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SCIENTIFIC SUB-COMMITTEE

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(+ Annex)

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17th Session
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O. Eng.

Brussels, 14 December 2001.

CLASSIFICATION OF A MEDICATED BONE GRAFT SUBSTITUTE CALLED "OSTEOSET®"

(Item II.15 on Agenda)

Reference documents :

NC0507E1 (HSC/28)
NC0510E2, Annex H/21 (HSC/28 – Report)

I. BACKGROUND

1. On 10 September 2001, the Secretariat received a request from the Jordanian Administration, together with a copy of a catalogue prepared by a US manufacturer, asking the Secretariat to submit the question of the classification of a medicated bone graft substitute called "OSTEOSET®" to the Harmonized System Committee at its 28th Session (see paragraphs 5 to 9 below).

2. In its reply, the Secretariat asked the Jordanian Administration to submit detailed information concerning the composition of the product and its presentation, preferably together with a sample, to enable the Secretariat to prepare a working document. On 7 October 2001, the Secretariat received a reply from the Jordanian Administration, stating that a sample was not available and that the catalogue mentioned above should be used as a basis for the working document.

3. At its 28th Session, in view of the technical nature of this question, the Committee decided to send it to the Scientific Sub-Committee for its views on the nature of the product, i.e., whether it should be considered to be a medicament or bone reconstruction cement.

4. Due to lack of detailed information with respect to the product, the Secretariat was instructed to obtain more information from interested administrations as well as from the Internet so as to prepare a new working document in good time for the next session of the Sub-Committee.

File No. 2887

II. NOTE FROM THE JORDANIAN ADMINISTRATION

5. "We are undecided on the classification of the product at issue. However, we are considering two HS headings :

(1) Heading 30.04, because of the therapeutic use of these pellets and in accordance with example (a) of Section (D) of the Explanatory Notes to Chapter 28 on page 264 (exclusions from Chapter 28).

(2) Heading 30.06, as bone reconstruction cement because these pellets help in bone formation (and given that there is no further explanation of bone reconstruction cements in the Explanatory Notes)."

Product description (excerpts from the catalogue)

6. "OSTEOSET®" pellets offer a framework into which a patient's bone can grow. The pellets are resorbed at a rate consistent with the new bone growth (an average of 4-8 weeks).

7. "OSTEOSET®" pellets were cleared by the [US] Food and Drug Administration in June 1996 and received CE mark later the same year. Since those clearances, "OSTEOSET®" has been used in thousands of cases and proven to be safe, predictable, and effective.

8. "OSTEOSET®" pellets are made of medical grade calcium sulfate containing 4 % tobramycin sulfate.

9. "OSTEOSET®" is a bone graft substitute made from medical grade calcium sulfate with the incorporation of tobramycin. *In vitro* and *in vivo* elution tests have shown sustained release of therapeutic levels of tobramycin locally with low to undetectable systemic levels. The results of the pre-clinical canine studies and clinical case presentations reported here demonstrate excellent bone healing response and biocompatibility of "OSTEOSET®" pellets. Thus, "OSTEOSET®" pellets have been shown to be effective in treating bone voids and provide therapeutic local levels of tobramycin for extended periods.

III. SECRETARIAT COMMENTS

"OSTEOSET®" pellets

10. According to the Web site of the manufacturer (www.wmt.com), calcium sulfate has been found to completely resorb and aid significantly in bone repair. By engineering the shape and size of the hemihydrate crystal, the resorption rate of the final product could be controlled (see paragraphs 12 to 18). "OSTEOSET®" pellets offer a biological framework into which new bone can form, and are resorbed at a rate consistent with natural bone formation.

11. The Secretariat also notes that "OSTEOSET®" pellets are not to be taken orally and are to be inserted inside a cavity of the fractured bone by using "OSTEOSET®" injectors (see the Annex).

12. Furthermore, the Secretariat has obtained details of the patent for the product (US Patent No. 5,614,206) from the US Patent and Trademark Office Web site (www.uspto.gov). The Secretariat has reproduced the descriptions related to the classification of the product as follows.

13. "This invention relates to the controlled release of calcium sulfate as well as to the controlled release of an additive to a calcium sulfate matrix such as medicaments or pesticides. The controlled release is achieved by a pellet comprising calcium sulfate. The pellet is prepared by the process comprising mixing powder consisting essentially of alpha-calcium sulfate hemihydrate, (…).

14. Calcium sulfate has been utilized as a filler for bone cavities as it is spontaneously adsorbed and replaced by bone. Calcium sulfate, formed from the hemihydrate, has been used as a controlled release agent alone for the filling of bone cavities and in combination with additives such as medicaments and pesticides.

15. The disadvantages to the use of calcium sulfate as a carrier, whether in vivo or not, however, are its rapid dissolution rate and the inability to control the rate of dissolution and, consequently, the rate of release of any additive.

16. "OSTEOSET® pellets “are provided by a pellet having a controllable dissolution rate, wherein said pellet comprises calcium sulfate and is prepared by the process comprising (a) mixing powder consisting essentially of alpha-calcium sulfate hemihydrate and, optionally, powder consisting essentially of beta-calcium sulfate hemihydrate with a solution comprising water to form a mixture, and (b) forming said mixture into a pellet, (…).

17. The calcium sulfate pellet of the instant invention may be used alone or as a matrix for an additive in order to control the release rate of said calcium sulfate matrix and/or additive. The pellet is prepared by mixing alpha-calcium sulfate hemihydrate powder and, optionally, beta-calcium sulfate hemihydrate powder in a solution consisting essentially of water and then formed by moulding or by applying pressure. The solution may also comprise sodium chloride, i.e., it may be a saline solution.

18. Examples of medicaments which may be mixed with the calcium sulfate matrix are antibiotics, chemotherapeutic agents, growth factors, and analgesics. Examples of antibiotics are tetracycline hydrochloride, vancomycin, cephalosporins, and aminoglycocides such as tobramycin and gentamicin. Examples of chemotherapeutic agents are cis-platinum, ifosfamide, methotrexate, and doxorubicin hydrochloride. Examples of growth factors are transforming growth factor beta, bone morphogenic protein, basic fiberblast growth factor, platelet-derived growth factor, and other polypeptide growth factors. Examples of analgesics are anesthetics such as lidocaine hydrochloride, bipivacaine hydrochloride, and non-steroidal anti-inflammatory drugs such as ketorolac tromethamine."

Bone reconstruction cements

19. The text of subheading 3006.40, with respect to bone reconstruction cements, was introduced in the first edition of the Harmonized System for the reason that bone reconstruction cements were very similar to dental cements, which already existed under the CCCN. In this context, the amendment of the Explanatory Note to heading 30.06 was limited to inserting only the reference to the cements at issue without any technical information. No other technical information remains in the Secretariat files.

20. The Secretariat has tried to find relevant information from technical literature but failed. Instead, it found a reference to "bone cements". According to the Encyclopedia of Chemical Technology (KIRK-OTHMER) (4th Edition, Volume 4, page 379), "a bone cement, a methacrylate, is often used to anchor the artificial joint materials into the bone". The Martindale Extra Pharmacopoeia (31st Edition) on page 1727 also indicates that "Methylmethacrylate forms the basis of acrylic bone cements used in orthopaedic surgery". Furthermore, bone cements are said to be filler materials as well as bone grafts by the European Edition of Wheeless' Textbook of Orthopaedics in the Belgian Orthoweb Web site (www.belgianorthoweb.be).

Classification

21. According to the catalogue, "OSTEOSET®" pellets are made of medical grade calcium sulfate with the "incorporation" of tobramycin; it is therefore clear that "OSTEOSET®" pellets are mixed products. Furthermore, the products at issue are pellets, 4.8 mm in diameter and 3.3 mm in height, and that their resorption rate can be controlled; the Secretariat considers that "OSTEOSET®" pellets would be regarded as products being put up in measured doses.

22. The product is potentially classifiable in heading 30.04 as a medicament put up in measured doses or in heading 30.06 as a bone reconstruction cement. By virtue of Note 4 to Chapter 30, heading 30.06 has priority over any other heading.

23. With regard to the definition of bone reconstruction cements, both the Nomenclature and the Explanatory Notes are silent. As mentioned in paragraph 19 above, the reference to "bone reconstruction cements" was introduced because of the similarity to dental cements. Moreover, as mentioned in paragraph 20 above, "bone cements", which appear to be similar to "bone reconstruction cements", are used to anchor the artificial joint materials into bone. On the other hand, "OSTEOSET®" pellets would be spontaneously adsorbed and replaced by bone. Therefore, the Secretariat considers that the role of the product does not fall into the category of cements and should be excluded from heading 30.06.

24. As mentioned in paragraph 11 above, the pellets offer a biological framework into which new bone can form, and are resorbed at a rate consistent with natural bone formation. They are inserted inside a cavity of the fractured bones by using injectors. Therefore, the product is intended for therapeutic use and would fall in heading 30.04.

25. As for the classification at subheading level, although there is no detailed information about the composition of the product, it appears that since it contains a certain amount of antibiotics, it would be classifiable in subheading 3004.20.

IV. CONCLUSION

26. The Sub-Committee is invited to give its views on the nature of the product, i.e., whether it should be considered to be a medicament or a bone reconstruction cement, taking the above information into account.

27. The Sub-Committee is also invited to give its views with respect to the scope of the expression “bone reconstruction cements”, taking into account paragraphs 19, 20 and 23 above.

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