

Description

The invention relates to a new material capable of being implanted into a living tissue, in particular osseous tissue. It is intended to provide a material having a rate of biodegradation adapted to the regeneration of the tissue and capable of being associated, if required, with an active substance so as to produce a prolonged therapeutic effect.

Materials or matrices for implantation into the living tissues, in particular osseous tissues, are known, by means of which it is possible to make good a tissue "defect" and to release an active substance if this is required. The implantation matrices can currently be classified in four categories.

In the first place there exist non-biodegradable matrices such as certain polymers (e.g. polymethylmethacrylate PMMA), which are used with a view to releasing active substances locally and thus avoiding their administration by systemic means. These matrices have the disadvantage of necessitating an additional surgical intervention in order to extract them once the active substance has been released (patent FR 74 13342). Moreover, a very small fraction of the initial active substance is released (about 6 %).

Other older matrices such as matrices based on calcium sulphate are biodegradable but their rate of degradation is fixed and cannot be adapted to the rate of regeneration of the tissue in question; since their degradation generally takes place at a rate which is too high for osseous tissues they frequently entail the occurrence of "defects" in said tissues. They also have the disadvantage of not promoting regeneration of the tissue.

Another type of implantation matrix is constituted by the polylactic-glycolic PLGA matrices, which, due to relative dosing of the two components, have the advantage of enabling some modulation of their rate of degradation so as to adapt the latter to the rate of regeneration of the

tissue in question. However, these matrices do not have any favourable effect on regeneration of the tissues and a more serious drawback is that they bring about inflammatory reactions due to depolymerisation in the course of
5 degradation (formation of acids).

Other polymers have been used for sealing the femoral canal or the bottom of the cotyle in order to avoid leakage of the osseous cement present in the medullary canal when performing an arthroplasty (patent FR-A-2 570 606). However,
10 the materials provided are not intended to replace the osseous tissue itself, their only function being to act as a sealing medium. Moreover, the time available for biodegradation is very short since they are required to remain in position only until the cement has hardened. As
15 with the aforementioned PLGA matrices, this type of material does not permit any modulation of the rate of degradation where a lengthy biodegradation time is required and does not have any favourable effect on regeneration of the tissues.

The latter category of implantation matrices is
20 constituted by matrices on the basis of tricalcic or apatitic phosphate, the cohesion of which is ensured either by sintering (porous ceramic as provided in patent DE 2 807 132) or by a binding agent such as collagen or elastin (patent DE 3 206 726). These matrices promote
25 osseous regeneration but their rate of biodegradability is very slow and cannot be modulated. This being the case, they inhibit normal reconstitution of the tissues in spite of their positive effect on osteogenesis. Moreover, when they are associated with an active substance of soluble type such
30 as gentamycine sulphate, they cause excessively rapid release of said substance, which is a major disadvantage as regards highly toxic substances and/or in cases in which a treatment necessitates prolonged application. In order to alleviate these disadvantages, the active substance is in
35 some cases converted into a salt of low solubility (such as hesperidin phosphate as cited in patent DE 3 206 706): owing to the fact that the product is made to some extent

hydrophobic, its release in situ is thus retarded but at the start of implantation said release remains very low and becomes effective only after a considerable time, which is a serious disadvantage when treating an ailment.

5 Furthermore, the patent EP 0 147 021 describes a liquid medicinal preparation (aqueous suspension) which can be introduced into the cavity of a bone by means of a drain tube in order to perform local treatment of an ailment (osteomyelitis) by releasing the active substance. However,
10 this is not an implantation material capable of temporarily replacing the tissue but a simple solution devoid of any mechanical characteristic, the sole function of which is to release the active substance locally and then to eliminate itself. Moreover, said active substance is released
15 immediately, without in any way acting over a period of time.

The present invention is intended to provide a new implantable material of the type based on calcium phosphate, having perfect biocompatibility and capable of promoting
20 osteogenesis without any detrimental reaction such as an inflammatory reaction; the principal object of the invention is to provide an implantable material possessing mechanical characteristics which enable it to substitute itself temporarily for the defective tissue while having a rate of
25 biodegradation adjusted to the rate of regeneration of said tissue.

Another object of the invention consists in associating the aforementioned material with an active substance endowed with groups that are appropriate to ensure
30 progressive release of said substance so as to give rise to a prolonged therapeutic effect.

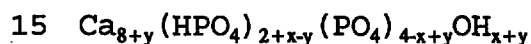
Another object consists in providing an implantation material which can be readily manufactured without heat by compaction of its various constituents.

35 To this end the process according to the invention for manufacturing the aforementioned implantable material

consists in mixing a calcium phosphate with a biodegradable oxide or polyoxide, and is characterised in that:

- . a calcium phosphate of apatitic or triclinic structure is selected which contains both HPO_4 and PO_4 groups,
- . a proportion of oxide or polyoxide is mixed, said proportion being the larger, the higher the desired rate of degradation of the material.

The calcium phosphate used may contain different cationic calcium substituents (magnesium, sodium) or anionic phosphate ion substituents (carbonates) or hydroxyl ion substituents (chlorine); it may also be non-substituted and correspond to the formula:



where $0 \leq y \leq 2$ and $0 \leq x < 1$.

The calcium phosphate of the aforementioned type and the oxide or polyoxide are preferably mixed in the form of powder and then compacted to a predetermined shape. The implants thus produced can be installed within the tissue, especially osseous tissue, after producing a receptacle adapted to the location of the "defect", or effectively immobilised within an existing cavity of the tissue with the aid of a biodegradable cement such as calcium sulphate or a phosphate-based cement.

In the light of the tests it has been possible to establish that the time in which the implantable material according to the invention is degraded varies between several days (3 to 4 days) and a much longer time of the order of several months (10 to 12 months) depending on the proportion of oxide or polyoxide admixed to the phosphate. Use may be made of different oxides or polyoxides, with the degradation times increasing in proportion to the molecular weight of this compound; it is thus possible to modulate the rate of biodegradation by appropriate selection of the oxide or polyoxide and by adjusting its proportion in relation to

the phosphate. By way of polyoside, use may in particular be made of dextran, the proportion of the latter being modulated between 1 % and 30 % as a function of the desired rate of degradation; inasmuch as said rate increases with the proportion of dextran, the amounts of dextran admixed to the phosphate are therefore the larger, the shorter one wishes the degradation times to be.

Furthermore, the implantable material according to the invention may be associated with an active substance capable of producing a desired therapeutic effect. According to one characteristic of the invention an active substance is selected which comprises amine groups enabling its attachment to the calcium phosphate endowed with HPO_4 and PO_4 groups.

Hence the three constituents of the material according to the invention cooperate so as to bring about progressive release of the active substance. It has been possible to show that the attachment of the active substance to the phosphate is linked to the simultaneous presence of HPO_4 and PO_4 groups, probably by adsorption owing to the amine groups of said substance, said attachment being such as to then result in a progressive release of said substance at the site of implantation. Surprisingly, the tests have made it possible to show that the presence of osides or polyosides has the property of regularising said release, thus making it possible to achieve immediately effective rates and to prolong the release for several weeks at a substantially constant rate. (A contrary effect might have been expected, seeing that osides and polyosides are highly soluble compounds).

It should be stressed, moreover, that in the process of compacting the material the osides or polyosides act as plastifiers considerably improving its cohesion; this seems to be due to the fact that the presence of said compound entails a considerable increase in the size of the phosphate granules, which promotes cohesion; this phenomenon of granule-size enlargement makes it possible to explain, at

least partly, the reduction and regularisation of the rate of release of the active substance; within large granules it is more difficult for this substance, which is fixed due to the HPO_4 and PO_4 groups of the phosphate, to detach itself; moreover, the reduction of the specific surface of the granules as their size increases contributes to a reduction in the kinetics of dissolution at the granular interfaces.

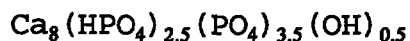
To summarise, the retarding effect and its characteristics (substantially constant rate of release and action over a longer period of time) are, according to the invention, achieved by attachment of the active substance to the matrix; this substance, which is preferably present in soluble form, is released by rupture of its bonds or interactions, with the oside or polyoside exerting a positive influence on the strength of said bonds or interactions. (On the other hand, according to the aforementioned patent DE 3 206 726, the matrix is inert with respect to the active substance and the retarded action of the medicament is due to the insoluble form imparted to the active substance).

The calcium phosphate, the active substance and the oside or polyoside are preferably mixed in the form of powder and compacted; at the usual compacting pressures this readily applicable compacting process confers upon the material a high degree of cohesion; the material can therefore be manufactured without heat and without modifying the active substance (which is generally sensitive to heat).

According to one preferred form of the material the phosphate selected is an apatitic octacalcic phosphate with the formula:

$\text{Ca}_8(\text{HPO}_4)_{2+x}(\text{PO}_4)_{4-x}(\text{OH})_x$, where $0 < x < 1$. This phosphate is the one having the highest number of HPO_4 groups per formula unit; within the scope of the invention, it provides the optimal characteristics (improved attachment of the active substance per unit mass of material, improved galenic properties). Good results are obtained by selecting for the parameter x a value of the order of 0.5 (within

about $\pm 20\%$), the formula of the material used then being approximately as follows:



5

It is known per se how to manufacture such phosphates; examples are given below together with the references of publications describing the manufacturing processes.

The mixed active substance advantageously takes the
10 form of a soluble salt, in particular in the case of netilmicine and/or gentamycine the form of a sulphate (which is the most soluble type); these substances are used very frequently in connection with bone diseases owing to their wide range of efficacy.

15 By way of non-restrictive example the material according to the invention may consist of a mixture of apatitic octacalcic phosphate with the above formula (parameter x close to 0.5), dextran, netilmicine and/or gentamycine in the form of a sulphate, in the following
20 proportions:

- . the proportion by weight of dextran amounts to between 1 % and 30 % in relation to the mixture (as a function of the desired rate of biodegradation).
- . the proportion by weight of active substance amounts
25 to between 0.1 % and 30 % in relation to the mixture (as a function of the activity of the substance and its desired effects).

The following description presents examples of implantation materials according to the invention and
30 illustrates their galenic, pharmacokinetic and physiological properties as well as the evolution of the latter as a function of the composition.

EXAMPLE 1Preparation of OCPa phosphate

5 100g of octacalcic phosphate of apatitic structure
with the formula $\text{Ca}_8(\text{HPO}_4)_{2.5}(\text{PO}_4)_{3.5}(\text{OH})_{0.5}$ are prepared by
precipitation in a medium obtained by adding the same
volumes of ethanol and aqueous solution, starting from a
solution (A) of calcium salt and an ammoniacal solution (B)
10 containing orthophosphate ions. The number of calcium ions
contained in the solution (A) is equal to the number of
phosphate ions in the solution (B). The solution (A) is
poured rapidly into the solution (B) at 37°C and subject to
stirring. Once it has been formed, the precipitate is
15 filtered with the aid of a Büchner funnel, whereupon it is
washed with a basic solution and dried in the oven at 80°C.
This results in a powder with a quasi-homogenous
granulometric distribution between 0.5 and 0.08 mm and a
time of flow (rheological analysis) of 4 s (AFNOR
20 standards). Examination of the compression of this powder
brought about with the aid of an alternative "Korsch type
EKO" compressing machine equipped with strain gauges so that
the compression parameters can be measured has shown that
the aggregation work amounts to 50 % and the transmission to
25 84 %

Production of a material without therapeutic effect

Dextran (supplied by "SIGMA" and of "Clinical Grade")
30 was added in variable proportion to the octacalcic phosphate
prepared as above; the proportion of dextran in the mixture
was caused to vary between 1 % and 30 % (a comparative test
was carried out without any dextran). The two components are
mixed thoroughly and compressed subject to a pressure of
35 approximately 2,000 DaN/cm², at the normal temperature. In
the presence of dextran the Stokes hardness of the tablets
produced, with a diameter of 6 mm and a thickness of 2 mm,

amounts to 15 and their friability to zero, whereas in the absence of dextran (pure OCPa) the hardness is no higher than 10 and their friability amounts to 1 %.

5 EXAMPLE 2

80 g octacalcic phosphate such as prepared in Example 1 are mixed thoroughly with 20 g of glucose and compressed under the aforementioned conditions. The Stokes hardness of the tablets produced amounts to 14 and their friability to zero.

EXAMPLE 3

15 Production of a material with therapeutic effect

90 g octacalcic phosphate such as prepared in Example 1, 5 g of netilmicine sulphate and 5 g of dextran are mixed thoroughly and compressed at normal temperature subject to a pressure of approximately 2,000 DaN/cm². The Stokes hardness of the tablets produced, with a diameter of 6 mm and a thickness of 2 mm, amounts to 15 and their friability to zero.

25 EXAMPLE 4

85 g of octacalcic phosphate prepared as in Example 1, 5 g of netilmicine sulphate and 10 g of dextran are mixed thoroughly and compressed at normal temperature subject to a pressure of 2,000 DaN/cm² so as to form tablets with a diameter of 6 mm and a thickness of 2 mm. The measured Stokes hardness amounts to 18 and the friability to zero.

EXAMPLE 5

80 g of octacalcic phosphate prepared as in Example 1, 5 g of netilmycine sulphate and 15 g of dextran are mixed thoroughly and compressed at normal temperature subject to a pressure of 2,000 DaN/cm² so as to form tablets with a diameter of 6 mm and a thickness of 2 mm. The measured Stokes hardness amounts to 18 and the friability to zero.

10 EXAMPLE 6

75 g of octacalcic phosphate prepared as in Example 1, 5 g of netilmycine sulphate and 20 g of dextran are mixed thoroughly and compressed at normal temperature subject to a pressure of 2,000 DaN/cm² so as to form tablets with a diameter of 6 mm and a thickness of 2 mm. The measured Stokes hardness amounts to 17 and the friability to zero.

EXAMPLE 7

20

In this example both the proportion of netilmycine and the proportion of phosphate were caused to vary in such a way that the sum of the two constituents remained constant and equal to 95 %, while the proportion of dextran remained constant and equal to 5 %.

The octacalcic phosphate was produced as in Example 1. Four medicaments with the following proportions were produced successively:

- . 85 % of octacalcic phosphate, 10 % of netilmycine sulphate and 5 % of dextran,
- . respectively 80 %, 15 % and 5 %,
- . respectively 75 %, 20 % and 5 %,
- . respectively 70 %, 25 % and 5 %.

The compaction was similar to that in the preceding examples and resulted in a substantially identical Stokes hardness amounting to 17 and in zero friability.

EXAMPLE 8

90 g of tricalcic phosphate of apatitic structure and with the formula $\text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5\text{OH}$ were prepared according to a protocol analogous to that in Example 1, the difference being that in this case the ratio between the number of calcium ions in solution (A) to the number of phosphorus ions in solution (B) no longer amounted to 1 but to 1.6; 5 g of netilmicine sulphate and 5 g of dextran were mixed thoroughly with these 85 g of tricalcic phosphate and compressed at normal temperature subject to a pressure of 2,000 DaN/cm². The measured Stockes hardness amounts to 13 and the friability to 0.5% by weight.

15 EXAMPLE 9

Octacalcic phosphate of triclinic structure and with the formula $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4$ was prepared according to BROWN's method, which consists in slow hydrolysis of brushite $\text{Ca}(\text{HPO}_4)2\text{H}_2\text{O}$ in a solution of 0.5 M sodium acetate at 40°C (W. BROWN et al, J. Am. Chem. Soc. 79 - p. 5318-9. 1957), 85 g of said phosphate, 5 g of netilmicine sulphate and 10 g of dextran being thoroughly mixed and compressed under the aforementioned conditions. The hardness of the tablets amounts to 15 and their friability to zero.

EXAMPLE 10

90 g of octacalcic phosphate prepared as in Example 1, 5 g of gentamycine sulphate and 5 g of dextran were mixed thoroughly and compressed as described above. The hardness of the tablets amounts to 15 and their friability to zero.

EXAMPLE 11

85 g of octacalcic phosphate of apatitic structure prepared as in Example 1, 5 g of netilmicine sulphate and 5 10 g of glucose were mixed thoroughly and compressed. The hardness of the tablets amounts to 16 and their friability to 0.5 %.

EXAMPLE 12

10

The effect of the proportion of dextran on the degradation of materials produced in Example 1 was examined by implantation after drilling a cavity in the bones of dogs, in the proximal metaphysial region of the ulna as well 15 as in the distal metaphysial region of the radius. Radiographic and anatomopathological examinations have shown that after two months the implanted materials are degraded only at the periphery if the proportion of dextran is zero (test) and that the degradation increases with the 20 proportion of dextran. With a proportion of dextran between 20 and 30 % the implant had disappeared and been replaced with spongy bone. During these two months the control radiographies did not show up any "defects" between the implant and the bone.

25

EXAMPLE 13

The influence of the type of oside or polyoside on the degradation of the materials produced in Examples 1 and 2 30 was examined as in Example 12 by implantation in dogs. It was found that with 20 % glucose the implant had been totally degraded after two months and that an osseous "defect" remained, whereas with dextran the implant had been degraded but replaced by bone. At the proportion examined 35 (20 %) the materials produced using glucose are degraded too quickly for the osseous tissues in question (ulna and radius) and do not enable a fresh growth of bone, whereas

this is the case with dextran, where the rate of degradation is adapted to the rate of osseous regeneration.

EXAMPLE 14

5

The influence of the proportion of dextran on the kinetics of netilmycine release was examined in vitro using a dissolution apparatus. This study was carried out with the aid of tablets produced in Examples 3 to 6. The release
10 protocol was as follows: for each medicament two 100 mg tablets were made to dissolve, subject to continuous stirring (60 rpm), in the tank of the apparatus which contained 500 ml of distilled water at a thermostatically controlled temperature of 37°C. Samples were taken
15 periodically. The netilmycine was dosed in accordance with an immuno-enzymological method.

It is found that contrary to what might have been expected the amount of antibiotic released after 50 h of dissolution at 37°C diminishes as the proportion of dextran
20 increases, even though the latter is hydrophylic. However, this hydrophylic character exerts an influence at the start of the kinetics, when it intensifies the release of the netilmycine in an advantageous manner, thus making it possible to achieve high concentrations exceeding the M.I.C.
25 ("Minimum Inhibiting Concentration") very quickly.

EXAMPLE 15

The influence of the type of antibiotic on its
30 kinetics of release was examined in vitro with the aid of a dissolution apparatus and using tablets produced in Example 3 and, by way of comparison, tablets produced under the same conditions but substituting for the netilmycine an active substance devoid of amine groups, specifically oxacillin.
35 This study shows that with oxacillin a total and very rapid release (1 h) is observed, whereas under the same experimental conditions this release amounts to only 30 %

after 50 h if netilmycine is used. The presence of amine groups in the aminosides exerts a determining influence on the mechanisms governing the release of active substance.

5 EXAMPLE 16

The influence of the chemical composition of the phosphate on the kinetics of aminoside release was examined in vitro using a dissolution apparatus and with the aid of tablets produced in Examples 3 to 8 and, by way of comparison, tablets produced under the same conditions but substituting for the octacalcic or tricalcic phosphate of apatitic structure hydroxyapatite which does not contain the HPO_4 group (formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). The latter compound was prepared according to TROMBE's method, which consists in slowly pouring a solution of diammonium phosphate into a solution of calcium acetate, the ratio of the number of calcium ions to the number of phosphorus ions in these solutions being equal to 1.66 (J.C. TROMBE, Ann. Chim. 8, 251, 1973). This study shows that the kinetics of release with the phosphates examined are directly linked to the proportion of hydrogen phosphate ions, HPO_4 . Hence the release of the aminoside is almost immediate in the case of hydroxyapatite (proportion of HPO_4 zero), retarded in the case of tricalcic phosphate (proportion of HPO_4 equal to 1) with a 60 % rate of release after 50 h, and extremely retarded in the case of octacalcic phosphate of apatitic structure, where after 50 h the rate amounts to 30 % (proportion of HPO_4 close to 2.5).

30

35

EXAMPLE 17

The influence of the type of oside used on the kinetics of release of the active substance was examined in vitro under the same conditions as those in Example 15 using tablets produced in Examples 4 to 11. This comparative study showed that the osides used exert a substantially comparable effect on the kinetics of release, there being, however, a preference for the dextran, which brings about a slower release.

EXAMPLE 18

The influence of the formulation of the tablets on their behaviour in vivo was studied by implanting them at osseous sites in animals, i.e. rabbits and dogs, and examining their biocompatibility and their rates of degradation. This study was carried out with the aid of tablets produced in Examples 3 to 11; for the purpose of comparison, medicaments have moreover been produced under the same conditions, in which the proportions of dextran and netilmcyne were either too low (total proportion less than 1 %) or too high (total proportion higher than 35 %). If the total proportion of dextran and netilmcyne is too low, the implant is not completely degraded after 3 months of implantation although it is perfectly tolerated. In this example of implantation at an osseous site, the implant was degraded too quickly if the total proportion of dextran and netilmcyne was too high, and an osseous "defect" remained. On the other hand, when the total proportion of dextran and netilmcyne amounted to between 4 % and 35 %, the perfectly biocompatible implant was largely degraded after three months and recolonised by spongy bone; the best results were obtained with the medicaments according to Examples 3 and 6. Hence the formulation of the tablets is such that it is possible to adjust the rate of degradation as required.



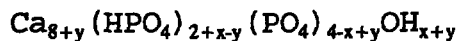
Claims

1 / - Process for manufacturing a material capable of being implanted in a living tissue and making it possible to produce a material having a rate of biodegradation which
5 can be adjusted as a function of the rate of regeneration of the tissue concerned, said process consisting in mixing a calcium phosphate with a biodegradable oxide or polyoxide, and characterised in that:

. a calcium phosphate of apatitic or triclinic
10 structure is selected which contains both HPO_4 and PO_4 groups.

. a proportion of oxide or polyoxide is mixed which is larger, the higher the desired rate of degradation of the material.

2 / - Process according to Claim 1, characterised
15 in that a calcium phosphate is selected having the formula:



where $0 \leq y \leq 2$ and $0 \leq x < 1$.

3 / - Process according to one of Claims 1 or 2, characterised in that the calcium phosphate and the oxide or
20 polyoxide are mixed in the form of powder and in that the mixture is compacted.

4 / - Process according to one of Claims 1, 2 or 3, with a view to manufacturing a material capable of implantation and having a prolonged therapeutic effect,
25 characterised in that an active substance capable of producing the desired therapeutic effect is added to the mixture, said active substance comprising amine groups enabling its attachment to the calcium phosphate endowed with HPO_4 and PO_4 groups.

30 5 / - Process according to Claim 4, characterised in that the calcium phosphate, the active substance and the oxide or polyoxide are mixed in the form of powder and in that the mixture is compacted.

6 / - Material capable of implantation into a
35 living tissue, manufactured by implementing the process according to one of Claims 1, 2 or 3, with a view to



achieving a rate of biodegradation adapted to the tissue, comprising:

(a) a calcium phosphate of apatitic or triclinic structure containing both HPO_4 groups and PO_4 groups.

5 (b) a biodegradable oside or polyoside.

7 / - Material according to Claim 6, in which the calcium phosphate is a phosphate with the formula:



where $0 \leq y \leq 2$ and $0 \leq x < 1$.

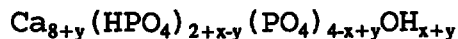
10 8 / - Material capable of implantation into a living tissue exhibiting a prolonged therapeutic effect and manufactured by implementing the process according to one of Claims 4 or 5, comprising:

(a) a calcium phosphate of apatitic or triclinic
15 structure containing both HPO_4 groups and PO_4 groups,

(b) a biodegradable oside or polyoside,

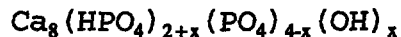
(c) at least one active substance comprising amine groups and capable of producing the desired therapeutic effect.

20 9 / - Material according to Claim 8 in which the calcium phosphate is a phosphate with the formula:



where $0 \leq y \leq 2$ and $0 \leq x < 1$.

10 / - Material capable of implantation according
25 to one of Claims 6 to 9, in which (a) the calcium phosphate is constituted by an apatitic octacalcic phosphate with the formula:



where $0 < x < 1$.

30 11 / - Material capable of implantation according to Claim 10, in which (a) the phosphate is the apatitic octacalcic phosphate, the parameter x of which is close to 0.5 (within about $\pm 20\%$), the formula of said octacalcic phosphate being approximately:





12 / - Material capable of implantation according to one of Claims 6 to 11, in which (b) the polyoside is constituted by dextran.

13 / - Material capable of implantation according to Claim 12, in which the proportion by weight of dextran amounts to between 1% and 30% in relation to the mixture.

14 / - Material capable of implantation according to Claim 8, in which (c) the active substance is present in the form of a water-soluble salt.

15 15 / - Material capable of implantation according to Claim 14, in which the active substance is netilmicine and/or gentamycine in the form of a sulphate.

16 / - Material capable of implantation according to Claim 8, comprising:

15 . a proportion by weight of dextran between 1% and 30% in relation to the mixture:

 . a proportion by weight of active substance between 0.1% and 30% in relation to the mixture.