

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

FINAL REPORT ON CLINICAL ASSESSMENT
OF THE MEDICAL DEVICE

HYPRO-OSS®

(1)

a) Administrative data:

1. Provider:

Kroměřížská nemocnice a.s. (Hospital of Kroměříž), Havlíčkova 660, Kroměříž 767 55
Company ID: 24660532, Tax ID: CZ27660532

2. Title of the clinical assessment:

Clinical assessment of the medical device Hypro-Oss®

3. List of medical devices submitted for clinical assessment:

Hypro-Oss®

4. Brief description of the clinical assessment:

The Hypro-Oss® medical device for surgery, orthopaedics and dentistry was assessed. Manufactured by HYPRO Otrokovice s.r.o. in Otrokovice, the device is intended for use by medical facilities (hospitals). Data from the available literature, technical documentation provided, and evaluations performed by licensed testing laboratories were used for the assessment.

Owing to its properties (materials involved, safety) this medical device meets the stringent requirements for use in the medical sector.

5. Sponsor:

Antonín Galatík, Birth Number: 7306174117, Komárov 69 763 61

Manufacturer:

HYPRO Otrokovice s.r.o., Přístavní 568, 76502 Otrokovice, Czech Republic

6. Investigator:

MUDr. Lumír Domes, Karla Čapka 1785, Kroměříž 76701
Birth Number: 521102263

7. Sponsor's assistant:

None appointed.

8. Stages of the clinical assessment:

A. Review of available literature concerned with the medical device of Hypro Otrokovice, s.r.o.

B. Familiarisation with the medical device, application of knowledge from the literature in the examination and testing of its properties and performance with focus on the suitability and effectiveness of its use while ruling out any harm to the patient when used in dentistry, orthopaedics, plastic surgery, and general practice.

9. Clinical assessment starting date:	15 June 2012
10. Date of premature termination of the assessment:	0
11. Clinical assessment termination date:	22 August 2012
12. Final report issue date:	27 September 2012

b) Content of the final report:

This final report on the clinical trial of the medical device – Hypro-Oss[®] composite bone implant for dentistry, orthopaedics, surgery and plastic surgery as well as for general medical practice – consists of 14 pages, annexes included.

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c) Abbreviations and glossary of terms:

All abbreviations and definitions of terms are explained in the text.

d) Qualification and experience of the investigator, MUDr. Lumír Domes:

Date of birth:	2 November 1952
Home address:	Karla Čapka 1758, 76701 Kroměříž, Czech Republic
Office address:	Hospital of Kroměříž, Havlíčkova 660, 76701 Kroměříž
Position:	Head of the Department of Urology
Education background:	1959-1972 Grammar School
	1972-1978 Faculty of Medicine in Volgograd, Russia
	1978-1983 Board certification in urology I
	1983-1988 Board certification in urology II
	1992- Head of Department of Urology
Number of years of experience:	30
Short-term attachments:	Germany, Sweden, France

Participation in studies: 1992-1996 participation in EORTC trials

00-OMN-01 Randomised, double-blind, placebo-controlled, parallel group, dose-response study of tamsulosin oral controlled absorption 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), formerly referred to as symptomatic benign prostatic hyperplasia (BPH).

02-OMN-02 Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety of tamsulosin oral controlled absorption 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 continuous treatment with cyproterone acetate. Evaluation of step-up therapy adding an LHRH agonist progression is included.

905-EC-001 Solifenacin in flexible dose regimes with tolterodine as an active comparator in a double-blind, double-dummy, randomised overactive bladder symptom trial.

20050103 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 assessment:

None

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

1. Purpose and justification:

- Assessment of the medical device with respect to its safety for the user and for third persons when providing medical care in accordance with the intended use defined in the original product documentation and catalogue.
- Verification of suitability of the medical device for the intended use and of its agreement with current clinical knowledge.
- Assessment of suitability of the medical device for providing medical care in accordance with the intended use defined in the original product documentation and catalogue.
- Assessment of suitability of the medical device for clinical use in the Czech Republic.

2. Related legislation

- Act no. 130/2003 amending Act no. 123/2000 on medical devices and on the amendment of some related laws and some other laws
- Government Regulation no. 180/1998 on technical requirements for medical devices, as amended by Government Regulation no. 130/1999

- Act no. 22/1997 on technical requirements for products, as amended by Act no.71/2000 and Act no. 205/2002
- Regulation of the Ministry of Health no. 316/2000 specifying requirements for final reports on clinical trials of medical devices

3. Clinical assessment design

The purpose of this clinical assessment is to assess the above medical device, product of HYPRO Otrokovice s.r.o., when used in the treatment of patients and when used for therapy in hospitals and other healthcare facilities, based on available literature, technical documentation and the investigator's own expertise. Focus will be particularly on assessment of the medical device's suitability, safety and potential adverse effects and risks associated with its use.

The following documents shall be provided to the principal investigator by the sponsor:

- Results of literature search relating to clinical experience and trials
- Risk management documentation as per ČSN EN ISO 14971, ČSN EN 12442 and Annex XII to Government Regulation no. 336/2004
- Declaration of conformity
- Sample of the device in the original packaging and of the package leaflet
- Reports on cytotoxicity tests in vitro and skin tolerance tests and on other tests performed by authorised institutions
- Technical documentation of the manufacturing process

The required clinical data will be taken from a summary of available documentation and literature known at the time when the clinical assessment will be performed.

The principal investigator shall study the literature, assess the performance and quality of the various medical devices and their suitability for use in hospitals. He shall elaborate expert assessment of the medical device Hypro-Oss® for dentistry, orthopaedics, surgery and plastic surgery as well as general practice and provide it to the sponsor, Hypro Otrokovice s.r.o. in Otrokovice.

The sponsor shall prepare a final report on the clinical assessment promptly and shall submit it to the management and Ethics Committee of the Hospital of Kroměříž (Kroměřížská nemocnice a.s.) for approval.

4. Clinical assessment of the medical device

Theoretical background and glossary of terms

Bone tissue is a complex component comprising both organic and inorganic constituents.

The organic part consists of an organic matrix and 3 cell types:

Osteoblasts, which are responsible for creation of the bone and are present on the surface of the bone formed. They are of mesenchymal origin from immature cells. They operate in 2 phases:

Determination phase: the cell is aware that it is designed to constitute bone tissue, definition of tasks for the cell, must be affected, has no memory or process timing – this is assisted by

the factors of formation, transformation of cells stemming from the periostum or cartilage into osteoblasts

Induction phase: the cells, already specified, are forced to propagate rapidly for bone formation in the required volume, proliferation, maturation, differentiation, mineralisation, division, rapid propagation – guarantee of rapid healing, can be obtained from various sources

Osteocytes: present in smaller quantities, do not form tissue, are incorporated into the bone architecture (in lacunes)

Osteoclasts: resorptive cells for remodelling processes in the bone

Organic matrix: tissue between the cells, organic tissue, initially prevailing and forming osteoid tissue, hardens after the penetration of minerals. About 35% of the dry bone weight is type I collagen – 90% (also in dentine, tooth enamel, cement), it is the dominant of the bone (there are more than one collagen type, however, type I is the strongest). The rest (10%) is formed by functional non-collagen proteins: BMP; building proteins: proteoglycans, glycoproteins.

Extracellular matrix integrates the components (combines all the elements). It is based on proteoglycans + hyaluronic acid: soft component; plus collagens I, II, III, V, XI (collagen I – very rigid – is most abundant): harder component

Extracellular matrix is kind of base for the various bone units (cells).

Inorganic matrix (60% to 70% dry weight) consists of apatite and hydroxyapatite ($\text{Ca}_3(\text{PO}_4)_2$).

The beginning is a mesenchymal stem cell, which forms the various specialised and specific cells – osteoblasts, chondroblasts, myoblasts, bone marrow cells, fibroblasts and other cells – under the effect of the bone morphogenetic protein (BMP). The initial bone is formed mostly by collagen, which then undergoes mineralisation, controlled by soluble substances (AP – alkaline phosphatase, pyrophosphate, fibrokinetin, osteontin, thrombospondin, and others).

The process of formation, reconstruction and regeneration of the bone mass is heterogeneous and is basically controlled by 3 mutually affecting processes:

Osteogenesis – ability to model the growing bone to the physiologically required shape (effect of the bone morphogenic protein (BMP)).

Osteoconduction – protects against the growing-in of soft tissues, supports the growth of osteoblasts, porosity, capability of integration into the growing new bone, affects the contents of the building components of the growing bone, i.e. hydroxyapatite and collagen.

Osteoinduction – promotion and acceleration of the new bone formation process (effect of the growth factors {Igf}).

Many skeleton diseases and skeleton injuries are associated with the formation of bone tissue defects. In order to prevent pathological fractures or when surgically treating such fractures, we replace the missing bone, restore its strength and stability. Only minor defects heal spontaneously, larger spaces (a few mm or more) must be filled or bridged.

Materials of 2 main groups are used for this purpose: biological, i.e. natural materials, and non-biological, i.e. artificial (man-made) materials. Terminologically, transfer of biological tissue into a defect is transplantation whereas transfer of a man-made material is implantation. The first group comprises primarily bone grafts, although cell cultures, growth factors and tissue agents with osteoinductive and osteogenic capabilities will also be included soon owing to advances in tissue engineering. The usability of biological replacement materials is governed by the genetic relation between the donor and the patient, particularly with respect to immunity. The usability of man-made replacement materials depends primarily on biocompatibility, i.e. live tissue's tolerance to the material

without the tendency to surround it with connective tissue or even to reject it. First of all, the material must be non-toxic, non-mutagenic and non-carcinogenic.

The following bone graft types are most widespread in bone surgery and dentistry:

- 1) Autogenous and isogenous grafts
- 2) Allogeneous (formerly homogeneous) grafts
- 3) Xenogeneous (formerly heterogeneous) grafts.

Autogenous bone grafts are taken from the same patient, from a site where withdrawal of a piece of bone would not cause serious functional disorders. Autogenous bone grafts possess osteoconductive, osteoinductive and osteogenic properties. Spongy, corticospongy and cortical vascularised, more frequently nonvascularised, bone grafts are used. Histocompatibility is the major advantage of autogenous bone grafts. The risk of transfer of infectious diseases is thus avoided. Drawbacks include, apart from their limited availability, morbidity at the site of withdrawal and the necessity of a secondary invasive procedure. An isogenous graft is a graft taken from the patient's twin. Once again, the potential for gaining isogenous grafts is very limited and problems can arise at the site of withdrawal.

An allogeneous graft is a graft from a donor of the same biological species or from a cadaverous bone. The withdrawal site problem is avoided but other problems arise. Allogeneous grafts are osteoconductive and potentially osteoinductive materials. Their biological activity seems to be conditional on proteins and various growth factors. The risk of HIV infection is a drawback of an allogeneous demineralised bone matrix. Osteoinductive potency is, regrettably, different, depending on the preparation procedure and on the donor. Spongy allografts possess osteoconductive and limited osteoinductive properties. Such properties are additionally suppressed by radiation during their preparation.

A xenogeneous graft is a graft from a donor of a biological species different from that of the recipient. Application of such grafts is very limited.

Implant material are categorised by their biological properties: **A. Biotolerant (bioacceptable)**, represented, e.g. by noble metals, general metals, alloyed steels; **B Biocompatible** (bioinert, bioinactive), which are either polymers (polysiloxane, silicone, polyethylene, polytetrafluoroethylene [PTFE], ...) or inert ceramic materials (biologically inactive aluminium and carbonic ceramics); **C. Bioactive** (bioreactive, bioconductive), which are the most important materials in this group from the implantology aspect. They form a strong chemical bond at the interface between the implant and the host tissue in the absence of reparative inflammatory processes. They contain a group of non-resorbable surfactants and resorbable substances (bioactive ceramics $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})]$ hydroxyapatite, $(\text{CaHPO}_4 \cdot 2\text{H}_2\text{O})$ dicalcium phosphate, $[\text{Ca}_3(\text{PO}_4)_2]$ tricalcium phosphate, $[\text{Ca}_4\text{P}_2\text{O}_9]$ tetracalcium phosphate, (CaSO_4) calcium sulphate combined with bone tissue by direct chemical bonding without formation of a connective tissue interlayer. Bioactive ceramic materials and glass-ceramic materials are most frequently used as bone tissue replacements in reconstructive surgery. Their biocompatibility and osteoconductivity have been demonstrated experimentally.) Such materials undergo controlled corrosion (by interaction with the body fluid) resulting in the formation of a layer of a corrosive material – calcium phosphate. This is a stimulus for osteoconduction – a process of live bone growth into the material giving rise to strong bonding to the bone – bonding osteogenesis. Responsible for the new bone formation is the diffusible BMP (bone morphogenetic protein), stimulating non-differentiated mesenchymal cells to differentiation into osteoprogenitor cells and initiating chondrogenesis and osteogenesis. Referred to as osteoinduction, this process is also capable of inducing heterotopic bone formation. **D. Biodegradable** – full hydrolysis (final products: CO_2 and H_2O) is assumed to be complete

in 12 months (such materials include, among others, polyglycolic acid [PGA], polymerised lactic acid [PLA], and polydioxinome).

While possessing adequate physical properties for tissue replacement, biomaterials must be virtually nontoxic to the recipient. About 2 to 3 million "nearly inert" biomaterials are estimated to be implanted annually. Resorbable, biodegradable materials have their own specific characteristics, because their degradation takes different periods of time and gives rise to substances with different physical and chemical properties. The degradation process and degradation products must be well recognised prior to the clinical use in order to avoid toxic damage of the tissues and the body. The implanted material must be adequately mechanically strong and resistant to wear. In fact, it has been found that the microscopic particles of the inert material can be fagocytated, and although unchanged, induce an inflammatory reaction, with adverse consequences for the performance and further fate of the implant. To sum up, a biocompatible material is a material that induces a minimal, negligible response in the host body. This property is characterised by a set of physical, chemical and biological reactions between the implant and the host.

Composites. Since different materials possess different physical, chemical and biological properties and each material has its assets and drawbacks, it is feasible to improve their quality as regards biocompatibility, mechanical strength, elasticity, durability and/or degradability by combining them suitably. The basic property of composite materials is that they mimic biological properties of the bone tissue. Examples of composites combining biological and nonbiological materials include Collagraft (hydroxyapatite, tricalcium phosphate and bovine collagen), Surgibone and Osteobiol Gen-Os (hydroxyapatite and collagen), Biovan H (hydroxyapatite) and the material under assessment – Hypro-Oss (hydroxyapatite and bovine type I atelocollagen). Materials showing promise in bone surgery include composites from gel polymers and porous bioceramic materials, playing the role of carriers of growth factors, bone morphogenetic proteins or immediately of tissue cultures of bone-producing cells.

Description of the medical device

Hypro-Oss[®] is a lyophilised native composite containing 68.1% hydroxyapatite $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ and 31.3% bovine type I atelocollagen in the form of crushed material 0.5 – 2 mm grain size.

This composition of the Hypro-Oss[®] medical device is protected under a patent. The patent document is entitled "A product supporting bone ossification, the method of its manufacture and its use", No. CZ 302 296 B6 dated 9 February 2011. The basic difference from similar medical devices is in the use of atelocollagen.

Atelocollagen is collagen freed from telopeptides which contain interspecies antigenic determinants, whereby tissue tolerance is enhanced. Collagen, especially type I, activates a cascade of interactive steps in blood, including activation of zymogen to thrombin which in turn induces proteolysis of fibrinogen giving rise to a soft granulation precipitate, which is re-formed to solid granulation mass. It has been demonstrated that type I, II and III collagens and their degradation products act as chemotactic stimulators of fibroblasts *in vivo* and help effectively repair the damaged tissue.

The starting material for the manufacture of atelocollagen (which is present in Hypro-Oss[®]) is bovine metatarsal bone, taken from an individually inspected animal intended for human consumption. The procedures of the bovine cortical bone withdrawal and processing are governed by corporate standard PN-4S. Animals constitute the sole existing source for the manufacture of atelocollagen; no alternative tissue source exists. The use of skin as a material is not suitable because it contains type I and type II collagen,

elastin and the muscle protein myosin which is a source of antigens. Although theoretically possible, the use of material from other animal species would increase potential risks such as immunology reactions to the collagen which is species different, whereby safety of the product would be compromised. Bovine collagen has been used for the manufacture of atelocollagen for the longest time and its use is best documented. Animal husbandry is liable to strict regulations and is under veterinary control. Domestic sources are sufficient, so a high material safety can be ensured.

Hypro-Oss® is manufactured in 8 variants (product numbers 070 – 077). It is granulated material 0.5 – 1 mm and 1 – 2 mm grain size, delivered as a medical device in vials 0.5 ml, 1 ml, 3 ml and 5 ml volume.

Analysis of potential risks

Hypro-Oss® tested **negative** in cytotoxicity and skin irritation tests performed by the National Institute of Public Health in Prague (24 May 2010), in genotoxicity and carcinogenicity tests performed by the Institute of Public Health in Ostrava (24 April 2011), and in microbial and chemical purity tests performed by the company MVDr.Šotola s.r.o. in Kroměříž (26 February 2010). Available documents include "Validace eliminace a/nebo inaktivace virů a agens přenosné spongiformní encefalopatie (TSE)" [Validation of elimination and/or inactivation of viruses and agents of transmissible spongiform encephalopathy (TSE)], prepared in accordance with ČSN EN ISO 22442-3:2008, and a very detailed study with many pictures "Hypro-Oss® bone substitution material, preclinical implantation study in Beagle dogs" developed by BioTest s.r.o. in Konárovice (28 July 2012). Histological examination of 16 Beagle dogs gave evidence of absence of any inflammatory reaction at the site of the medical device and demonstrated stimulation and growth of new bone tissue at the site of application. No differences in the healing process when using different grain size materials were observed.

The documentation appended (Risk analysis and risk management plan of May 2012, prepared in compliance with ČSN EN ISO 14971, ČSN EN 12442 and Annex XII to Government Regulation no. 336/2004) clearly demonstrates that the issues of safe material withdrawal, validation and inspection have been fully managed by the manufacturer. All aspects of the good manufacturing practice have been treated with the aim to minimise any potential adverse effects exerted by the medical device as much as possible. The document includes a detailed list of all potential risks associated with the use of the medical device and estimate of the risks for each hazard. It can be concluded that the risks associated with the origin of the material, its processing, manufacture and subsequent use are minimal to negligible if all rules for application as specified in the package leaflet are complied with.

Packing

The medical device is packed in a combined packaging comprising a glass vial with a butyl rubber septum and an aluminium crimp cap. The outer packaging is a double PET blister. Each unit is accompanied by a package leaflet all the components are accommodated in a paper folder.

The packed products are sterilized by gamma radiation (outsourced service). The packaging includes chemical indicator marks documenting validation of the sterilization process. The packaging contains the following bilingual (Czech, English) information about the medical device:

- Name of the medical device
- Volume in ml

- Grain size in mm
- Composition of the medical device
- Indication of the presence of a package leaflet
- Address of the manufacturer
- International batch number symbol, product number, date of manufacture, expiry, sterilization data, packaging label, indication of a disposable medical device, data of the notified body
- Bar code

All the basic data are printed on the glass vial, on the blister and on the paper folder.

The packaging design is free from any faults and is aesthetically adequate. We did not find any defects on the packaging that might compromise sterility. The packaging is easy to store and does not require much space, which is an important factor in medical facilities.

It is also easy to handle, can be opened comfortably, and the device itself can be easily removed from the packaging without the risk compromising its sterility, which exists if the packaging does not open easily. The design of the medical device is free from any defects and the quality of manufacture of all sizes is excellent.

Indications:

The medical device is intended for filling and reconstructions of aseptic bone defects.

Indications in maxillofacial surgery and in dental surgery:

- Implantology, periodontology and oral surgery
- Completion of maxillary antrum
- Horizontal augmentation
- Intrabone defects
- Peri-implant defects
- Extraction beds
- Vertical augmentation
- Furcation defects
- Cyst filling
- Periodontal defects
- Bone defect filling after removal of benign tumours and cysts

Indications in orthopaedic surgery and in traumatology:

- Bone defect filling in juxta-articular fractures
- Acetabular defect filling following implant replacement
- Bone defect filling after removal of benign tumours and cysts
- Bone cyst filling
- Tissue defect filling during cartilage and bone transplantation
- Bone defect filling at autogenous bone removal sites

Contraindications:

- Acute and chronic infections at the implantation site
- Defects in the open epiphyseal disk area
- Severe bone diseases of endocrine etiology
- Severe bone metabolism disorders
- Current treatment with glucocorticoid and mineralocorticoid drugs affecting calcium metabolism

- Severe or inadequately controlled diabetes mellitus
- Immunosuppressive therapy
- Tumorous diseases and bone metastases

Principles of use of the medical device

The amount of the medical device to be used depends on the bone defect size. Hypro-Oss[®] is a single-use medical device intended for implantation during surgical procedures (surgery, orthopaedics, dentistry). It serves as a permanent implant.

To obtain a stable implant, Hypro-Oss[®] must be implanted manually into the live and well-pretreated bone cavity by applying mild pressure. Particularly well suited for use in trabecular bone defects, Hypro-Oss[®] should be implanted so that its surface is in intimate contact with the natural bone tissue (as far as possible).

The bone defect should be completely filled with Hypro-Oss[®] or with a mixture of Hypro-Oss[®] and an autograft. The implantation site should be pre-prepared by exposing the surface of the adjacent bone. The surgical procedure will be dependent on the bone defect site, extent and type.

A stable intrabone implant must maintain direct contact with the bone freed from connective tissue. The structure of Hypro-Oss[®] supports the role of an osteoconductive environment for the newly growing tissue which will create firm bonding between the medical device and the bone tissue. Stabilization devices (external fixing, metallic osteosynthesis) reducing the load at the implantation site may be necessary until the bone regeneration process is complete. If the Hypro-Oss[®] granulate is to be used in mixture with autogenic trabecular bone, the 1:1 mixing ratio is recommended.

Where Hypro-Oss[®] is implanted into mechanically stressed areas, stabilisation by means of, e.g., metallic osteosynthesis or a firm dressing is recommended. Published data indicate that Hypro-Oss[®] will find application especially in dental implantology. Guided tissue regeneration (GTR) has become the basic therapeutic procedure for the treatment of periodontal bone defects as well as of bone defects of periimplantitis and during augmentation procedures prior to the placement of implants. The term guided bone regeneration (GBR) is used in this context. Research has given evidence that a barrier membrane can help prevent the growth of epithelisation cells or fibroblasts into the bone defect, thus promoting bone reconstruction through slow bone tissue growth. This concept has been applied to the treatment of parodontal defects aimed at the reconstruction of cement, periodontal connection and the bone.

Comparison between medical devices based on bone composites

Medical devices of this type have been available in clinical practice for more than 50 years now and many types are currently present in the market. The best-known of them are, for example, Surgibone[®], Osteobiol Gen-Os[®], ChronOs[®] inject, OssaBase[®]-HA, Poresorb[®]-TPC, Maxresorb[®], and Osbone[®]. Some contain pure hydroxyapatite, other contain synthetic calcium phosphate and some combine the two constituents in various proportions. The composition of Surgibone[®] and Osteobiol Gen-Os[®] is similar to that of Hypro-Oss[®], i.e. a mixture of hydroxyapatite and collagen, the latter being modified to atelocollagen in Hypro-Oss[®].

Advantages of Hypro-Oss[®]

- Ability to integrate into the newly growing bone tissue
- High biocompatibility of the material
- Osteoconductive effect – accelerates the growth of osteoblasts on the implanted

material and thus the formation of the new bone.

- Owing to its high collagen content the device arrests bleeding in the wound.
- The material activates a cascade of coagulation factors in blood plasma in a natural way, thereby supporting the formation of coagulate.
- The collagen component of the composite promotes significant release of the growth factors TGF and PTGF in thrombocytes.
- The material prevents growth of endothelial cells into the bone defect.
- It inhibits collagenolytic activities of the wound exudate.
- It promotes adhesion and propagation of the tissue cells while not supporting the growth of microorganisms, it has a mild bacteriostatic effect.
- It is an excellent product for guided bone regeneration.

Conclusion:

The following conclusions can be made based on published information from preclinical, clinical and comparison studies:

1. Hypro-Oss[®] is an efficient medical device which is well suited as a material for bone fillings and bone tissue substitutions.
2. It activates a cascade of coagulation factors in blood in an absolutely natural way.
3. It exhibits a high degree of biocompatibility, is antiallergenic and antimutagenic, is implantable and completely biologically absorbable and apyrogenic.
4. Once integrated into the bone tissue it actively supports osteoconduction and growth factor activation, thereby accelerating the formation of new tissue and the healing process.
5. Hypro-Oss[®] does not support growth of microorganisms, inhibits serine proteases, thus exerting a mild bacteriostatic effect.
6. Hypro-Oss[®] compares well with the competitive products Surgibone[®] and Osteobiol Gen-Os[®] in all the clinical parameters examined and proves to be a valuable product. It is superior to the two competitive products in the proprietary use of type I atelocollagen.
7. Hypro-Oss[®] meets all qualitative requirements put on products intended for use in medicine. It has been used for a long time in clinical practice. The material and the manufacturing processes meet the recommended standards, as documented by certificates and a detailed risk analysis.
8. It is a simple medical device which poses no risk of harm to the patient if used for the recommended purposes in accordance with the instructions for use.
9. Based on our experience the medical device is fully comparable with similar medical devices which are used in medicine.

Concluding assessment:

I recommend the medical device Hypro-Oss[®], which is manufactured by HYPRO OTROKOVICE s.r.o. and was the object of this clinical assessment, for use in clinical practice. This medical device complies with legal provisions applicable to the use by third parties.

(2)

Annexes to the final report on clinical assessment

- a) Ethics Committee's written consent with the clinical assessment
- b) Ethics Committee's statement on compliance of the completed clinical assessment with ethic principles
- c) References
 1. Hypro-Oss bone substitution material, Preclinical implantation study in Beagle dogs, BioTest s.r.o., Interim report of 9 March 2012
 2. Hypro-Oss bone substitution material, Preclinical Implantation Study in Beagle Dogs, BioTest s.r.o., Interim report of 3 September 2012
 3. Přípravek pro podporu osifikace kostí, způsob jeho výroby a jeho použití [A product supporting ossification of bones, the method of its manufacture and its use]. Patent CZ30296-B6, Buletin no. 6/2011 of 9 February 2011
 4. Protokol laboratorního vyšetření [Laboratory examination report] of 5 March 2010, MVDr.Šotola s.r.o., Food analysis laboratories
 5. Odborný posudek k provedené zkoušce na cytotoxicity in vitro a zkoušce stanovení kožní dráždivosti., [Expert opinion on the completed cytotoxicity test and skin irritation test] of 24 May 2010, National Institute of Public Health in Prague
 6. A new implantant material for use in reconstructive surgical procedures – Surgibone (Boplant), JAMA, 14 March 1966, Vol. 195, No.11, pages 951-952.
 7. Jensen S,S., DDS, Terheyden H., MD, DDS, PhD.: Bone augmentation procedures in localized defects in the alveolar ridge: Clinical results with different bone grafts and bone-substitute materials.. International Journal of Oral & Maxillofacial Implants, Vol. 24, Supplement 2009, pages 218-236
 8. Reynolds M.A., DDS, PhD, Aichelmann-Reidy M.E., DDS, Branch-Mays G.L., DDS, PhD: Regeneration of peridental tissue: Bone replacement grafts. Dent. Clin. N. Am., Vol. 54, 2010, pages 55-71
 9. Salgado A.J., Cputinho O.P., Reis R.L.: Bone tissue engineering: State of the art and future trends, Macromol. Biosci., 2004, Vol. 4, pages 743-765
 10. Bone-graft substitutes: Facts, fiction & applications, American Academy of Orthopedic Surgeons, 75th Annual Meeting, 5-9 March 2008, San Francisco, California, USA
 11. Mardas N., Chadha V., Donis N.: Alveolar ridge preservation with guided bone regeneration and a synthetic bone substitute or a bovine-derived xenograft: a randomized, controlled clinical trial., Clin. Oral Implants Res., 2010, Jul, 21 (7), 688-698
 12. Buser D., DDS: 20 years of guided bone regeneration in implant dentistry. Quintessence Publishing Co., Inc., 2010
 13. Kohli, M., Suarez, D., Ruffieux, K.: The bone graft substitute beta-TCP in oral surgery and dental application: A literature review, 20 January 2009
 14. Freihofner, H.P.M., et al.: Autogenous bone and bovine bone mineral as grafting materials in maxillofacial surgery. ISBN: 90-901381-8, Merx, Nijmegen, 2000
 15. Develioglu, H., Saraydin, U., Kartal, U.: The bone-healing effect of a xenograft in a rat calvarial defect model. Dental Materials Journal, 2009, 28(4): 396-400
 16. Dumitrescu, A.L.: Bone grafts and bone substitutes in periodontal therapy. Chemicals in Surgical Therapy, DOI:10.1007/978-3-642-18225-9-2., Heidelberg 2011

17. Laurencin, C.T., Calhoun, J.S.: Bone graft substitute materials. <http://emedicine.medscape.com/article>
18. Urban, K., Šponer, P.: Možnosti náhrady kostní tkáně [Possibilities of bone tissue substitution]. Lék. Zpr. LF UK [Medical Report, Faculty of Medicine,] Hradec Králové, 2004:49 (7-8): 259-267
19. Ondruš, Š., Straka, M., Bajarová, J.: Trikalciumpfosfát v kombinaci s autologní kostní dřením v léčbě cystických kostních defektů v dětském věku [Tricalcium phosphate in combination with autologous bone marrow in the therapy of cystic bone defects in pediatric patients]. Acta Chirurgiae Orthopaedicae, 78, 2011, p. 544-550
20. Kohout, A., Šimůnek, A., Kopecká, D.: Histologické nálezy u subantrální augmentace [Histological findings in subantral augmentation]. Česko-Slovenská Patologie, 42, 2006, No. 1, p. 29-33
21. Zkouška cytotoxicity a kožní dráždivosti [Cytotoxicity and skin irritation tests], Státní zdravotní ústav Praha [National Institute of Public Health in Prague], 24 May 2010
22. Zkouška na genotoxicitu a karcinogenitu [Genotoxicity and carcinogenicity test], Zdravotní ústav v Ostravě [Institute of Public Health in Ostrava], 24 April 2011
23. Zkouška mikrobiální a chemické čistoty, Protokol laboratorního vyšetření [Microbial and chemical purity test, Laboratory analysis report], MVDr. Šotola s.r.o., Kroměříž, 26 February 2010
24. Validace eliminace a/nebo inaktivace virů a agens přenosné spongioformní encefalopatie (TSE) [Validation of elimination and/or inactivation of viruses and agents of transmissible spongiform encephalopathy (TSE)], Hypro s.r.o., Otrokovice, May 2012
25. Hypro-Oss[®] bone substitution material, preclinical implantation study in Beagle dogs, Final report, BioTest s.r.o., Konárovice, 28 July 2012
26. Analýza rizika a plán jejich řízení [Risk analysis and plan of risk management], Hypro s.r.o., Otrokovice, 05/2012-10-02
27. Technical documentation and corporate standard PN-45, Hypro s.r.o., Otrokovice, 05/2012

d) Annexes:

Clinical assessment of a medical device

- contract between the sponsor and the investigator and the medical establishment performing the assessment.
- Investigator's statement

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Hospital of Kroměříž
 represented by Ing. Pavel Calábek
 Chairman of the Board of Directors

.....
Lumír Domes, M.D.
 Investigator

.....
Hypro Otrokovice s r.o.
 represented by Antonín Galatík
 Acting Secretary

Otrokovice, 5 October 2012