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(54) Benævnelse: **KNOGLECEMENT I PASTAFORM**

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**Bone cement in paste form**

The present invention relates to a kit, the use of a kit for preparing a paste for the mechanical fixation of joint prostheses, covering skull defects, filling bone cavities, for femoroplasty, for vertebroplasty, for kyphoplasty, for the preparation of spacers or for the production of support materials for local antibiotic therapy as well as molds.

Conventional polymethylmethacrylate bone cements (PMMA bone cements) have been known for decades and go back to the seminal work of Sir Charnley (Charnley, J.: "*Anchorage of the femoral head prosthesis of the shaft of the femur";* J. Bone Joint Surg. 42 (1960) 28-30). The basic structure of PMMA bone cements has since remained basically the same. PMMA bone cements consist of a liquid monomer component and a powder component. The monomer component generally contains (i) the monomer methyl methacrylate and (ii) an activator dissolved therein (for example, N,N-dimethyl-p-toluidine). The powder component comprises (i) one or more polymers which are produced by polymerisation, preferably by suspension polymerisation, based on methyl methacrylate and comonomers such as styrene, methyl acrylate or similar monomers, (ii) an X-ray opacifier, and (iii) an initiator (for example) dibenzoyl. Mixing the powder component with the monomer causes swelling of the polymers of the powder component in the methyl methacrylate of the monomer component resulting in a plastically deformable dough. Simultaneously, the activator N,N-dimethyl-p-toluidine reacts with dibenzoyl which decomposes to form free radicals. The radicals thus formed initiate the radical polymerisation of the methylmethacrylate. With progressive polymerisation of the methylmethacrylate, the viscosity of the cement increases until the cement dough solidifies and is thus cured.

The essential disadvantage of the conventional PMMA bone cements for the medical user is that the user must mix the liquid monomer with the powder component in a mixing system or in crucibles immediately prior to application of the cement. Mixing errors may easily occur which adversely affect the quality of the cement. Moreover, the mixing of the components must take place rapidly. It is important that all the cement powder is mixed with the monomer without forming lumps, and the introduction of air bubbles avoided during the mixing process. The formation of air bubbles in the cement paste is largely prevented by using vacuum mixing systems instead of manual mixing. Examples of mixing systems are disclosed in the publications US 4,015,945, EP-A-0 674 888 and JP 2003-

181270. Vacuum mixing systems do, however, require an additional vacuum pump and are therefore relatively expensive. After mixing the monomer with the powder component, it is necessary to wait a certain time, depending on the type of cement, until the cement dough is tack-free and can be applied. Appropriately trained personnel are also needed due to the many possibilities of error during mixing of conventional PMMA bone cements. The corresponding training is associated with considerable cost. In addition, when mixing the liquid monomer component with the powder component, the user is exposed to monomer vapor and the release of powdery cement particles.

As an alternative to conventional powder-liquid polymethyl-acrylate bone cements, paste-like polymethyl-acrylate bone cements were disclosed in publications DE-A-10 2007 052 116, DE-A-10 2007 050 762, DE-A-10 2007 050 763 and DE1010 2005 5759. Here, the bone cements are provided to the user as premixed, storage-stable pastes. These pastes contain a radically polymerisable methacrylate monomer, a polymer that is soluble in this methacrylate monomer and a particulate polymer that is insoluble in this methacrylate (since both pastes contain an insoluble particulate polymer, such systems are referred to as "symmetric"). One of these pastes also contains a radical polymerisation initiator, while the other paste contains a polymerisation activator. As a result of the selected composition, the bone cement made from these pastes has a sufficiently high viscosity and cohesion to withstand bleeding pressure until curing is complete. Upon mixing of the two pastes, the polymerisation initiator reacts with the accelerator to form radicals which initiate radical polymerisation of the methacrylate monomers.

Barbiturates in combination with heavy metal ions and halide ions are proposed as initiator systems in the listed publications. Furthermore, the redox initiator system dibenzoyl peroxide/tertiary aromatic amine is mentioned.

EP 0 659 859 A1 discloses an adhesive which contains a hydroperoxide in a first component in addition to monomers and a heavy metal salt and a sulfimide in a second component in addition to monomers. The use of tertiary amines as co-accelerator is not mentioned.

A two-part adhesive composition is also disclosed in DE 33 209 18 A1. The one part of the adhesive comprises a polymerisable acrylate or methacrylate, a peroxide, optionally a sulfimide and optionally a hydrazine derivative. The second part of the adhesive contains a polymerisable acrylate or methacrylate, a transition metal salt and, optionally, an amine

as a co-accelerator. Our own experiments have shown that mixtures of methacrylate monomer (ethylene glycol), cumene hydroperoxide and saccharin (sulfimide) at elevated temperature (50 °C) and within a few days of their mixture with mixtures of methacrylate monomer and copper(II)-2-ethylhexanoate and N,N-dimethyl-p-toluidine dissolved therein, stored at room temperature, decrease in terms of the onset of exothermic polymerisation. This effect is apparently due to an oxidative decomposition of saccharin by the action of the cumene hydroperoxide.

DE 195 01 933 A1 discloses an aerobically curable adhesive based on methacrylate having a boiling point greater than 120 °C. This two-component adhesive contains a hydroperoxide in a first paste, and at least one heavy metal compound in the second paste. Accelerators sulfimides, tertiary amines and hydrazine derivatives are proposed. The particular advantage of these adhesives is that, due to the use of methacrylate monomers having a boiling point greater than 120 °C, there is no sticky layer (dispersion layer) at the interface with the air. The dispersion layer is formed by interference with the polymerisation due to the action of atmospheric oxygen and also contains unreacted monomers in addition to oligomers and polymers. The dispersion layers may cause compatibility problems upon contact with human tissue.

The present invention had the object of overcoming the disadvantages arising from the prior art in connection with bone cement-based systems involving at least two pastes.

In particular, the present invention had the object of providing a polymethylmethacrylate bone cement kit based on two radically polymerisable pastes, wherein the pastes, as long as they are separated from one another, are characterized by a very high polymerisation stability (i.e. as low as possible a tendency to spontaneous polymerisation). After mixing the two pastes, the resulting paste can cure automatically within a few minutes through radical polymerisation. The speed with which the radical polymerisation of the pastes is carried out after mixing, should be as consistent as possible and, in particular, regardless of how long the pastes had been stored separately.

The present invention also had the object of providing a polymethyl methacrylate bone cement kit on the basis of two radical polymerisable pastes that automatically cure within a few minutes after mixing through radical polymerisation, and yield a polymer that preferably has a dispersion layer on its surface as little noticeably sticky as possible.

A contribution towards achieving the abovementioned objects is a bone cement kit comprising a paste A and a paste B,

wherein

(a) Paste A contains

(a1) at least one radically polymerisable monomer having a boiling point of less than 120 °C at a pressure of 1013mbar,

(a2) at least a peroxide as a polymerisation initiator, and

(a3) at least one tertiary amine, at least one amidine or a mixture of at least one tertiary amine and at least one amidine as a co-polymerisation accelerator, and

(b) Paste B contains

(b1) at least one radically polymerisable monomer having a boiling point of less than 120 °C at a pressure of 1013 mbar,

(b2) at least one heavy metal compound as the polymerisation accelerator, and

(b3) at least one sulfimide, at least one dicarboximide or a mixture of at least one sulfimide and a dicarboximide as the co-polymerisation accelerator

wherein at least one of the pastes A and B contains at least a filler as component (a4) or (b4) that is insoluble in (a1) or (b1).

The invention is based, inter alia, on the surprising finding that tack-free polymers surfaces can be produced from pastes with the peroxide/sulfimide/tertiary amine initiator system even when using methacrylate monomers having a boiling point less than 120 °C, which is contrary to the teaching of DE 195 01 933 A2. Thus, these polymers are compatible with human tissue upon contact when using appropriate monomers.

According to the invention, a "kit" is understood to mean a system of at least two components. Although reference is made in the following to two components (i.e. Paste A and Paste B), the kit may, if necessary, also contain more than two components, for example three, four, five or more than five components. The individual kit components are preferably separated before packaging, so that the components of a kit are not in contact with the components of another kit. For example, it is possible for the respective kit components to be packaged separately from each other and then stored together in one reservoir.

Paste A contains a radically polymerisable monomer having a boiling point of less than 120 °C at a pressure of 1013 mbar as component (a1), wherein it is preferably a monomer which becomes liquid at a temperature of 25 °C and a pressure of 1013 mbar.

The radically polymerisable monomer (a1) is preferably a methacrylate monomer, especially a methacrylic ester. Preferably, wherein the methacrylic acid esters (a1) is a monofunctional methacrylic acid ester. This is preferably hydrophobic. By the use of hydrophobic monofunctional methacrylic acid esters (a1), a subsequent increase in the volume of the bone cement as a result of water absorption and thus damage to the bone can be prevented. According to a preferred embodiment, the monofunctional methacrylic acid ester is hydrophobic if it contains no other polar groups apart from the ester group. Preferably, the mono-functional, hydrophobic methacrylic has no carboxyl groups, hydroxyl groups, amide groups, sulfonic acid groups, sulfate groups, phosphate groups or phosphonate groups.

The esters are preferably alkyl esters. Cycloalkyl is also included among alkyl esters according to the invention. According to a preferred embodiment, the alkyl esters are esters of methacrylic acid with alcohols having 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms and most preferably from 1 to 4 carbon atoms. The alcohols may be substituted or unsubstituted and are preferably unsubstituted. Moreover, the alcohols may be saturated or unsaturated and are preferably saturated.

According to a particularly preferred embodiment, the radically polymerisable monomer (a1) is methyl methacrylate, ethyl methacrylate or a mixture of these two monomers.

The radically polymerisable monomer (a1) used according to the invention preferably has a molecular weight of less than 1000 g/mol. This also includes radically polymerisable monomers which are part of a monomer mixture, wherein at least one of the radically polymerisable monomers of the monomer mixture has a defined structure having a molecular weight of less than 1000 g/mol.

The radically polymerisable monomer (a1) is preferably distinguished in that an aqueous solution of the radically polymerisable monomer (a1) has a pH in the range of 5 to 9, preferably in the range of 5.5 to 8.5, more preferably in the range from 6 to 8 and most preferably in the range of 6.5 to 7.5.

Paste A contains 15 to 85 wt .-%, preferably 20 to 70 wt .-%, more preferably 25 to 60 wt .-% and most preferably 25 to 50 wt .-%, each based on the total weight of the paste A of the at least one radically polymerisable monomer (a1).

Paste A further contains at least a peroxide as component (a2) which preferably has a half-life >10 hours, more preferably > 24 hours, and even more preferably > 48 hours, in each case measured at 70 °C. In determining the half-life, the peroxide content is determined through iodine titration, wherein the iodide ions are oxidised to iodine through the peroxide.

Particularly preferably, the peroxide (a2) is selected from the group consisting of cumene hydroperoxide, 1,1,3,3-tetramethylbutyl hydroperoxide, t-butyl hydro-peroxide, t-amyl hydroperoxide, di-isopropylbenzene-mono-hydroperoxide, di-t-butyl peroxide, dicumyl peroxide, and t-butylcumyl peroxide.

Paste A contains the at least one peroxide (a2) preferably in an amount in a range from 0.01 to 10 wt .-%, more preferably in a range from 0.1 to 8 wt .-%, and even more preferably in the range from 1 to 5 wt .-%, each based on the total weight of the paste A.

Paste A further contains, as component (a3), at least one tertiary amine, at least one amidine or a mixture of at least one tertiary amine and at least one amidine as co-polymerisation accelerator.

The tertiary amine is preferably an amine selected from the group consisting of tributylamine, triethanolamine, N,N-dimethyl-p-toluidine, N,N-bis(2-hydroxyethyl)-p-toluidine and N,N- dimethylaniline. Particularly advantageous is the combination of N,N-dimethyl-p-toluidine and N,N-bis(2-hydroxyethyl)-p-toluidine. With this combination, the curing behavior of the mixed paste C can be controlled very effectively by varying the ratio of N,N-dimethyl-p-toluidine to N,N-bis(2-hydroxyethyl)-p-toluidine.

Instead of the tertiary amine (or in combination with the tertiary amine), an amidine can also be used as base. In this case, 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) and 1,5-diazabicyclo(4.3.0)non-5-ene(DBN) are particularly preferred.

Paste A contains the co-polymerisation accelerator (a3) preferably in a quantity ranging from 0.1 to 20 wt .-%, more preferably in a range from 0.5 to 10 wt .-%, and even more preferably in a range from 1 to 5 wt .-%, each based on the total weight of the paste A.

Paste B likewise contains a radically polymerisable monomer having a boiling point of less than 120 °C at a pressure of 1013 mbar as component (b1), which is preferably a monomer that becomes liquid at a temperature of 25 °C and a pressure of 1013 mbar. The radically polymerisable monomer (b1) may be identical to the radically polymerisable monomer (a1) in a kit or different from this, wherein it is preferable that the radically polymerisable monomer (al) and the radically polymerisable monomer (b1) are identical.

The radically polymerisable monomer (b1) is preferably a methacrylate monomer, especially a methacrylic acid ester. Preferably, the methacrylic acid ester (b1) is a monofunctional methacrylic acid ester. It is preferably hydrophobic.

A later increase in volume of the bone cement as a result of water absorption and consequent damage to the bone can be prevented by the use of hydrophobic monofunctional methacrylic acid esters (b1). According to a preferred embodiment, the monofunctional methacrylic acid ester is hydrophobic if it contains no other polar groups in addition to the ester group. Preferably, the mono-functional, hydrophobic methacrylic has no carboxyl groups, hydroxyl groups, amide groups, sulfonic acid groups, sulfate groups, phosphate groups or phosphonate groups.

The esters are preferably alkyl esters. Cycloalkyl is also included among alkyl esters according to the invention. According to a preferred embodiment, the alkyl esters are esters of methacrylic acid with alcohols having 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms and most preferably 1 to 4 carbon atoms. The alcohols may be substituted or unsubstituted and are preferably unsubstituted. The alcohols may further be saturated or unsaturated and are preferably saturated.

According to a particularly preferred embodiment, the radically polymerisable monomer (b1) is methyl methacrylate, ethyl methacrylate or a mixture of these.

According to a further preferred embodiment, the radically polymerisable monomer (b1) is not a methacrylic acid ester derived from bisphenol A.

The inventively used radically polymerisable monomer (b1) preferably has a molecular weight of less than 1000 g/mol. These also include radically polymerisable monomers which are part of a monomer mixture, wherein at least one of the radically polymerisable monomers of the monomer mixture has a defined structure having a molecular weight of less than 1000 g/mol.

The radically polymerisable monomer (b1) is preferably distinguished in that an aqueous solution of the radically polymerisable monomer (b1) has a pH in the range from 5 to 9, preferably in the range from 5.5 to 8.5, more preferably in the range from 6 to 8 and most preferably in the range from 6.5 to 7.5.

Paste B contains preferably 15 to 85 wt .-%, more preferably 20 to 70 wt .-%, still more preferably 25 to 60 wt .-% and most preferably 25 to 50 wt .-%, each based on the total weight of the paste B, of at least one radically polymerisable monomer (b1).

Paste B further contains at least the heavy metal compound as a polymerisation accelerator as component (b2), wherein the heavy metal compound may be a heavy metal salt or heavy metal complex. According to a particularly preferred embodiment, the heavy metal compounds (b2) are compounds of metals, which can change their oxidation state. According to the invention in this context, the preferred compounds are copper (II ), iron (II), iron (III), manganese (II), manganese (III), cobalt (ll) and cobalt (III), wherein copper (II) compounds are most preferred. In this connection, particularly preferred heavy metal compounds (b2) are selected from the group consisting of copper (II) hydroxide, copper (II) methacrylate, copper (ll) acetylacetonate, copper (II) 2-ethylhexanoate, cobalt (II) hydroxide, cobalt (II) -2-ethylhexanoate and basic copper (II) carbonate.

Paste B contains the heavy metal compound (b2) preferably in an amount in a range from 0.0005 to 0.5 wt .-%, more preferably in a range from 0.001 to 0.05.% and particularly preferably in a range from 0.001 to 0.01 wt .-%, each based on the total weight of the paste B.

Paste B further contains as component (b3) at least a sulfimide, at least a dicarboximide or a mixture of at least a sulfimide and at least a dicarboxylic acid imide as a co-polymerisation accelerator, wherein saccharin is a particularly preferred sulfimide, while phthalimide, maleimide and succinimide are particularly preferred dicarboximides. In addition, the use of tetracarboxylic diimides as pyromellitic acid imide is preferred.

Paste B includes the co-polymerisation accelerator (b3) preferably in an amount in a range from 0, I to 10 wt .-%, more preferably in a range from 0.5 to 8 wt.% and particularly preferably in a range from 1 to 5 wt .-%, each based on the total weight of the paste B.

The kit according to the invention is further characterised in that at least one of the pastes A and B comprises at least a filler that is insoluble in (a1) or (b1) as component (a4) or (b4). Provided that one of the pastes comprises an insoluble filler while the other paste

comprises absolutely no insoluble filler, or an insoluble filler in a negligible amount compared to the amount in the other paste, then it is a so-called "asymmetric" kit. If, however, a roughly comparable amount of the insoluble filler is present in both pastes, it is a so-called "symmetric" kit.

The filler (a4) (in the case of paste A) and (b4) (in the case of paste B) is a solid substance at room temperature which is capable of increasing the viscosity of the aggregate mixture of the other ingredients contained in paste A or paste B. The filler (a4) and (b4) should be biocompatible.

According to a preferred embodiment, the filler (a4) and (b4) is selected from polymers, inorganic salts, inorganic oxides, metals and metal alloys.

The filler (a4) and (b4) is preferably particulate. According to a particularly preferred embodiment, the filler (a4) or (b4) has an average particle size ranging from 10 nm to 100 µm and more preferably in the range from 100 nm to 10 µm. By average particle size in this case, is meant a size range occupied by at least 90 percent of the particles.

In the context of the invention, both homopolymers and copolymers are collectively referred to as polymers.

The polymer used as the filler (a4) or (b4) is preferably a polymer having a weight average molecular mass of at least 150,000 g/mol. The molecular mass herein refers to the particular viscosimetric molecular weight. For example, the polymer may be a polymer or copolymer of a methacrylic ester. According to a particularly preferred embodiment, the at least one polymer is selected from the group consisting of polymethyl methacrylate (PMMA), polymethyl methacrylate ester (PMAE) polymethyl methacrylate propyl ester (PMAP), polymethacrylic acid isopropyl ester, poly(methyl methacrylate-co-methyl acrylate) and poly (styrene-co-methyl methacrylate). However, the polymer may be also selected from the group consisting of polyethylene, polypropylene or polybutadiene. The polymer may also be crosslinked or uncrosslinked, wherein crosslinked polymers are especially preferred. The crosslinking is preferably carried out with a difunctional compound. The difunctional compound may, for example, be selected from the group consisting of alkylene glycol methacrylates. For example, ethylene glycol dimethacrylate has proven itself as a crosslinker.

The inorganic salt used as the filler (a4) or (b4) may be a soluble or insoluble salt in a radically polymerisable monomer (a1) or (b1). Preferably the inorganic salt is a salt of an

element selected from the second main group of the Periodic Table of Elements. According to a preferred embodiment, the inorganic salt is a salt of calcium, strontium or barium. According to a particularly preferred embodiment, the inorganic salt is calcium sulfate, barium sulfate or calcium carbonate.

The inorganic oxide used as the filler (a4) or (b4) may preferably be a metal oxide. According to a preferred embodiment, the inorganic oxide is an oxide of the transition metals. According to a particularly preferred embodiment, the inorganic oxide is titania or zirconia.

The metal used as the filler (a4) or (b4) may be, for example, a transition metal. According to a preferred embodiment, the metal is tantalum or tungsten.

The metal alloy used as the filler (a4) or (b4) is an alloy of at least two metals. Preferably, the alloy contains at least one transition metal. According to a particularly preferred embodiment, the alloy contains at least tantalum or tungsten. The alloy may also be an alloy of tantalum and tungsten.

The filler (a4) or (b4) in the radically polymerisable monomer (a1) or (b1) is insoluble. According to the invention, the filler (a4) or (b4) in the radically polymerisable monomer (a1) or (b1) is insoluble when the filler (a4) or (b4) at a temperature of 25 °C, has a solubility in the radically polymerisable monomer (a1) or (b1) of less than 50 g/l, preferably less than 25 g/l, more preferably less than 10 g/l and even more preferably less than 5 g/l.

According to the invention, it is particularly preferred that the at least one insoluble polymer in (a1) or (b1) is selected from the group consisting of crosslinked poly(methyl methacrylate-co-methyl acrylate), cross-linked poly (methyl methacrylate) or a mixture of these two polymers.

Further, according to the invention, the paste A, the paste B or the paste A and paste B, but more preferably the paste A and the paste B, contain(s) a soluble polymer (a5) or (b5) in (a1) or (b1). According to the invention, this polymer (a5) or (b5) is soluble in the polymerisable monomer contained in the paste, in which the soluble polymer is also contained, when the polymer in this polymerisable monomer is dissolved to at least 10 g/l, preferably to at least 25 g/l, more preferably to at least 50 g/l and very particularly preferably to at least 100 g/l. The soluble polymer (a5) or (b5) in the polymerisable monomer (a1) or (b1) may be a homopolymer or a copolymer. This polymer (a5) or (b5) is

preferably a polymer having a weight average molecular weight of at least 150,000 g/mol. For example, the polymer (a5) or (b5) may be a polymer or copolymer of a methacrylic ester. According to a particularly preferred embodiment, the at least one polymer (a5) or (b5) is selected from the group consisting of polymethyl methacrylate (PMMA), polymethyl methacrylate ester (PMAE) polymethyl methacrylate propyl ester (PMAP), polymethacrylic acid isopropyl ester, poly(methyl methacrylate-co-methyl acrylate) and poly (styrene-co-methyl methacrylate).

The amount of the soluble polymer (a5) and (b5) in the radically polymerisable monomer (a1) or (b1) in the paste containing this polymer, depends on whether the corresponding paste contains an insoluble filler (a4) or (b4) in the radically polymerisable monomer (a1) or (b1). Usually, the amount of the soluble polymer (a5) and (b5) in the radically polymerisable monomer (a1) or (b1) in the paste contains this polymer, in a range from 1 to 85 wt .-%, based on the total weight of the paste, which contains this soluble polymer.

In addition to the above-described constituents, the pastes A and B may comprise further components. These other components may be contained in either paste A, or paste B or in the paste A and paste B.

According to a preferred embodiment, at least one of the pastes A and B contains at least an opacifier. The opacifier may be a customary opacifier. Suitable opacifiers may be insoluble or soluble in the radically polymerisable monomer (a1) or the radically polymerisable monomer (b1). The opacifier is preferably selected from the group consisting of metal oxides (such as zirconia), barium sulfate, toxicologically acceptable heavy metal particles (such as tantalum), ferrite, magnetite (possibly supra magnetic magnetite) and biocompatible calcium salts. This opaquer preferably has an average particle diameter ranging from 10 nm to 500 µm. Esters of 3,5-bis(acetamido)-2,4,6-triiodobenzoic, gadolinium compounds such as gadolinium chelate with the esters of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra acetic acid (DOTA), may also be considered as opacifiers.

According to a further preferred embodiment, at least one of the pastes A and B contains at least one dye. The dye may be a conventional dye and preferably a food dye. Furthermore, the dye in the at least one radically polymerisable monomer (a1) or in the at least one radically polymerisable monomer (a2) may be soluble or insoluble. In a

particularly preferred embodiment, the dye is selected from the group consisting of E101, E104, E132, E141 (chlorophyllin), E142, riboflavin and lissamine. The term dye according to the invention also includes color coatings, for example the green color coating wherein the aluminum salt is a mixture of E104 and E132.

According to a further preferred embodiment, there is at least one active pharmaceutical ingredient in at least one of the pastes A and B. The at least one active pharmaceutical ingredient may be contained in at least one of the pastes A and B in dissolved or suspended form.

The pharmaceutical ingredient may preferably be selected from the group consisting of antibiotics, antiphlogistics, steroids, hormones, growth factors, bisphosphonates, and cytostatic gene vectors. According to a particularly preferred embodiment, at least one of the active pharmaceutical ingredients is an antibiotic.

The at least one antibiotic is preferably selected from the group consisting of aminoglycoside antibiotics, glycopeptide antibiotics, lincosamide antibiotics, gyrase inhibitors, carbapenems, cyclic lipopeptides, glycylcyclines, oxazolidones and polypeptide antibiotics.

According to a particularly preferred embodiment, the at least one antibiotic is selected from the group consisting of gentamicin, tobramycin, amikacin, vancomycin, teicoplanin, dalbavancin, lincosamides, clindamycin, moxifloxacin, levofloxacin, ofloxacin, ciprofloxacin doripenem, meropenem, tigecycline, linezolid, eperezolid, ramoplanin, metronidazole, tinidazole, imidazol and colistin and salts and esters thereof.

Accordingly, the at least one antibiotic can be selected from the group consisting of gentamicin sulfate, gentamicin hydrochloride, amikacin sulfate, amikacin hydrochloride, tobramycin sulfate, tobramycin hydrochloride, clindamycin hydrochloride, lincosamin hydrochloride and moxifloxacin.

The at least one anti-inflammatory agent is preferably selected from the group consisting of NSAIDs and glucocorticoids. According to a particularly preferred embodiment, the at least one anti-inflammatory agent is selected from the group consisting of acetylsalicylic acid, ibuprofen, diclofenac, ketoprofen, dexamethasone, prednisone, hydrocortisone, hydrocortisone acetate and fluticasone.

The at least one hormone is preferably selected from the group consisting of serotonin, somatotropin, testosterone and estrogen.

The at least one growth factor is preferably selected from the group consisting of the *Fibroblast Growth Factor* (FGF), the *Transforming Growth Factor* (TGF), the *Platelet Derived Growth Factor* (PDGF), the *Epidermal Growth Factor* (EGF), the *Vascular Endothelial Growth Factor* (VEGF), the *Insulin-Like Growth Factors* (IGF), the *Hepatocyte Growth Factor* (HGF), the *Bone Morphogenetic Protein* (BMP), interleukin-IB, interleukin 8 and the nerve growth factor.

The at least one cytostatic agent is preferably selected from the group consisting of alkylating agents, platinum analogs, intercalating agents, mitosis inhibitors, taxanes, topoisomerase inhibitors, and antimetabolites.

The at least one bisphosphonate is preferably selected from the group consisting of zoledronate and aledronate.

According to a further preferred embodiment, at least one of the pastes A and B contains at least one biocompatible elastomer. The biocompatible elastomer is preferably particulate. Preferably, the biocompatible elastomer is soluble in the at least one radically polymerisable monomer (a1) or in the at least one radically polymerisable monomer (b1). The use of polybutadiene has proven particularly suitable as a biocompatible elastomer.

According to a further preferred embodiment, at least one of the pastes A and B contains at least one monomer with adhesive groups. The adhesive group may be, for example, an amide group. The monomer with adhesive group may therefore be, for example, methacrylamide. The use of at least one monomer with adhesive groups can favorable influence the binding of the bone cement in joint endoprostheses.

According to a further preferred embodiment, at least one stabiliser is contained in at least one of the pastes A and B. The stabiliser should be capable of preventing a spontaneous polymerisation of the radically polymerisable monomers contained in the pastes A and B (a1) and (b1). In addition, the stabiliser should present no interfering interactions with the other components contained in the pastes. Such stabilisers are known from the prior art. According to a preferred embodiment, the stabiliser is 2,6-di-tert-butyl-4-methylphenol and/or 2,6-di-tert-butyl-phenol.

According to a first particular embodiment of the inventive kit, the kit is an "asymmetric" kit. In this context, it is preferable that the paste A contains 20 to 70 wt .-%, preferably 25 to 60 wt .-%, more preferably 30 to 55 wt .-% and most preferably 34 to 47 wt .-% based on the total weight of paste A, of the insoluble filler (a4) in (a1), while paste B

contains less than 5 wt .-%, preferably less than 1 wt .-%, more preferably less than 0.1 wt .-%, and more preferably less than 0.01 wt .-%, each based on the total weight of paste B, of the insoluble filler (b4) in (b1), wherein it is most preferable the paste B in general does not contain any insoluble filler (b4) in (b1).

Furthermore, it is preferred in connection with this first particular embodiment of the kit of the invention that paste A contains a soluble polymer (a5) in (a1) in an amount in a range from 1 to 25 wt .-%, preferably in a range from 2 to 20 wt .-%, more preferably in a range from 2 to 18 wt .-% and most preferably in a range from 3 to 16 wt .-%, each based on the total weight of the paste A, while paste B contains a soluble polymer (b5) in (b1) in an amount in a range from 25 to 85 wt .-%, preferably in a range from 35 to 85 wt .-%, more preferably in a range from 40 to 80 wt .-%, and most preferably in a range of 50 to 75 wt .-%, each based on the total weight of paste B.

Furthermore, it is preferred in connection with this first particular embodiment of the kit of the invention, that the weight ratio of insoluble filler (b4) in (b1) to the at least one soluble polymer (b5) in (b1) is at most 0.2, preferably at most 0.15, more preferably at most 0.1, even more preferably at most 0.05, particularly preferably at most 0.02, and most preferably 0.

According to a second special embodiment of the inventive kit, the kit is a "symmetrical" kit. In this context, it is preferable that the paste A contains 15 to 85 wt .-%, preferably 15 to 80 wt .-%, and more preferably 20 to 75 wt .-%, each based on the total weight of the paste A, of the insoluble filler (a4) in (a1), while paste B contains 15 to 85 wt .-%, preferably 15 to 80 wt .-%, and more preferably 20 to 75 wt .-%, each based on the total weight of paste B, of the insoluble filler (b4) in (b1).

Furthermore, it is preferred in connection with this second particular embodiment of the kit of the invention, that paste A contains a soluble polymer (a5) in (a1) in an amount in a range from 5 to 50 wt .-%, preferably in a range from 10 to 40 wt.% and more preferably in a range from 20 to 30 wt .-%, each based on the total weight of the paste A, and/or paste B contains a soluble polymer (b5) in (b1) in an amount in a range from 5 to 50 wt .-%, preferably in a range from 10 to 40 wt .-% and more preferably in a range from 20 to 30 wt .-%, each based on the total weight of the paste B.

According to the invention, the kit, which contains at least the pastes A and B, is used for the preparation of bone cement.

For this purpose, the at least two pastes A and B are mixed with one another, whereby again a paste, paste C, is obtained.

The mixing ratio is preferably 0.5 to 1.5 parts by weight of paste A and 0.5 to 1.5 parts by weight of paste B. According to a particularly preferred embodiment, the proportion of the paste A is 30 to 70 wt .-% and the proportion of paste B is 30 to 70 wt .-%, based on the total weight of the pastes A and B.

The mixing can be carried out using conventional mixing equipment, for example a static mixer or a dynamic mixer.

The mixing can be done under vacuum. However, the use of the inventive initiator system also allows for the vacuum-free mixing of the pastes A and B without impairing the properties of the bone cement.

After mixing the pastes of the kit, the paste C eventually obtained according to ISO 5833 is tack-free and can be processed immediately.

The bone cement resulting from the curing of paste C achieves high strength about 3 to 15 minutes after the mixing of the pastes contained in the kit.

The invetive kit can be used in a preferred embodiment for the mechanical fixation of joint prostheses, for covering cranial defects, for filling bone cavities, for femoroplasty, for vertebroplasty, for kyphoplasty, for the production of spacers and for the preparation of support materials for local antibiotic therapy.

By the term "*spacer*" according to the invention is meant implants to be used temporarily as placeholders as part of the two-stage prosthetic replacement in septic revisions.

Carrier materials for local antibiotic therapy may be formed as spheres or sphere-like bodies or as a bean-shaped body. In addition, it is also possible to produce rod-shaped or disc-shaped carrier materials to receive the bone cement prepared by the inventive kit for the production of bone cement. Furthermore, the carrier materials may be strung in beads on absorbable or non-absorbable suture material.

The uses of bone cement described above and according to the invention are known from the literature and widely described there.

According to the invention, the kit is used for the applications described above, preferably by mixing a paste from the pastes contained in the kit, and using it analogously to pastes known from the prior art for the described applications.

A contribution towards achieving the above-mentioned objects is also obtained in the form of a molded article through polymerisation according to the invention, or through the polymerisation of a paste by mixing the paste A and paste B of the inventive kit. Molded bodies according to the present invention may be any three-dimensional body, in particular the above-described "spacer".

The invention is illustrated by the examples described below.

EXAMPLES

The pastes A of the examples A1-21 were prepared by simple mixing of the components. The pastes thus formed were then stored overnight at room temperature.

Paste A

| | Composition of the pastes A | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Example No. | CH [g] | BH [g] | EG [g] | MA [g] | MMA [g] | PL 1 [g] | PL2 [g] | $ZrO_2$ [g] | Stab [mg] |
| A1 | 0,50 | 0,8 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A2 | 0,50 | 1,0 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A3 | 0,50 | 1,2 | 0,4 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A4 | 0,10 | 1,2 | 0,4 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A5 | 0,10 | 1,2 | 0,7 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A6 | 0,10 | 1,2 | 1,0 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A7 | 0,10 | 1,2 | 1,0 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A8 | 0,05 | 1,2 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A9 | 0,05 | 2,0 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A10 | 0,10 | 2,0 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A11 | 0,05 | 1,2 | 0,7 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A12 | 0,05 | 0,6 | 0,7 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A13 | 0,05 | 1,2 | 1,3 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A14 | 0,20 | 2,0 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |

CH: cumene hydroperoxide

BH: N,N-bis (2-hydroxyethyl)-p-toluidine

EC: ethylene glycol methacrylate

MA: methacrylamide

MMA: methyl methacrylate

PL1: linear poly(methyl methacrylate-co-methyl acrylate) Mw <500,000 g/mol

PL2: particulate, insoluble, crosslinked polymethyl methacrylate

ZrO2: zirconia

Rod: 2,6-di-t-butyl-4-methylphenol

**Paste A**

| Example No. | CH [g] | BH [g] | DM [g] | EG [g] | MA [g] | MMA [g] | PL1 [g] | PL2 [g] | $ZrO_2$ [g] | Stab [mg] |
|---|---|---|---|---|---|---|---|---|---|---|
| A15 | 0,05 | 1,6 | 0,4 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A16 | 0,05 | 0,8 | 0,4 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A17 | 0,10 | 1,6 | 0,4 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A18 | 0,05 | 1,4 | 0,6 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A19 | 0,05 | 1,2 | 0,8 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A20 | 0,05 | 1,4 | 0,6 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |
| A21 | 0,05 | 1,4 | 0,6 | 0,1 | 0,4 | 17,7 | 5,6 | 15,5 | 4,8 | 20 |

CH: cumene hydroperoxide

BH: N,N-bis (2-hydroxyethyl)-p-toluidine

DM: N,N-dimethyl-p-toluidine

EC: ethylene glycol methacrylate

MA: methacrylamide

MMA: methyl methacrylate

PL1: linear poly(methyl methacrylate-co-methyl acrylate) Mw <500,000 g/mol

PL2: particulate, insoluble, crosslinked polymethyl methacrylate

ZrO2: zirconia

Rod: 2,6-di-t-butyl-4-methylphenol

The pastes of examples B1-B21 were also prepared by simple mixing of the components. The pastes formed were then stored overnight at room temperature.

**Paste B**

| | Composition of the pastes B | | | | | |
|---|---|---|---|---|---|---|
| Example No. | SAC [g] | CuOct [mg] | MMA [g] | PL1 [g] | Gentamicin-sulfat [g] | Stab [mg] |
| B1 | 1,0 | 25 | 21,2 | 17,5 | - | 35 |
| B2 | 1,0 | 25 | 21,2 | 17,5 | - | 35 |
| B3 | 1,0 | 40 | 21,2 | 17,5 | - | 35 |
| B4 | 1,0 | 40 | 21,2 | 17,5 | - | 35 |
| B5 | 1,0 | 45 | 21,2 | 17,5 | - | 35 |
| B6 | 1,0 | 45 | 21,2 | 17,5 | - | 35 |
| B7 | 1,0 | 45 | 21,2 | 17,5 | - | 35 |
| B8-B19 | 1,0 | 55 | 21,2 | 17,5 | -- | 35 |
| B20 | 1,0 | 55 | 21,2 | 17,5 | 1,2 | 35 |
| B21 | 1,0 | 55 | 21,2 | 17,5 | 2,4 | 35 |

| | |
|---|---|
| SAC: | Saccharin |
| CuOct: | copper (II)-2-ethylhexanoate |
| MMA: | methyl methacrylate |
| PL1: | linear poly(methyl methacrylate-co-methyl acrylate) Mw < 500,000 g/mol |
| Rod: | 2,6-di-t-butyl-4-methylphenol |

The pastes A and B of examples A1-21 and B1-21 were mixed together in the weight ratio of 1: 1. Tack-free pastes C were immediately produced, and cured after 4-15 minutes.

With the pastes C (weight ratio of 1 to 1 of paste A to paste B) produced from the pastes A and B of examples 1-21, strip-shaped test specimens with the dimensions (75 mm x 10 mm x 3.3 mm) were produced for the determination of flexural strength and flexural modulus, and cylindrical bodies (diameter 6 mm, height 12 mm) were produced for the determination of compressive strength. The specimens were then stored in air for 24 hours at 23 ± 1 °C. Thereafter, the 4-point flexural strength, the flexural modulus and the compressive strength of the test specimens were determined with a Zwick universal testing machine.

| Pastes C | Pastes C | Composition of the pastes C | 4-point flexural strength [MPa] | Compressive strength [MPa] | Flexural modulus [MPa] |
|---|---|---|---|---|---|
| P1225 | C1 | A1 + B1 | 60,1 ± 3,7 | 2346 ± 183 | 81,2 ± 6,0 |
| P1227 | C2 | A2 + B2 | 60,9 ± 3,5 | 2409 ± 113 | 92,4 ± 3,7 |
| P1232 | C3 | A3 + B3 | 62,8 ± 2,2 | 2484 ± 26 | 88,2 ± 4,0 |
| P1233 | C4 | A4 + B4 | 62,9 ± 2,6 | 2509 ± 86 | 89,7 ± 3,7 |
| P1234 | C5 | A5 + B5 | 64,7 ± 1,3 | 2593 ± 74 | 93,6 ± 3,2 |
| P1235 | C6 | A6 + B6 | 64,6 ± 1,5 | 2533 ± 25 | 94,3 ± 2,3 |
| P1236 | C7 | A7 + B7 | 60,9 ± 3,7 | 2362 ± 96 | 95,1 ± 2,0 |
| P1238 | C8 | A8 + B8 | 60,4 ± 1,5 | 2380 ± 52 | 91,5 ± 2,3 |
| P1240 | C9 | A9 + B9 | 60,2 ± 0,6 | 2407 ± 27 | 86,7 ± 4,0 |
| P1242 | C10 | A10 + B10 | 64,3 ± 1,1 | 2667 ± 103 | 100,8 ± 3,4 |
| P1244 | C11 | A11 + B11 | 60,2 ± 1,8 | 2470 ± 43 | 89,2 ± 2,9 |
| P1245 | C12 | A12 + B12 | 58,7 ± 1,3 | 2382 ± 38 | 78,1 ± 3,7 |
| P1246 | C13 | A13 + B13 | 55,0 ± 1,8 | 2186 ± 96 | 89,1 ± 4,1 |
| P1248 | C14 | A14 + B14 | 63,5 ± 0,8 | 2473 ± 26 | 88,8 ± 5,8 |
| P1249 | C15 | A15 + B15 | 57,6 ± 1,9 | 2229 ± 100 | 85,0 ± 3,0 |
| P1250 | C16 | A16 + B16 | 67,8 ± 2,6 | 2618 ± 94 | 97,6 ± 4,0 |
| P1251 | C17 | A17 + B17 | 67,1 ± 3,0 | 2969 ± 131 | 92,6 ± 3,1 |
| P1252 | C18 | A18 + B18 | 65,0 ± 1,7 | 2462 ± 67 | 91,7 ± 1,3 |
| P1253 | C19 | A19 + B19 | 67,1 ± 2,6 | 2569 ± 100 | 85,1 ± 2,6 |
| P1254 | C20 | A20 + B20 | 58,1 ± 2,2 | 2278 ±93 | 80,1 ± 2,8 |
| P1255 | C21 | A21 + B21 | 54,4 ± 2,5 | 2272 ± 68 | 80,4 ± 1,7 |

In addition, other pastes B were prepared analogously to the paste B20 but with vancomycin hydrochloride, clindamycin, daptomycin and octenidine instead of gentamicin sulfate. After mixing these pastes B with the paste A20 in a weight ratio of 1 to 1, the mixed pastes C exhibited a similar curing behavior to that of the combination of the paste A20 with the paste B20 in a weight ratio of 1: 1.

In addition, pastes using barium sulfate instead of zirconia were prepared. These pastes had a similar curing behavior to that of the pastes C produced from pastes A1-21 and B1-21.

Furthermore, pastes A were also prepared analogously to example A1 using t-butyl hydroperoxide, t-amyl hydroperoxide and dicumyl peroxide in place of cumene hydroperoxide. After mixing these pastes A with the paste B1 in a weight ratio of 1 to 1, the

mixed pastes showed a similar behavior to the combination of the pastes A1 with the paste B1.

**KNOGLECEMENT I PASTAFORM**

PATENTKRAV:

1. Knoglecementkit, som omfatter en pasta A og en pasta B, hvor

(a) pasta A indeholder

(a1) mindst én monomer til radikalpolymerisation, som har et kogepunkt på mindre end 120°C ved et tryk på 1.013 mbar,

(a2) mindst ét peroxid som polymerisationsinitiator og

(a3) mindst én tertiær amin, mindst én amidin eller en blanding af mindst én tertiær amin og mindst én amidin som co-polymerisationsaccelerator, og

(b) pasta B indeholder

(b1) mindst én monomer til radikalpolymerisation, som har et kogepunkt på mindre end 120°C ved et tryk på 1.013 mbar,

(b2) mindst én tungmetalforbindelse som polymerisationsaccelerator og

(b3) mindst ét sulfimid, mindst ét dicarboxylsyreimid eller en blanding af mindst ét sulfimid og mindst ét dicarboxylsyreimid som co-polymerisationsaccelerator,

hvor mindst én af pastaerne A og B som bestanddel (a4) og/eller (b4) indeholder mindst ét fyldstof, som er uopløseligt i (a1) og/eller (b1).

2. Kit ifølge krav 1, hvor den mindst ene monomer til radikalpolymerisation (a1) og/eller (b1) er en methacrylatmonomer.

3. Kit ifølge krav 1 eller 2, hvor pasta A og pasta B indeholder en mængde af den mindst ene monomer til radikalpolymerisation (a1) og/eller (b1) i intervallet fra 15 til 85 vægtprocent, hver i forhold til den samlede vægt af pasta A og/eller pasta B.

4. Kit ifølge et hvilket som helst af de foregående krav, hvor det mindst ene peroxid (a2) har en halveringstid på > 10 timer ved 70°C.

5. Kit ifølge krav 4, hvor det mindst ene peroxid (a2) er valgt fra gruppen bestående af cumen-hydroperoxid, 1,1,3,3-tetramethylbutyl-hydroperoxid, t-butyl-hydroperoxid, t-amyl-hydroperoxid, di-isopropylbenzen-mono-hydroperoxid, di-t-butyl-peroxid, dicumylperoxid og t-butylcumylperoxid.

6. Kit ifølge et hvilket som helst af de foregående krav, hvor pasta A indeholder en mængde af det mindst ene peroxid (a2) i intervallet fra 0,01 til 10 vægtprocent, hver i forhold til den samlede vægt af pasta A.

7. Kit ifølge et hvilket som helst af de foregående krav, hvor den mindst ene tertiære amin (a3) er valgt fra gruppen bestående af tributylamin, triethanolamin, N,N-dimethyl-p-toluidin, N,N-bis(2-hydroxy-ethyl)-p-toluidin og N,N-dimethyl-anilin.

8. Kit ifølge et hvilket som helst af de foregående krav, hvor den mindst ene amidin (a3) er valgt fra gruppen bestående af 1,8-diazabicyclo[5.4.0]undec-7-en og 1,5-diazabicyclo[4.3.0]on-5-en.

9. Kit ifølge et hvilket som helst af de foregående krav, hvor pasta A indeholder en mængde af co-polymerisationsacceleratoren (a3) i intervallet fra 0,1 til 20 vægtprocent, hver i forhold til den samlede vægt af pasta A.

10. Kit ifølge et hvilket som helst af de foregående krav, hvor den mindst ene tungmetalforbindelse (b2) er valgt fra gruppen bestående af kobber(II)hydroxid, kobber(II)metharylat, kobber(II)acetylacetonat, kobber(II)-2-ethylhexanoat, cobalt(II)hydroxid, cobalt(ll)-2-ethylhexanoat og basisk kobber(ll)carbonat.

11. Kit ifølge et hvilket som helst af de foregående krav, hvor pasta B indeholder en mængde af den mindst ene tungmetalforbindelse (b2) i intervallet fra 0,0005 til 0,5 vægtprocent, i forhold til den samlede vægt af pasta B.

12. Kit ifølge et hvilket som helst af de foregående krav, hvor det mindst ene sulfimid (b3) er saccharin.

13. Kit ifølge et hvilket som helst af de foregående krav, hvor det mindst ene dicarboxylsyreimid (b3) er phthalimid, maleimid eller succinimid.

14. Kit ifølge et hvilket som helst af de foregående krav, hvor pasta B indeholder en mængde af co-polymerisationsacceleratoren (b3) i intervallet fra 0,1 til 10 vægtprocent, i forhold til den samlede vægt af pasta B.

15. Kit ifølge et hvilket som helst af de foregående krav, hvor det mindst ene fyldstof (a4) og/eller (b4), som er uopløseligt i (a1) og/eller (b1), er en partikelformig polymer.

16. Kit ifølge et hvilket som helst af de foregående krav, hvor det mindst ene fyldstof (a4) og/eller (b4), som er uopløseligt i (a1) og/eller (b1), er en uopløselig polymer valgt fra gruppen bestående af tværbundet poly(methylmethacrylat-co-methylacrylat), tværbundet poly(methyl-methacrylat) og en blanding af de to polymerer.

17. Kit ifølge et hvilket som helst af de foregående krav, hvor pasta A, pasta B eller pasta A og pasta B indeholder en polymer (a5) og/eller (b5), som er opløselig i (a1) og/eller (b1).

18. Kit ifølge et hvilket som helst af de foregående krav, hvor polymeren (a5) og/eller (b5), som er opløselig i (a1) og/eller (b1), er valgt fra gruppen bestående af poly(methacrylsyremethylester), poly(methacrylsyreethylester), poly(methylmethacrylsyrepropylester), poly(methacrylsyre-isopropylester), poly(methylmethacrylat-co-methacrylat) og poly(styren-co-methyl-methacrylat).

19. Anvendelse af et kit ifølge et hvilket som helst af de foregående krav til fremstilling af en knoglecementpasta til mekanisk fiksering af ledproteser, til dækning af kraniedefekter, til udfyldning af knoglekaviteter, til femurplastik, til vertebroplastik, til kyphoplastik, til fremstilling af spacere og til fremstilling af bæremateriale til lokal antibiotikaterapi.

20. Formlegeme, som er opnået ved polymerisation af en pasta, der kan opnås ved at blande pasta A og pasta B fra knoglecementkittet, som defineret ifølge et hvilket som helst af kravene 1-18.