HYPRO OTROKOVICE, s.r.o. (Ltd.)
Přístavní 568, 765 02 Otrokovice

MEDICAL DEVICE CLINICAL TRIAL FINAL REPORT

PRODUCT "HYPRO-FLEX"

(1)

a) Administrative data:

1. Provider:
Kroměřížská nemocnice a.s., Havlíčkova 660, Kroměříž 76755
ID: 24660532, TAX ID: CZ27660532

2. Name of the clinical trial:
Clinical trial of the "Hypro-Flex" products

3. List of medical devices for clinical trial:
"Hypro-Flex"

4. Brief description of the clinical trial:
The sterile dressings were evaluated - the "Hypro-Flex" products for dermatovenerology, plastic surgery, burn units and general practice - medical devices are intended for use in the health-care establishments and are manufactured by HYPRO Otrokovice s.r.o. Otrokovice. Data from the available literature, provided technical documentation and evaluations performed by the the state testing laboratory were used for the evaluation.

With their properties (the used material, safety) these medical devices comply with the strict requirements for health-care operation.

5. Sponsor:
Antonín Galatík, ID: 7306174117, Komárov 69 763 61

Manufacturer:
HYPRO Otrokovice s.r.o., Přístavní 568, 76502 Otrokovice

6. Investigator:
Lumír Domes, M.D., Karla Čapka 1785, Kroměříž 76701 ID: 521102263

7. Assistant of the sponsor:
Not appointed.

8. The single parts of the clinical trial include:
A. Review of the available literature about the submitted medical device of Hypro Otrokovice, s.r.o. (Ltd.)
B. Identification of the medical device, application of the knowledge from the literature in examination and testing of its properties and functions. The emphasis was put on its usability, suitability of operation and an exclusion of possible negative effects on a patient during its use in dermatovenerology, plastic surgery, burn units and general practice.

9. Clinical trial was started on: 15.01. 2009

10. Clinical trial was prematurely ended on: 0

11. Clinical trial was ended on: 22 02. 2009

12. Date of preparation of the final report: 25.02.2008

b) Content of the final report on the clinical trial:

Content of the medical device clinical trial final report - dressing material "Hypro-Flex'.'@ for dermatovenerology, plastic surgery, burn units and general practice - has 11 pages including appendices.

c) List of abbreviations and terms used:

None

d) Lumír Domes M.D. Qualification and Experience, Examiner

Date of birth:	November 2, 1952
Home address:	Karla Čapka 1758, 76701 Kroměříž, Czech republic
Employment address:	Nemocnice v Kroměříži, Havlíčkova 660, 76701 Kroměříž
Employment:	Head of Department of Urology
Education:	1959-1972 Grammar School 1972-1978 Faculty of Medicine in Volgograd, Russia 1978-1983 Certification of Urology I 1983-1988 Certification of Urology II. 1992-Head of Departmentof Urology
Length ofpractice:	30 years Short-term attachmentts: BRD, Sweden, France
Participation in studies:	1992-1996 participation in trials EORTC

00-ONIN-0l A randomised, double-blind, placebo-controlled, parallel group, dose-response study of tamsulosin oral controlled absoption system (OCAS) 0,4 mg, 0,8 mg and 1,2 mg tablets once daily in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO), former1y known as symptomatic benign prostatic hyperplasia (BPH).
02-OMN-02 A randomised, double-blind, placebo-controlled study to evaluate efficacy and safety of tamsulosin oral controlled absoption system (TOCAS) 0,4 mg, 0,8 mg and 1,2 mg tablets once daily, tamsulosin modified release 0,4 mg capsules (OMNIC) once daily and placebo in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO), formerly referred to as symptomatic benign prostatic hyperplasia (BPH).
A309904 Open randomised study of previously untreated metastatic prostate cancer patients comparing intermittent to contineous treatment with cyproterone acetate. Evaluation of step-up therapy adding an LHRH agonist progression is ic1uded.
90S-EC-00l Solifenacin in flexible dose regimes with tolterodine as an active comparator in a double-blind, double-durruny, randomised overactive bladder symptom trial.
200S0103 A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer

e) List of other persons participating in the clinical trial:

None

f) Data on verification of suitability of the medical device for the defined purpose of use:

l. Purpose and rationale:

• evaluation of the medical device with regard to its safety for the user and a third person in providing the health care in the extent of use stated in the original product documentation, catalogue
• verification of suitability of the medical device for the defined purpose of use and in accordance with the current clinical knowledge
• evaluation of the usability in providing the health care in the extent of use stated in the original product documentation, catalogue
• evaluation of suitability for the clinical use in the Czech Republic

2. Related provisions:

• Act no. 130/2003 Coll., which amends Act no. 123/2000 Coll. on medical devices and amendments of some related laws and some other laws.
• Governmental provision no. 180/1998 Coll. on technical requirements on medical devices as amended by the governmental provision no. 130/1999 Coll.
• Act no. 22/1997 Coll. on technical requirements on products as amended by Act no. 711/2000 Coll. and Act no. 20S/2002 Coll.
• Decree of the MoH No. 316/2000 which specifies the terms of the medical device clinical trial final report

3. Clinical trial plan:

To evaluate the above stated medical device of the company HYPRO Otrokovice s.r.o. (Ltd.) based on the available literature, technical documentation and own knowledge and experience for the use in the health-care establishments in the treatment and care of patients. To focus especially on the evaluation of suitability, safety or possible side effects and risks during the use.

The sponsor will provide the principal investigator with the following documents:

- clinical trials from three health-care departments
- risk management documentation ČSN EN ISO 14971, ČSN EN 12442 and appendices XII NV no. 336/2004 Coll.
- Declaration of conformity
- sample in the original packaging and package insert
- test protocol for cytotoxicity in vitro and the tests of skin tolerance dated December 18, 2008

The needed clinical data will be taken from the available documentation and literature corresponding to the time when the clinical trial will be performed.
The principle investigator will study the indicated literature, evaluate functionality and quality of single medical devices and their suitability for the use in the health-care establishment. The principal investigator will prepare the expert evaluation of the medical device "Hypro-Flex" for dermatovenerology, plastic surgery, burn units and general practice and provide it to the sponsor, Hypro Otrokovice s.r.o. (Ltd.) located in Otrokovice.
The medical device clinical trial final report will be immediately prepared by the sponsor and submitted to the Kroměřížská nemocnice a.s. andto the relevant ethics committee for approval.

4. Clinical trials in medical devices:

Name and type designation of the medical device:

Hypro-Flex, absorbable atelocollagen dressing with hyaluronan, sterile, diameters 65x110 mm or 65x55 mm

Composition of the medical device:
The medical device consists of:
Atelocollagen type I, bovine -95%
magnesium-sodium hyaluronate -5%

The combined dressing HYPRO-FLEX consists of atelocollagen fibrous material to which the molecules of a high-molecular hyaluronan are bound by means of coordination, metalocomplex bindings consisting of small amounts of basic magnesium salts.

Atelocollagen is a telopetide-free collagen which contains interspecific antigenic determinants which increases a tolerance of tissues. Collagen, especially type 1, activates a cascade of interactive steps in blood which include activation of zymogen to thrombin. Thrombin causes proteolysis of fibrinogen followed by production of soft granulation clot which is formed to stiff granulation mass. It was found that type I, II and III collagens and their degradation products acted as chemotactic stimulators of fibroblasts in vivo and help effectively repair the damaged tissue.

The starting material for production of atelocollagen which represents 95% of composition of Hypro-Flex is bovine heel tendon that is removed from the veterinary controlled animal

intended for use in human. Because there is no alternative source of the tissue for the manufacture of atelocollagen which is the most effective known haemostatic agent with a perfect tissue tolerance, absorbability, non-imunogenicity and which supports healing of skin lesions, we cannot use any other source then animals. The use of skin as a material is not suitable because it contains collagen of type I and III, elastin and the muscle protein myosin which is a source of antigens. The use of the material from any other animal species is theoretically possible but it would increase the possible risks such as the immunology reactions to collagen which is species different and it would reduce the product safety. The bovine collagen has been used in the manufacture of absorbable haemostatics for the longest time and its use is best documented. Animal husbandry is liable to strict regulations and is veterinary controlled. The domestic sources are sufficient and therefore a high material safety can be ensured.

Hyaluronic acid is a natural polysacharide with marked physico-chemical properties, huge hydration ability and viscoelasticity. These properties are responsible for its therapeutic use. The research results show that hyaluronan is a substance which can speed up healing of the wounds and acceleration of healing of inflammations was also found. Healing of burns is accelerated almost by 50%. The efficacy of hyaluronan is directly dependent of the time of its activity. In the used collagen hyaluron composites hyaluronan is mostly too quickly washed out by exudate. However, in the evaluated medical device hyaluronan is continually released together with the slow release of atelocollagen and it contains trace amounts of magnesium salts which is used in the formation of the new tissue (metaloenzymes) and is often deficient.

It is contained in many animal tissues, especially in fibrous tissues, it is obtained for example from the umbilical cords, vitreous body, synovial fluid and especially from the cockscombs. Since the end of 80's hyaluronan has been prepared biotechnologically - by cultivation of bacteria of the Streptococcus species. Hyaluronam significantly accelerates healing of inflammations, supports granulation and epitelization of the wounds and increases the viscosity of exudate. It has also a strong hydration ability which is important for maintenance of moisture in the wound. Hyaluronan of animal origin and biotechnologically produced hyaluronam are chemically identical and both types are currently used in various medical devices. However only biotechnologically produced hyaluronan is used in Hypro-Flex. There are currently some risks associated with hyaluronan of animal origin and its method of manufacture, for example the poultry diseases, e.g. bird flu and the method of collection and purification of the material for the pharmaceutical quality is more demanding as well as it almost always contain residua of animal protein, which may be a source of immune or allergic reactions in some patients. However this risk is significantly lower in bacterial hyaluronic acid because the different method of preparation excludes the presence of tissue proteins. The total amount of foreign substances is also significantly lower already in the starting material and the purification process to the pharmaceutical quality does not require so many steps to achieve the same purity of the material. The process of purification is more regardful and the obtained hyaluronic acid of pharmaceutical quality has a higher molecular weight which is very important for the quality of the product. It appears that the only disadvantage of bacterial hyaluronan is the fact that it may contain also endotoxins which, in case of a high concentration and if they rich the bloodstream (e.g. injection form of the product), may cause septic infection. However, it is known that smaller doses of endotoxins may be advantageous for the host body (adjuvant effects for antibody production, increased activity of macrophages, antineoplastic effects). The efficacy of hyaluronan is directly dependent of the time of its activity. Inflammatory exudate is often present in chronic wounds. This commonly causes a quick elimination of all substances which are applied in the wound, especially in the form of a solution. This combination with a collagen carrier ensures a long-term exposure in a direct contact with the target tissues and a continual release of hyaluronan together with a slow dissolution of collagen. A prolongation of the effects of hyaluronan is achieved by chemical cross-linking, so called inoculation of both polymer by metalocomplexes of the salts of biologically essential elements, especially magnesium. This enabled reduction of the total amount of hyaluronan in the product as well as prolongation of the

time of its effects during healing. Hypro-Flex contains only 5% of hyaluronan which is a small amount. Standard table 65x55mm Hypro-Flex contains approximately 6.25mg of hyaluro-nan. It is clear from the above that the risks which could be caused by endotoxins in Hypro-Flex are small because their concentration would be low and their possible release would be gradual.

Indications

- healing of chronic wounds
- healing of varicose ulcers
- treatment of decubitus ulcers
- healing of superficial skin lesions
- dressing for superficial injuries and scratches
- dressing for the sites from which the skin implants were collected
- dressing for treatment of burns

Principles of application

Medical device Hypro-Flex can be used as a biological dressing supporting healing of wounds. A contact of the medical device with the patient's body is needed for a correct use of Hypro-Flex. It is a product which comes to a contact with the open wound when used in the first phase to stop capillary bleeding and for treatment of open skin lesions such as varicose ulcers or decubitus ulcers. Hypro-Flex is sterile, it does not support growth of pathogenic microorganisms but on the contrary it has a mild antimicrobial effect as it binds and inactivates enzymes which are necessary for metabolism of microorganisms. Hypro-Flex does not cause inflammatory or other tissue reactions. The used amount is not limited, however the amount of implanted Hypro-Flex should be only such that does not cause pressure in the wound. A contact of Hypro-Flex with the central nervous system may occur during the application (in case of use in neurosurgery) and an intraocular application (in ophtalmology) may occur during haemostasis and surgical drying. Medical devices Hypro-Flex are intended for application on the healthy mucous membranes, e.g. conjunctiva where they are used for intensive drying.

Hypro-Flex can be used alone or in combination with other medicinal products without excessive denaturation of protein collagen. The respective therapeutic substance is kept on the base of the wound. It is used for example together with antibiotics or disinfection products and other dressing materials. It is suitable to apply the ointment and oil products on Hypro-Flex after its dry application on the wound on its external side.

Packaging

Medical device is packed in the combined packaging of paper and transparent foil of the company Wipak Medical (Steriking). The packed products are sterilized by gamma radiation by the contract partner and the chemical indicator markers about validation of the sterilization procedure are a part of the packaging. The packaging contains the following bilingual information (Czech, Slovak) about the medical device:

- Name of the medical device
- Size in mm
- Number of pieces in the packaging
- Composition of the medical device
- Warning on the package insert
- Address of the manufacturer
- International designation of batch number, catalogue number, date of manufacture, shelf-life, sterilization data, indication of a medical device for single use, information about notified body
- Bar code

The packaging is prepared without any defects, it is esthetically satisfactory and we did not find any defects in the submitted samples which would impair their quality. Packaging is easily

storable and do not require much space which is an importat factor in the health-care establishments. Two widths of the dressing are available which enables the user to select from various types according to the purpose of the use.

Handling with the packaging is easy, the packaging can be opened comfortably, removal of the dressing is easy and there is no risk of impairment of sterility of the dressing which could occur in case of difficult opening of the packaging. The dressing is without any defect and the quality of manufacture of all sizes is excellent.

Analysis of possible risks

1. Risk of material selection
2. Risk of contamination by bacteria, fungi or yeasts
3. Risk of contamination by viruses or infection agens, prions, BSE
   - Animals
   - Origin
   - Characteristics of the used starting material
   - Methods used for inactivation or removal of the infectious agent
   - Amount of the starting animal material needed for manufacture of one unit of the medical device
   - Amount of material of animal origin which comes to the contact with patients and users
   - Method of application
4. Control of origin, collection and handling
   - Determination of a geographic origin, i.e. the country where the cattle was bred, its condition and criteria of acceptability
   - Requirements for hygiene and quality assurance during slaughter.
   - Process of collection, preservation, handling, storage and transport of tendons.
   - Records
   - Control
     a. Procedures
     b. Workers
     c. Monitoring of the current requirements
     d. Origin of the animal material
     e. Control of the origin of the animal material, certification and origin traceability
     f. Occurrence of spongiform encephalopathies
     g. Documentation of procedures and a history of feeding
     h. Method of stunning
     i. Collection and handling
     j. Validation of elimination and/or inactivation of viruses and infectious agents
     k. General principles of elimination of BSE
     1. Continual monitoring and control of the decisive elimination parameters
     m. Review of the evaluation

It is clear from the submitted documentation that the manufacturer has a detailed system of safe collection of the material, validation and control. All aspects of the good manufacturing practice are similarly prepared with the aim to maximally minimize possible side effects of the medical device. The material includes detailed list of all risks associated with the use of the evaluated medical device and a possible estimation of the risks for each hazard. Generally we can conclude that the risks associated with the origin of the material, its processing, manufacture and its subsequent use if all rules for application in the package insert are kept are minimal and negligible.

Evaluation of the dressing Hypro-Flex
The main advantages of the atelocollagen dressings with hyaluronan compared to the common dressings are as follows:

1. The dressing material is exclusively of biological origin: atelocollagen and hyaluronan which are natural to human body tissue.

2. Atelocollagen is the adjusted collagen from which the terminal parts, so called telopeptides were enzymatically removed which contain the aminoacid sequences acting as interspecific antigenic determinants. By removal of these telopeptides the bovine collagen becomes acceptable for the human tissue without any possible antigenic inflammatory reactions.

3. Atelocollagen, in contrast to collagen, has a mild bacteriostatic effect.

4. Atelocollagen is slowly absorbed in the wound which is caused by the tissue collagenases. By this process the extracellular matrix is enriched by aminoacids needed in the biosynthesis of a new collagen. This process causes a dissolution and shedding of the dressing from the wound side, i.e. occlusion which reduces adhesion to the granulation tissue and makes removal of the dressing easier. The unoccluded parts of the dressing behind the wound edge can be easily removed after moisturizing with water or saline solution.

5. Hyaluronan facilitates granulation of the wound and accelerates healing in all phases of the healing process.

6. Hyaluronan increases the viscosity of exudate which enhances the rigidity and robustness of the formed granulate.

7. Hyaluronan has a strong hydration ability and supports the water content and hence the metabolic processes in the wound.

8. Hyaluronan is species unspecific biopolymer and therefore it is accepted by the human tissue as a natural material without any tissue immune reaction.

9. Hyaluronam significantly accelerates healing of inflammations, supports granulation and epitelization of the wounds and increases the viscosity of exudate. It has also a strong hydration ability which helps to maintain moisture in the wound.

10. The exogenous trace amounts of magnesium salts in the healing tissue are desirable because the essential element is concerned which is also deficient and a necessary part of metaloenzymes, synthetases which take part in the metabolic processes in the cells of the haling tisssue.

Summary of evaluation:
The evaluated product fulfils the requirements for quality which are requested forthe products intended for use in medicine. It has been used for a long time in the clinical practice and the material and manufacturing processes correspond to the recommended standards which is documented by the certificates and a similarly prepared
risk analysis.
It is a medical device of simple nature and if used for the recommended purposes and according to the instructions there is no risk of damage to health of a patient due to the use of the medical device. Based on our experience the submitted medical device is fully comparable with the similar medical devices which are used in medicine.

Final assessment:

I recommend the medical device "Hypro-Flex" of the company HYPRO OTROKOVICE s.r.o. (Ltd.) which was evaluated in the clinical trial to be used in the clinical practice and this medical device complies with the legal provisions for use by the third party.

(2)
Appendices of the clinical trial final report:

a) Written consent of the ethics committee with the clinical trial (see appendix). b) Ethics committee opinion in accordance with the performed clinical trial with ethical principles (see appendix).
c) List of used literature
d) Appendices:
Application for medical device clinical trial
-contract between sponsor and investigator and health-care establishment that performs the trial.
-Declaration of the investigator

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Kroměřížská nemocnice a.s. (Kroměříž hospital, corp.) represented by Ing. Pavel Calábek Chairman of the Board	Lumír Domes, M.D. investigator	Hypro Otrokovice s r.o. (Ltd.) deputy Antonín Galatík

In Otrokovice on: February 25, 2009

List of used literature:

1) Peretz D. 2006. Inactivation of Prions by Acidic Sodium Dodecyl Sulfate. JOURNAL OF VIROLOGY, Jan. 2006, p. 322-331 Vol. 80, No. 1
2) Bauman, P. A. 2006. Critical factors influencing prion inactivation by sodium hydroxide. Vox Sanguinis: Volume 91, Number 1, July 2006, pp. 34-40(7)
3) Suyama K. 2007, Prion inactivation by the Maillard reaction. Biochemical and Biophysical Research Communications, Volume 356, Issue 1, Pages 245-248
4) Paspaltsis I. 2006. Titanium dioxide photocatalytic inactivation of prions. Journal of General Virology (2006), 87, 3125-3130
5) Postlethwaite, A.E., Seyer, J.M., Kang, A.H.: Chemotactic Attraction of human fibroblastes to type I, II and III collagens and collagen-derived peptides. Proc. Natl. Acad. Sci. USA, Vol. 75, No. 2, pp 871-875, february 1978, Cell Biology
6) Nazarko, L.: Choosing the right dressing for different wounds. Nursing & Residential Care, October 2005, Vo1.7, No.10
7) Brychta, P., Adler, J., Horký, D., Franců, M., Koupil, J., Menšík, I.: Užití dermální náhrady k rekonstrukci lidské kůže. Forum Medical, ISSN 1212-2696, 1/200
8) Hayward, P.G., Morrison, W.A.: Current concepts in wound dressings. Australian Prescriber, 3.1.09, 19:51
9) Park, Si-Nae., Lee, H.J., Lee, K.H., Suh, H.: Biological characterization of EDC-crosslinked collagen-hyaluronic acid matrix in dermal tissue restoration. Biomaterials 24(2003), 1631-1641
10) Doillon, Ch.J., Silver, F.H.: Collagen-based wound dressing: Effects of hyaluronic acid and fibronectin on wound healing. Biomaterial 1986, Vol.7, January
11) Analýza rizik a plán jejich řízení - Hypro-Flex Date: January 7 2009, Document validity: since January 7 2009 PRO-012-2009 Page: 17 / 17 Revision: 0, Hypro Otrokovice, s.r.o., Přístavní 568, 765 02 Otrokovice, Česká republika
12) Odborný posudek k provedené zkoušce na cytotoxicitu in vitro a zkoušku kožní snášenlivosti u Hypro-Sorb R (kolagen) a Hypro-Flex (kolagen+hyaluronan) jako zdravotnického prostředku. Státní zdravotní ústav, Šrobárova 48, Praha 10, 100 42