation in force concerning medical devices (Italian Legislative Decree No. 46 - 24/02/1997: Implementation of directive 93/42/EEC, concerning medical devices) and active implantable medical devices (Italian Legislative Decree No. 507 - 14/12/1992: Implementation of the Directive 90/385/EEC, on the approximation of the laws of the Member States relating to active implantable medical devices) in order to attain the CE marking and thus ensure that a medical device meets the quality and safety essential requirements. The clinical evaluation consists of a review of the data available concerning the MD regarding its safety, performance and effectiveness in the clinical use. It aims at providing data and information (clinical evidence) that can ensure that the MD is suitable for the intended use established by the manufacturer, according to an acceptable level of safety, with reference to the current state of the art, of technology and of the clinical methods.

The purpose of this document is to perform a clinical evaluation of the medical device called "ANTIFUNGAL PLASTER".

This clinical evaluation was prepared according to the following guidelines: European Commission, Enterprise and Industry Directorate-General, **MEDDEV 2.7.1 (rev. 4)**, complying with the aspects introduced by the European Directive 2007/47/EC. Its structure reflects these guidelines, as evidence of the application of item 1.1 of the MDD.

It aims at demonstrating that the family of products in question complies with the MDD safety requirements and is comparable, in terms of both safety and effectiveness, with other similar devices currently on the market.

The evaluation has been conducted by the following team:

- Alessandra Vecchiato: Expert of the clinical application concerning the intended use and of the production activity of the medical device;
- Roberto Fossa: Entrusted with the drafting of this document.

This evaluation will be reviewed at least once a year during the management review, in the light of:

- possible bibliographic update emerged from the research in the main European databases using the following rationale:
  - Studies on partially or totally equivalent devices.
    The concept of equivalence refers here to:
    - The CLINIC one (clinical condition or medical utility, anatomic site, affected population, critical performance)
    - The TECHNICAL one (conditions of use, specifications and characteristics, operating principle)
    - The BIOLOGICAL ones (materials, type of contact, interaction with surrounding materials)
  - Studies in English or Italian;
  - Studies with a good number of patients involved and with a sufficient number of observations such as to guarantee the scientific validity of the conclusions.
  - Studies carried out under conditions similar to those of normal use of the device
  - Studies in which all relevant characteristics were examined, including those related to the safety and performance of the device

- feedback from the market (in terms of both customer satisfaction and improvement indications, complaints, incident reports, etc.)
- updating of preclinical data (updating of tests, process validations, etc.).

***Device description***

The medical device covered by this technical dossier is used for the topical treatment of mycosis on toenails and fingernails. Onychomycosis (or nail mycosis) is an infection affecting one or more nails and is caused by a fungus; it is generally not a dangerous disorder, yet it is an unaesthetic problem that can become difficult to treat, especially when neglected.

Generally, it involves a change in the color and shape of the nail, which also tends to become thicker; when the fungus spreads deeper under the nail, it can cause the appearance of stains, thickening and increased friability of the nails, which tend to crumble on the sides: all these are aesthetically unpleasant symptoms, which can be potentially painful.

It can affect both fingernails and toenails, although it is more common in the latter.

The 40% of Urea contained in the plaster acts by modifying the pH of the area subject to treatment, weakening the part of the diseased nail with the consequent selective detachment of such part and facilitating its cutting and, therefore, its removal. After applying the plasters containing the disc with urea (the manufacturer recommends to replace the products on a daily basis for a total treatment duration of 1 to 3 weeks), an improvement in the nail status can be noticed, thanks to the physical mechanism featured by the product, which, acting on the pH of the environment, creates the optimal conditions to prevent the development of the fungus.

Therefore, the defect will stop and the nail will grow back healthy moving forward the damaged part that has to be progressively eliminated with the regular nail cut.

It is essential to start the treatment right when the first signs of mycosis are detected, in order to obtain more rapid and effective results.
Said device consists of urea discs and occlusive fixing plasters, if any.

***Classification of the device***

The involved "ANTIFUNGAL PLASTERS" were classified as medical devices of **class I,** according to rule 1 of Annex IX of the MDD.

***Preclinical Evaluation***

Within the framework of the "Preclinical Evaluation", the company has verified the following aspects:

- biocompatibility of raw materials;
- validation of the shelf-life and stability of the urea concentration;
- antimicrobial efficacy test according to ASTM E 2180

***Bibliographic evaluation***

The medical device "ANTIFUNGAL PLASTERS" is a product whose use is now well established in terms of application of urea to onychomycosis cases.

Therefore, this clinical evaluation will aim at demonstrating the equivalence of the use of some components of the medical device covered by this technical dossier with those described in the scientific literature applying the following two paths envisaged by the guidelines MEDDEV 2.7.1 (rev. 4):

A) Clinical equivalence

1. use in the same clinical conditions and for the same purposes;
2. use with reference to the same part of the body;

3. use on the same type of patient (for example, factors such as age, anatomy and physiology have to be considered).

B) Technical equivalence

1. use under the same use conditions;
2. same specifications and properties;
3. similar design;
4. similar operating modes.

***Bibliographic evaluation***

The weight of each article analyzed is calculated by assigning specific indices related to the reliability of the article itself.

*Relevance of the medical device (Index: **Ip**)*

The type and intended use of the described medical device is considered in relation to the potential benefits assumed by Do.Tobell S.r.l. and the potential risks. The evaluation of the relevance corresponds to the assignment of an "Ip" index ranging from 1 to 5 according to the following criteria:

- 5 = the article describes the clinical efficacy and contraindications of devices similar to the one to be evaluated;
- 4 = the article describes procedures or contraindications featuring (indirect) relevance with devices similar to the one to be evaluated;
- 2 = the article deals with topics related to the experimentation of the procedure used;
- 1 = the article describes use methods or contraindications concerning the procedures used.

*Article Source (Index: **Io**)*

Here it is evaluated how reliable the article is based on the authors or the scientific society or the publisher that published it. Each article shall be assigned an "Io" index ranging from 1 to 5 according to the following criteria:

- 5 = The article was published by an international medical scientific society, with internationally recognized authors;
- 4 = The article was published by an international medical scientific society, with not necessarily internationally recognized authors;
- 3 = The article was published by a national medical scientific society, with at least nationally recognized authors;
- 2 = The article was published by a national medical scientific society, with not necessarily nationally recognized authors;
- 1 = The article was published by non-scientific journals.

*Date and repetition of the publication (Index: **Id**)*

The date of publication and its repetition are evaluated in this case. The more recent the article, the more reliable it is considered. It is necessary to avoid granting excessive weight to some authors particularly prolific in the publication of articles, therefore, less weight shall be granted to the less recent articles of these authors drafted on a clinical research carried out in the same time span and on an equal number of enrolled patients. In descending order of importance, the characteristics of the article are associated with an "Id" index ranging from 5 to 1 as follows:

- 5 = Publication of the first article with date included in the last two years of research;
- 4 = Publication of the first article with date included between the last two years and five years;
- 3 = Publication of the first article with date included between the last five years and fifteen years;

- 2 = Publication of second articles with date included in the last two years of research;
- 1 = Publication of second articles with date included between the last two years and fifteen years.

*Article quality (Index: **Iq**)*

The scientific reliability of the article is evaluated by rating it based on its content. Ideally, a well-performed study must comply with the good clinical practice (GCP) principles, i.e., it has to:

- be obtained from a controlled clinical research;
- be designed appropriately (with an approved protocol on an appropriate number of controlled cases);
- report well-documented clinical cases;
- carried out by the clinical experts.

The assigned "Iq" index is as follows:

- 5 = the article fully meets the GCP criteria;
- 4 = the article meets 3/4 of the GCP criteria;
- 3 = the article meets 2/4 of the GCP criteria;
- 2 = the article meets 1/4 of the GCP criteria;
- 1 = the article does not meet any of the GCP criteria.

*Calculation of the resulting weight **P***

At the end of the evaluation, each article, included in the bibliographic survey, is assigned the resulting relative weight (P), obtained as the sum of the 4 factors stated above:

**P = Ip + Io + 0.5*Id + Iq** where 0.5 of "Id" is a correction value

The result P will be evaluated for values included between 3.5 and 17.5.

A bibliographic research has also been carried out starting from the scientific literature collected on the Internet (for example, articles concerning clinical investigations and reports of adverse events for the device in question or for equivalent devices), taking into consideration:

- the source and type of data to be used for the clinical evaluation;
- if data derived from equivalent devices can be used to support the safety and/or performance of the device in question.

*Methodology*

Date of research: July 2018

Name of the person who carried out the research: **Roberto Fossa**

Curriculum vitae enclosed to Section 8

Research sources: Scientific databases: PUBMED

*Specifications used for the research:*

The research has been carried out without any temporal restriction; the term chosen has been the following: "UREA"

*Selection criteria for the articles:*

Weights have been applied as indicated in the previous pages.

*Summary of the clinical data*

The clinical research related to the device led to finding 1 article.

**P = 5 + 5 + 0.5*3 + 4 = 15.5**

Int J Dermatol. 1997 Jan;36(1):67-9.

**Treatment of onychomycosis: a randomized, double-blind comparison study with topical bifonazole-urea ointment alone and in combination with short-duration oral griseofulvin.**

Friedman-Birnbaum R[1], Cohen A, Shemer A, Bitterman O, Bergman R, Stettendorf S.

The analysis of the document shows the effectiveness of the use of urea in the removal of the mycosis from the nail thanks to the modification of the environment pH; in the specific case of the bibliographic article, the effectiveness is enhanced by the presence also of the 1% bifonazole which in the case of the product proposed by Do.Tobell is not present.

***Evaluation with respect to the competition***

A large number of competitors features products that overlap with those produced by Do.Tobell S.r.l. thus demonstrating the consolidated use of the product.

The comparison evaluation used the following evaluation criteria and the evidence of the perfect overlapping of our products with the comparison ones is highlighted by capitalized letters:

- description of the devices (configuration overlapping):
  ADHESIVE PLASTERS.
- use indications (use overlapping):
  MEDICATION IN PLASTER WITH UREA SPREADING IN CONTACT WITH THE MYCOSIS.
- treatment (use overlapping):
  TOPICAL TREATMENT OF TOENAILS AND FINGERNAILS MYCOSIS.
- technical characteristics (technical overlapping):
  TNT PLASTER.
- materials (technical overlapping):
  UREA SPREAD ON PLASTER.
- drawings (technical overlapping):
  PLASTERS.

Therefore, carefully analyzing the characteristics of the medical device "ANTIFUNGAL PLASTERS" and comparing them with those of competitors in terms of:

- Use indications
- Specific treatment
- Technical features
- Materials used

it can be inferred that the medical device "ANTIFUNGAL PLASTERS" is equivalent (with the exception of the application mode, compared to the competitors who use the cream form, Do.Tobell uses urea applied to the plaster) and features all the characteristics to be able to place itself on the reference market as a mirror image compared to the competition.

To corroborate the declaration provided in this section concerning the "consolidated use of the product" and the fact that a "high number of competitors feature products overlapping in terms of use with those produced by Do.Tobell", by way of example, such products, overlapping with ours in terms of use, are listed here below:

1. **"TROSYD U40 – 40% UREA" manufactured by Giuliani**

   Gel with 40% Urea for topical use to be applied on nails affected by mycosis

   Class I CE medical device.

Package leaflet facsimile

**TROSYD® U40**
**40% UREA**

**GIULIANI**

NAIL CHANGES DUE TO TRAUMA OR PSORIASIS
- It reduces the thickening of the nail plate, promoting its renewal.
- It prepares the nail for treatment with medication, even in cases of onychomycosis.

## NAIL ALTERATIONS

The nail plate may undergo changes due to traumatic events or psoriasis. These are malformations of the nails that can lead to changes in the structure of the nail in terms of coloring (variations from yellow to matt gray), surface (loss of uniformity) and thickness (variable).

Changes in the nail plate may not be related to trauma or psoriasis but rather to the presence of a fungus (onychomycosis). The affected nail, while continuing to grow, may show alterations in terms of color, structure (thickening, brittleness till the nail plate breakage) and shape.

## TROSYD® U40 BASED ON 40% UREA FOR TOPICAL USE

Trosyd® U40, 10 ml fluid gel.

Product based on 40% Urea for topical use.

Transparent fluid gel contained in a wand equipped with a dispensing spout with an airtight cap.

Thanks to the keratolytic properties of the highly concentrated Urea and to the innovative dispensing method, Trosyd® U40 **is indicated in cases of changes in the nail plate due to trauma or psoriasis**.

The use of the product in fact, by removing the keratin on the surface, allows to smooth the nail and decrease its thickness, promoting the renewal of the nail plate.

Trosyd® U40 can also be used to prepare the nail for treatments with topical antifungals.

The 40% urea allows for a greater absorption of the medicinal product, reducing the healing time.

In fact, often the nail, particularly that of the big toe, represents a compact barrier for the penetration of the medicinal product.

The use of Urea removes the keratin on the surface, making the nail more permeable while promoting the renewal of the nail plate.

## WAY OF USE

We recommend an application in the evening, alternating cycles of 15 days of treatments to cycles of 15 days of suspension.

**Nail changes due to trauma or psoriasis:** 2 months of treatment are recommended.

**Nail preparation for treatment with topical antifungals:** it is recommended to apply the product throughout the period of treatment with the medicinal product, following the cycles of 15 days of use and 15 days of suspension.

The application of the medicinal product should be subsequent to that of Trosyd® U40 and should occur when the latter has totally dried.

Trosyd® U40 is easily applied on the nails, the particular shape of the dispensing wand allows an easy and homogeneous application of the gel.

During use, do not press the dispensing wand, the content comes out after simple contact with the surface to be treated.

## WARNINGS

Keep out of reach of children under 12 years of age.

Prolonged use of Urea at a 40% concentration may lead to nail ablation.

The presence of white crystals inside the cap, due to the crystallization of Urea, is normal and does not affect the validity of the product.

Do not apply on the mucous membranes and on the skin.

Avoid contact with eyes, rinse thoroughly in case of accidental eye contact.

Store at room temperature. Product for external use.

Do not use after the date on the package.

## INGREDIENTS

Aqua, Urea, Propylene glycol, Sodium polyacrylate.

## MANUFACTURER

Giuliani S.p.A.
Via P. Palagi, 2
20129 Milan, Italy

EXTERNAL USE

MEDICAL DEVICE CE

For information: +39 0220541

rev. 17D118 C2030510

From the evaluation of the competitor product indicated above (CE certified as a class I medical device for the same intended use), it is clear that the medical device manufactured by Do.Tobell S.r.l. is overlapping in terms of composition (Urea 40%), intended use and way of use.

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Considering what is described herein (Bibliographic evaluation and evaluation with respect to the competition), including the related enclosures, it is confirmed that:

- the medical devices offered by Do.Tobell Srl are effective for the suggested clinical indications;
- the medical devices are intended for non-specialized personnel, considering the consolidated use of the plasters;
- medical devices are equipped with labeling and IFU properly complying with the intended use.

***Evaluation with reference to incident reports***

The research focused on consulting dedicated websites (MHRA and Ministry of Health):

- http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/index.htm
- http://www.salute.gov.it/dispositivi/archivioAvvisiDispo.jsp?menu=avvisi&lingua=italiano

and it was carried out in order to find incidents, safety warnings and other problems related to this category of medical devices, not directly highlighted by the analysis of the chosen literature. Not any competitor product was

identified, which showed adverse events, which could, therefore, enrich what already found in the evaluation of the chosen bibliography.

## ***Conclusions***

From what it is described in this clinical evaluation document, we can declare that when the medical devices "*ANTIFUNGAL PLASTERS*" are used according to the ways of use and for the intended uses foreseen by the manufacturer (see the validation of the labeling plan provided in Chapter 06), the performance of the medical device does comply with the essential requirements set forth in Annex I of the European Directive 93/42/EEC as subsequently amended and supplemented (e.g.: European Directive 2007/47/EC); finally, any risks associated with the intended use of the medical device, which is by now a consolidated use, are of an acceptable level (as emerges from the risk assessment carried out by the company – see Chapter 08) when compared to the benefits to the patient and are compatible with a high level of protection of the health and safety of the patient.

The Management

Alessandra Vecchiato

Vecchiato Alessandra