Part A

SmartSet GHV Gentamicin Bone Cement
SmartSet HV Bone Cement
(Including pre-filled systems)

Part B

SmartSet GMV Gentamicin Bone Cement
SmartSet MV Bone Cement

DePuy International Ltd.
T/A DePuy CMW
Cornford Road
Blackpool, FY4 4QQ
England

File Ref: CP / RF 497 / Tender / Feb 2009

Part A - Table of Contents

Appendices

1.0 Introduction

1.1 Medical Rationale

The clinical success of hip arthroplasties has been demonstrated over the years and total joint replacement is now commonplace. In a review of the literature, Charnley reported a 96.4% success rate in patients followed not less than 5 years after replacement [(1)]. Charnley and Cupic reported the 9 and 10-year follow-up results from replacement with a success rate of 92% [(2)]. Wrobleski reported 15 to 21 year results with a clinical success rate of 96.5%. Most patients maintained good pain relief and function [(3).]

Successful treatment of the arthritic hip using total replacement arthroplasty has led to the development and use of prosthesis designed for other affected joints particularly the knee, elbow and shoulder. It is well established that the fixation of components in total joint arthroplasty has a significant effect on the long-term survivorship of the prosthesis.

Unmedicated bone cements have been available in the market for over 50 years. In more recent times both high and medium viscosity cements have been developed and introduced into the marketplace, also cements containing antibiotic which deal directly with deep infection. Infection under such circumstances can result in surgical failure, demanding further surgical intervention and even removal of the implant. Such an outcome for the patient, in terms of quality of life, is dismal.

Both SmartSet GHV Gentamicin Bone Cement (medicated) and SmartSet HV Bone Cement (unmedicated) are available from DePuy CMW either in pack, which can be mixed manually in a bowl or in a prefilled system i.e. a syringe that mixes under vacuum. Alternatively the product can be supplied in a pack, then prior to surgery be loaded and mixed in an empty vacuum mixing like Cemvac or SmartMix Cemvac. Full ranges of product listings are available in Section 3.0.

2.0 Manufacturer's Details

DePuy International Limited T/A DePuy CMW
Cornford Road
Blackpool
Lancashire
FY4 4QQ
UK

3.0 Product Codes

Table 1 – Product Codes

Product Description	***Product Code/s***	***Shelf Life***
SmartSet GHV Gentamicin Bone Cement	3095020 3095040	2 years 2 years
SmartSet HV Bone Cement	3092020 3092040	2 years 2 years
SmartMix Cemvac pre-filled with SmartSet GHV Gentamicin Bone Cement	8195060 8195080 *8195100	2 years 2 years 2 years
SmartMix Cemvac pre-filled with SmartSet HV Bone Cement	8192060 8192080 *8192100	2 years 2 years 2 years
SmartMix Cemvac Syringe (empty)	831615	2 years
Standard Cemvac Syringe (Single)	831215	2 years
Standard Cemvac Syringe (Double)	831220	2 years

The last 3 digits of the Product Code donate the unit size in grams
For example xxxx020 = 20g product
** Product not manufactured*

4.0 Product Classifications

4.1 Medicated Bone Cements

The following products have been determined to be a Class III device within the scope of the European Directive 93/42/EEC of 14th June 1993 concerning medical devices under Rule 13, Annex IX for devices that incorporate a medicinal substance:

- SmartSet GHV Gentamicin Bone Cement
- SmartMix Cemvac prefilled with SmartSet GHV Gentamicin Bone Cement

The relevant certificates for the products listed above are available in Appendix 1.

4.2 Unmedicated Bone Cements

The following products have been determined to be a Class IIb device within the scope of the European Directive 93/42/EEC of 14th June 1993 concerning medical devices under Rule 8, Annex IX for devices that are surgically invasive long term implantable devices.

- SmartSet HV Bone Cement
- SmartMix Cemvac prefilled with SmartSet HV Bone Cement

The relevant certificates for the products listed above are available in Appendix 2.

4.3 Accessories

The following products have been determined to be Class IIa devices within the scope of the European Directive 93/42/EEC of 14th 1993 concerning medical devices under Rule 6 of Annex IX for devices that are surgically invasive intended for transient use.

- SmartMix Cemvac Syringe
- Standard Cemvac Syringe (single pack)
- Standard Cemvac Syringe (double pack)

The relevant certificates for the products listed above are available in Appendix 3.

5.0 Product Composition

The qualitative and quantitative compositions of the SmartSet Bone Cements are specified in the table below:

Table 2 – Cement Compositions

	SmartSet GHV Gentamicin Bone Cement	**SmartSet HV Bone Cement**
	SmartMix Cemvac prefilled with SmartSet GHV Gentamicin Bone Cement	**SmartMix Cemvac prefilled with SmartSet HV Bone Cement**
Bone Cement Powder:		
Gentamicin Sulphate (% w/w)	4.22*	-
Methyl Methacrylate / Methyl Acrylate Copolymer (% w/w)	80.45	84.00
Benzoyl Peroxide (%w/w)	0.96	1.00
Zirconium Dioxide (% w/w)	14.37	15.00
Bone Cement Liquid		
Methyl Methacrylate (%w/w)	97.50	97.50
N, N-Dimethyl -p-toluidine (%w/w)	≤2.50	≤2.50
Hydroquinone (ppm)	75	75

* Equivalent to 1.0g (1.0 M.I.U) Gentamicin base in a 40g unit

6.0 Description of the Devices

6.1 SmartSet GHV Gentamicin and SmartSet HV Bone Cements (standard packs)

SmartSet GHV Gentamicin and SmartSet HV Bone Cements are high viscosity cements intended for either digital or syringe application. The cements are self-curing, radiopaque, polymethyl methacrylate based cements, available as either medicated or un-medicated and are used for securing metal or polymeric prosthesis to living bone in arthroplasty procedures. The bone cements have no intrinsic adhesive properties, but rely instead on close mechanical interlock between the irregular bone surface and the prosthesis.

Each product is supplied as a two-component system, consisting of separate, sterile liquid and sterile powder components, which are mixed together at the point of use to produce the cement.

The liquid component is a colourless, flammable liquid with a distinctive odour. Its major component is the monomer methyl methacrylate. Hydroquinone is present in the liquid component as a stabiliser to prevent premature polymerisation following mixing of the liquid and powder components. The liquid component is sterilised by membrane filtration and aseptically filled into a sterile glass ampoule. The ampoule is contained within a sealed blister pack, which is sterilised using ethylene oxide.

The powder component is a white, finely divided powder, composed of polymethyl methacrylate based polymer. Benzoyl peroxide is present in the powder component to initiate cement polymerisation when the powder and liquid components are mixed. The powder component contains the radiopaque agent zirconium dioxide. The powder component is contained in a double paper / film pouch which is then sterilised by ethylene oxide. The sterile powder component is supplied within an outer, protective, non-sterile, laminated foil pouch.

The 20g unit consists of a double paper / film peelable pouch containing 20g of sterile bone cement powder and a glass ampoule containing 9.44g of bone cement liquid. The 40g unit is consists of a double paper / film peelable pouch containing 40g of sterile bone cement powder, the glass ampoule contains 18.88g of bone cement liquid

Standard packs of SmartSet GHV Gentamicin Bone Cement and SmartSet HV Bone Cement

6.2 SmartMix Cemvac and Cemvac Mixing Systems

The surgical techniques of hip replacements, together with methods to reduce infection have been greatly enhanced with time. Additionally, there have been improvements in the preparation techniques of bone cements.

In total hip arthroplasty, fracture and subsequent premature loosening are directly related to the strength of the cement mantle serving as an interface between bone and prosthesis. The cement has been shown to be weakened by porosity, which enhances the formation of micro fractures that contribute to crack propagation [(4)].

Potential sources of porosity are:

- Air initially surrounding the powdered polymer beads.
- Air trapped during the "wetting" of the powder.
- Air stirred into the liquid cement during spatulation.
- Air trapped during transfer to a non-vented cement gun or specimen mould.
- Monomer boiling during polymerisation of very thick specimens.
- Mixing under too high a vacuum, resulting in boiling of the liquid monomer.

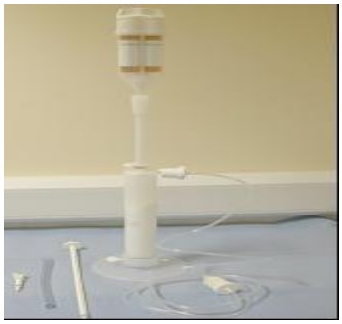
Vacuum mixing of bone cement has been shown to significantly reduce porosity and enhance the cement strength [(4-14)].

The methyl methacrylate liquid monomer is known to be volatile, flammable and a potent respiratory sensitiser to individuals working with it. A short-term (15 minutes) exposure limit has been set at 100ppm [(15)]. Hospitals should seek to comply with the Control of Substances Hazardous to Health Regulations, and adjust work practices as appropriate. Consequently, vacuum mixing systems are increasingly being employed so as to control monomer fumes during preparation of bone cement.

SmartMix Cemvac can be prefilled with either SmartSet GHV Gentamicin Bone Cement or SmartSet HV Bone Cement. Unit sizes are either 60g or 80g. Product codes are available in section 3.0.

Each prefilled SmartMix Cemvac system consists of a syringe barrel prefilled with either 60g or 80g of sterile bone cement powder, 2 glass ampoules containing sterile bone cement liquid presented within an ampoule cartridge (60g = 2 x 14.16g / 80g = 2 x 18.88g) and a sterile components pouch containing a disposable mixing stand, a vacuum tube adaptor, a central mixing rod and a vacuum hose with attached filter.

See photographs overleaf.



Prefilled SmartMix Cemvac system

The empty SmartMix Cemvac system consists of a syringe barrel assembly with disposable funnel attached. The components consist of a disposable mixing stand, mixing rod, airline with filter attached and a vacuum tube adaptor all of which are sterile and packed into a double peelable pouch.

Empty SmartMix Cemvac syringe barrel assembly

SmartMix Cemvac components

The Cemvac syringe is slightly smaller that the SmartMix Cemvac syringe. The Cemvac syringe mixing system consists of a syringe barrel assembly with disposable funnel attached. The components consist of a disposable mixing stand, mixing rod, airline with filter attached and a vacuum tube adaptor all of which are sterile and packed into a double peelable pouch. The Cemvac syringe systems are available as either a single or double unit. Refer to section 3.0 for details of product codes.

Empty Cemvac syringe barrel and components

7.0 Indications / Contraindications

7.1 SmartSet GHV Gentamicin Bone Cement

7.1.1 Indications

SmartSet GHV Gentamicin Bone Cement is indicated for the fixation of prostheses to living bone in arthroplasty procedures of joints in which infection by Gentamicin sensitive organisms is a potential risk.

7.1.2 Contraindications

SmartSet GHV Gentamicin Bone Cement is contraindicated in the presence of the condition Myasthenia Gravis. SmartSet GHV Gentamicin Bone Cement is contraindicated in patients with hypersensitivity to Gentamicin or to any other of the cement components.

7.2 SmartSet HV Bone Cement

7.2.1 Indications

SmartSet HV Bone Cement is indicated for the fixation of prostheses to living bone in orthopaedic musculoskeletal surgical procedures for rheumatoid arthritis, osteoarthritis, traumatic arthritis, osteoporosis avascular necrosis, collagen disease, severe joint destruction secondary to trauma or other conditions, and revision of previous arthroplasty.

7.2.2 Contraindications

SmartSet HV Bone Cement is contraindicated in the presence of active or incompletely treated infection, which could involve the site where the cement is applied. SmartSet HV Bone Cement is contraindicated in patients with hypersensitivity to any of the cement components.

8.0 Finished Product Specifications

8.1 SmartSet GHV Gentamicin and SmartSet HV Bone Cements

Table 3 – Powder Component, finished product specifications

POWDER COMPONENT	**SmartSet GHV Gentamicin Bone Cement**	**SmartSet HV Bone Cement**
Appearance	A fine to off white free flowing powder in sealed paper / poly pouches	
Target weight / uniformity of fill	20.0g unit: +/- 0.5g 40.0g unit: +/- 1.0g	20.0g unit: +/- 0.5g 40.0g unit: +/- 1.0g
Identification:		
Gentamicin Sulphate	Positive	Not applicable
Methyl Methacrylate/Methyl Acrylate copolymer	Positive	Positive
Zirconium Dioxide	Positive	Positive
Gentamicin Assay	The precision of the assay is such that the fiducial limits of error of the assay (P=0.95) are not less than 95% and not greater that 105% of the estimated potency.	Not applicable
Release limits (1)	Calculated from assays having acceptable fiducial limits, the lower fiducial limit is not less than 95% and the upper fiducial limit is not more than 120% of the stated content.	Not applicable
Control limits (2)	Calculated from assays having acceptable fiducial limits, the lower fiducial limit is not less than 120% and the upper fiducial limit is not less than 95% of the stated content.	Not applicable
Assay Benzoyl Peroxide Release limit (1)	0.76 to 1.50 (%w/w)	0.76 to 1.50 (%w/w)
Control limit (2)	0.60 to 1.50 (%w/w)	0.60 to 1.50 (%w/w)
Sterility of final packs	Complies with the European & United States Medical Device requirements for sterility.	
Ethylene Oxide Residuals	≤ 25 ppm	

(1) Release limits apply at the time of manufacture
(2) Control limits apply over shelf life of the product

Table 4 – Liquid Component, finished product specifications

LIQUID COMPONENT	**SmartSet GHV Gentamicin Bone Cement**	**SmartSet HV Bone Cement**
Appearance	A clear mobile liquid with a characteristic odour contained in a sealed amber neutral glass ampoule.	
Target weight / uniformity of fill	20.0g unit: 9.44g +/- 0.46g 40.0g unit: 18.88 +/- 0.94g	20.0g unit: 9.44g +/- 0.46g 40.0g unit: 18.88 +/- 0.94g
Identification:		
Methyl Methacrylate	Positive	Positive
Assay N,N–dimethyl-p-toluidine	2.50 maximum (%w/w)	2.50 maximum (%w/w)
Liquid Stability	The flow time shall not increase by more than 10% at 60°C ±2°C for 72 h ± 2 hours	The flow time shall not increase by more than 10% at 60°C ±2°C for 72 h ± 2 hours
Sterility of final packs	Complies with the European & United States Medical Device requirements for sterility.	

Table 5 – Constituted Cement, finished product specifications

CONSTITUTED CEMENT	**SmartSet GHV Gentamicin Bone Cement**	**SmartSet HV Bone Cement**
Appearance	A dough setting to an off white solid	
Physical Properties:		
Dough time Release Limit (1)	≤ *1:00	≤ *1:00
Control Limit (2)	≤ *1:30	≤ *1:30
Setting Time Release Limit (1)	*9:00 to *11:00	*9:00 to *11:00
Control Limit (2)	*8:00 to *12:30	*8:00 to *12:30
Exotherm		
Temperature (^{o}C)	90 maximum	90 maximum
Setting time	*7:00 to *12.:00	*7:00 to *12:00
Compressive strength (MPa)	≥ 70	≥ 70
Bending modulus (MPa)	≥ 1800	≥ 1800
Bending strength (MPa)	≥ 50	≥ 50
Sterility of final packs	Complies with the European & United States Medical Device requirements for sterility.	

*Minutes: seconds

(1) Release limits apply at the time of manufacture

(2) Control limits apply over shelf life of the product

8.2 SmartMix Cemvac prefilled with SmartSet GHV Gentamicin and SmartSet HV Bone Cements

Table 6 – Prefilled system, powder component, finished product specifications

POWDER COMPONENT	**SmartMix Cemvac prefilled with SmartSet GHV Gentamicin Bone Cement**	**SmartMix Cemvac prefilled with SmartSet HV Bone Cement**
Appearance	A fine to off white free flowing powder presented in a close syringe barrel	
Target weight / uniformity of fill	60.0g unit: +/- 1.5g 80.0g unit: +/- 2.0g	60.0g unit: +/- 1.5g 80.0g unit: +/- 2.0g
Identification:		
Gentamicin Sulphate	Positive	Not applicable
Methyl Methacrylate/Methyl Acrylate copolymer	Positive	Positive
Zirconium Dioxide	Positive	Positive
Gentamicin Assay	The precision of the assay is such that the fiducial limits of error of the assay (P=0.95) are not less than 95% and not greater that 105% of the estimated potency.	Not applicable
Release limits (1)	Calculated from assays having acceptable fiducial limits, the lower fiducial limit is not less than 95% and the upper fiducial limit is not more than 120% of the stated content.	Not applicable
Control limits (2)	Calculated from assays having acceptable fiducial limits, the lower fiducial limit is not less than 120% and the upper fiducial limit is not less than 95% of the stated content.	Not applicable
Assay Benzoyl Peroxide **Release limit** (1)	0.76 – 1.50 (%w/w)	0.76 – 1.50 (%w/w)
Control limit (2)	0.60 – 1.50 (%w/w)	0.60 – 1.50 (%w/w)
Sterility of final packs	Complies with the European & United States Medical Device requirements for sterility.	
Ethylene Oxide Residuals	≤ 25 ppm	

(1) Release limits apply at the time of manufacture
(2) Control limits apply over shelf life of the product

Table 7 – Prefilled systems, liquid Component, finished product specifications

LIQUID COMPONENT	**SmartMix Cemvac prefilled with SmartSet GHV Gentamicin Bone Cement**	**SmartMix Cemvac prefilled with SmartSet HV Bone Cement**
Appearance	A clear mobile liquid with a characteristic odour contained in a sealed amber neutral glass ampoule.	
Target weight / uniformity of fill	60.0g unit: 2 x 14.16g +/- 0.70g 80.0g unit: 2 x 18.88 +/- 0.94g	60.0g unit: 2 x 14.16g +/- 0.70g 80.0g unit: 2 x 18.88 +/- 0.94g
Identification:		
Methyl Methacrylate	Positive	Positive
Assay N,N–dimethyl-p-toluidine	2.50 maximum (%w/w)	2.50 maximum (%w/w)
Liquid Stability	The flow time shall not increase by more than 10% at 60°C ±2°C for 72 h ± 2 hours	The flow time shall not increase by more than 10% at 60°C ±2°C for 72 h ± 2 hours
Sterility	Complies with the European & United States Medical Device requirements for sterility.	

Table 8 – Prefilled systems, constituted cement, finished product specifications

CONSTITUTED CEMENT	**SmartMix Cemvac prefilled with SmartSet GHV Gentamicin Bone Cement**	**SmartMix Cemvac with SmartSet HV Bone Cement**
Appearance	A syringe-able dough setting to an off white solid	
Physical Properties		
Setting Time Release Limit (1)	*7:30 - *10:30	*7:30 - *10:30
Control Limit (2)	*7:00 - *12:30	*7:00 - *12:30
Exotherm Temperature (^{o}C)	≤ 90	≤ 90
Setting time	7:30 - 11:30	7:30 - 11:30
Compressive strength (MPa)	≥ 70	≥ 70
Bending modulus (MPa)	≥ 1800	≥ 1800
Bending strength (Mpa)	≥ 50	≥ 50
Sterility	Complies with the European & United States Medical Device requirements for sterility.	

*Minutes: seconds

(1) Release limits apply at the time of manufacture

(2) Control limits apply over shelf life of the product

9.0 Summary of Design Verification

SmartSet GHV Gentamicin Bone Cement is a high viscosity bone cement with the similar physicomechanical and gentamicin elution properties to the original DePuy CMW 1 Gentamicin and Palacos R40 Gentamicin bone cements.

The data used to support SmartSet GHV Gentamicin Bone Cement can be extrapolated to support SmartSet HV Bone Cement; the unmedicated version which is an equivalent cement apart from the absence of the gentamicin.

Data to support these similarities, demonstrating the safety and efficacy of SmartSet GHV Gentamicin Bone Cement follows below.

9.1 Factors Affecting Choice of Combination

9.1.1 General Properties of Gentamicin

Gentamicin is an amino glycoside antibiotic derived from Micromonospora purpurea. It is commercially available as a pharmacopoeial material (BP, Ph.Eur), which is comprised of a complex mixture of the sulphates of Gentamicin C_1, Gentamicin C_{1A}, Gentamicin C_2 and, to a lesser extent, Gentamicin C_{2A}. The Gentamicins are characterised by 4, 6-substitution on a central 2-deoxystreptamine ring with cyclic amino-sugars attached by glycosidic linkages; they are broad-spectrum, basic, heat stable, water soluble antibiotics which may be sterilised by ethylene oxide.

The Gentamicin complex is bactericidal and is thought to interfere with bacterial protein synthesis by binding irreversibly to the 30S subunit of the bacterial ribosome. It is effective against many strains of Gram-negative bacteria including species of Escherichia, Enterobacter, Klebsiella, Salmonella, Serratia, Shigella, Proteus and Pseudomonas aeruginosa. Although less active against Gram-positive bacteria, Staphylococcus aureus is highly sensitive; Bacillus, Clostridium and Corynebacterium species and Listeria monocytogenes may also be susceptible. Gentamicin is also active against some strains of Mycobacteria, and Mycoplasmas have been reported to be sensitive; fungi are resistant.

9.1.2 Mode of Action of Bone Cement

Each unit of bone cement consists of a polymeric powder component and a monomeric liquid component. The powder contains benzoyl peroxide (BPO) and the liquid contains N, N-dimethyl-ρ-toluidine (DMpT). When the liquid is added to the powder and mixed in accordance to the instructions for use, a cement of doughy consistency is formed.

The BPO from the powder and DMpT from the liquid react to generate free radicals by means of a redox reaction. The free radicals react with the monomeric liquid causing polymerisation and hardening of the cement.

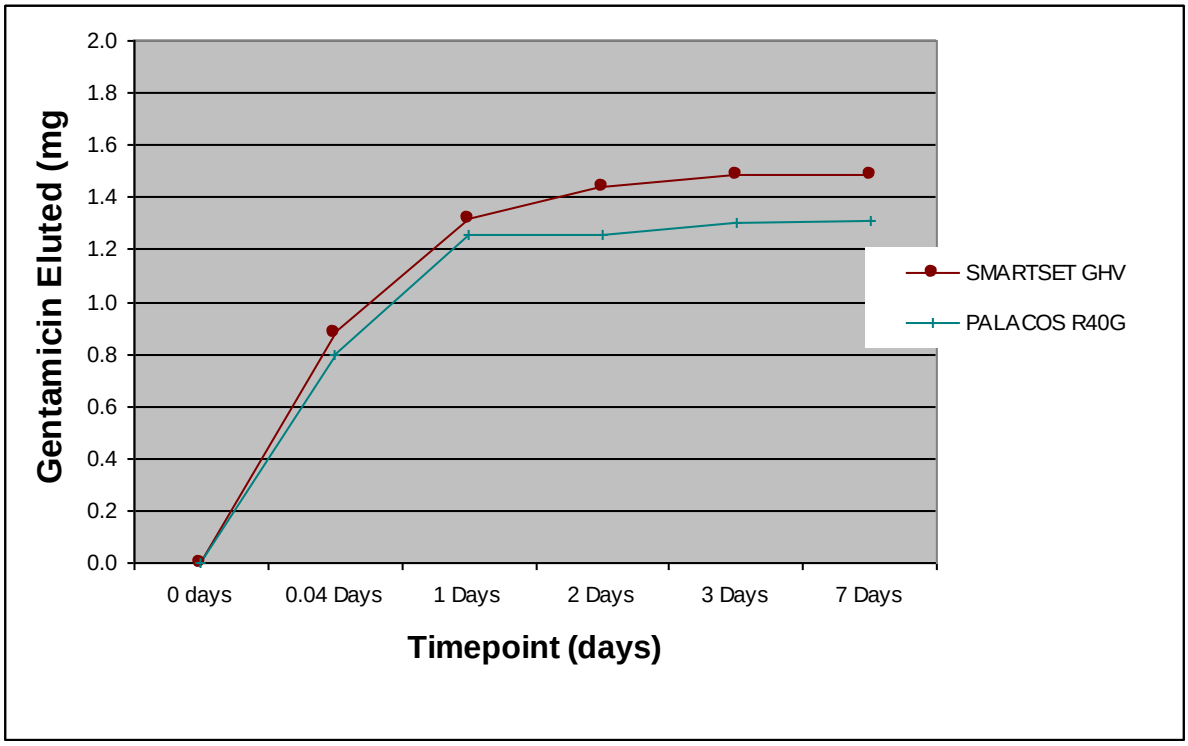
The surgeon applies the cement either digitally or by a syringe applicator, inserting the prosthesis into the cement when it is in a doughy state. The cement dough polymerises exothermally in-situ and secures the prosthesis in place.

For SmartSet GHV Gentamicin Bone Cements the gentamicin will elute directly from the cured bone cement into the surrounding body fluids.

9.2 Gentamicin Elution Studies

Elution studies were conducted on SmartSet GHV to confirm the level of gentamicin incorporated into the product (i.e. 1.0g as base per 40g powder and 0.5g base per 20g powder). The results are shown below in graph 1.

Graph 1 - Summary of SmartSet GHV v Palacos Gentamicin Bone Cements

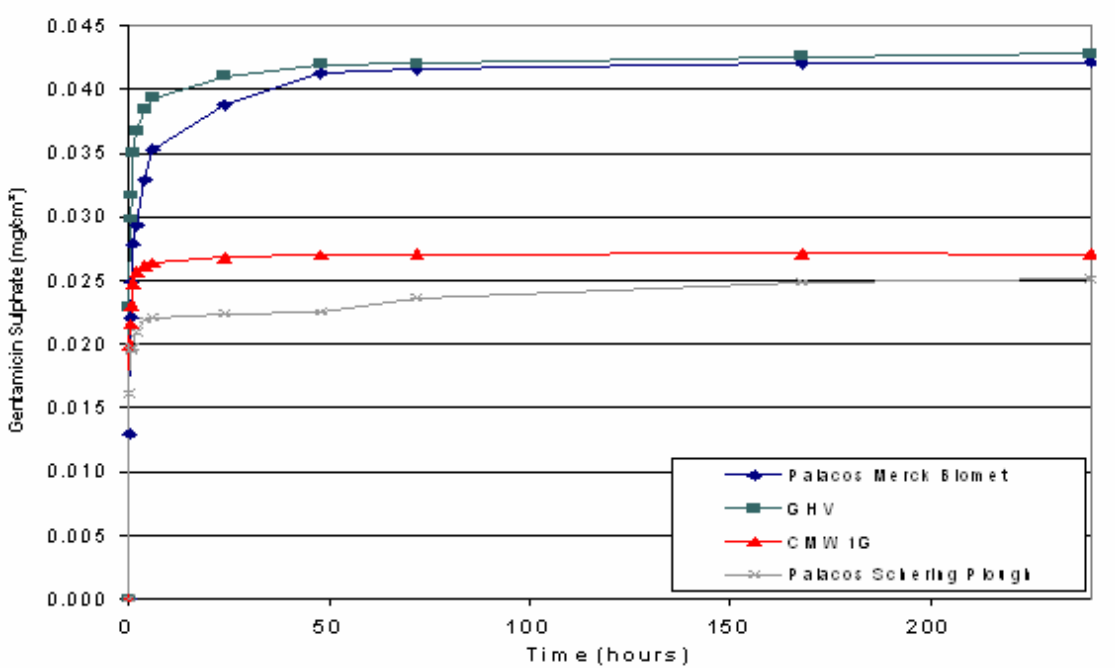


The elution profile in graph 1 shows the amount of gentamicin eluting from both SmartSet GHV Gentamicin Bone Cement and alternative commercially available cement Palacos R40 with gentamicin. The tests were conducted at zero time point, again at 1-hour time point (0.04 days) then at 1 day through to 7 days. The results confirm that the elution profile of SmartSet GHV Gentamicin Bone Cement is comparable to Palacos R40G.

9.2.1 Independent Elution Testing

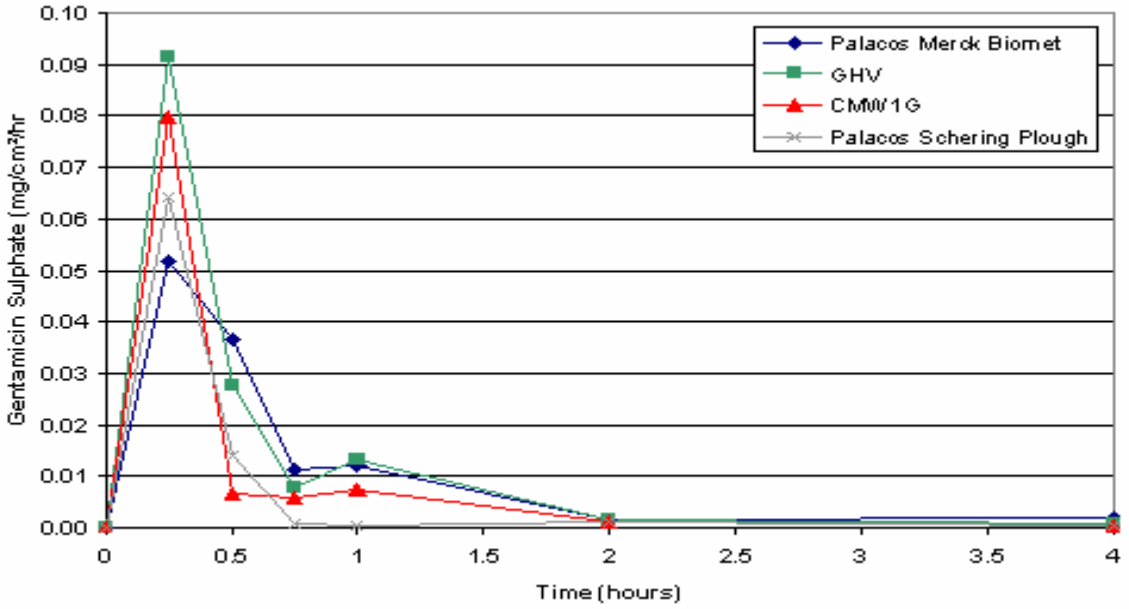
Dr Frommeld, an antibiotics and microbiology expert at the Endoklinik in Hamburg has conducted independent elution studies for DePuy CMW. The study compared cumulative elution (graph 2) and maximum elution (graph 3) rates of SmartSet GHV Gentamicin Bone Cement (referred to as GHV), DePuy CMW 1 Gentamicin (referred to as CMW 1G) and Palacos R Gentamicin from 2 different manufacturers (Merck Biomet and Schering Plough).

Graph 2 - Cumulative Elution of Gentamicin containing Acrylic Bone Cements



Graph 2 clearly shows that the results of this testing show cumulative elution of SmartSet GHV Gentamicin Bone Cement to be equivalent to Palacos R Gentamicin (Merck Biomet) and greater than both DePuy CMW 1 Gentamicin and Palacos R Gentamicin (Schering Plough).

Graph 3: Maximum Elution Rate for Gentamicin Containing Acrylic Bone Cements



Graph 3 shows the maximum elution rates of SmartSet GHV Gentamicin Bone Cement were slightly greater than DePuy CMW 1 Gentamicin Bone Cement. A bigger difference in maximum elution rate is seen between SmartSet GHV Gentamicin Bone Cement and both of the Palacos brands.

These results support the elution work carried out at DePuy CMW on SmartSet GHV Gentamicin Bone Cement and provide further evidence of the *in-vitro* similarities of SmartSet GHV Gentamicin Bone Cement and other commercially available bone cements.

9.3 Physicomechanical Properties

The physicomechanical properties SmartSet GHV Gentamicin and SmartSet HV Bone Cements were evaluated and compared with the commercially available bone cement Palacos R40 Gentamicin. Refer to the table 9.

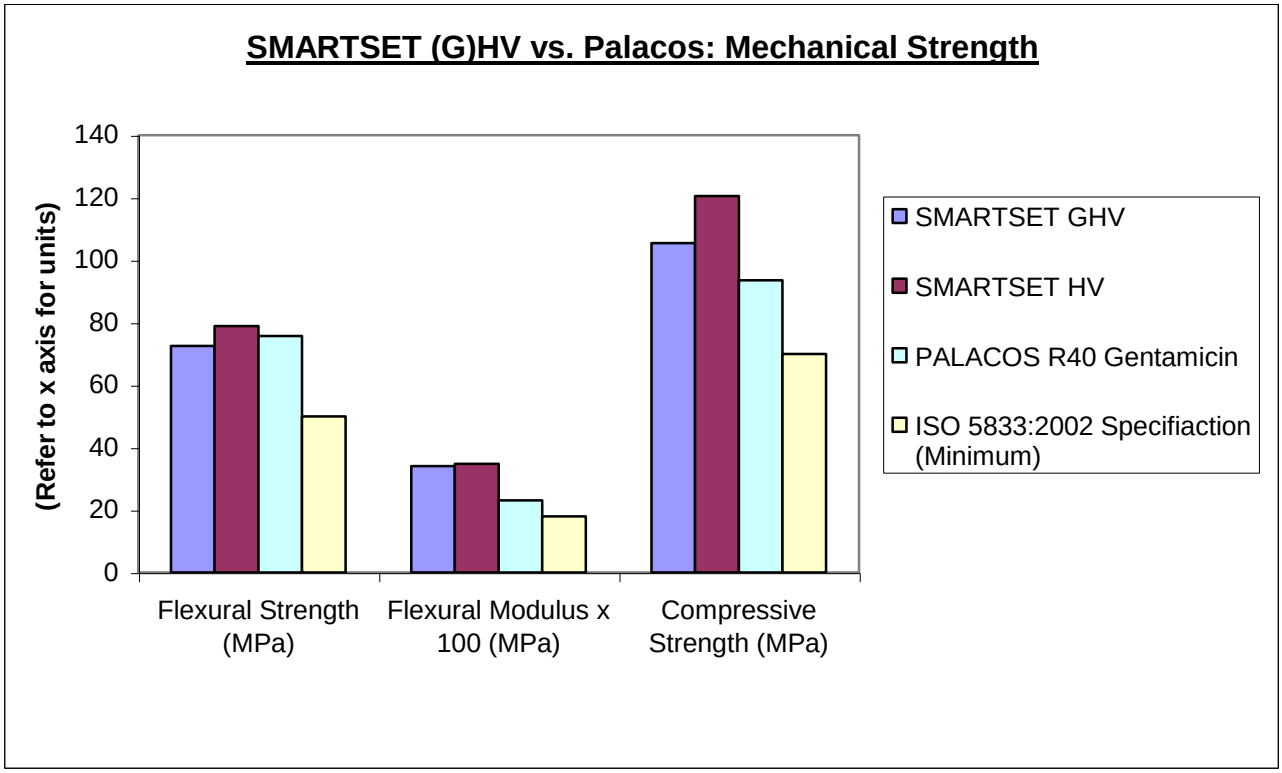
Table 9 – Comparison of Physicomechanical Properties

Physicomechanical Properties	**ISO 5833:2002 Specification**	**SmartSet GHV Gentamicin Bone Cement [1]**	**SmartSet HV Bone Cement [2]**	**Palacos R40 Gentamicin Bone Cement[3]**
Dough Time (Min: sec)	CMW specifications ≤1:00[4]: ≤ 1:30[5]	00:51	1:15	00:56
Setting Time (Min: sec)	CMW specifications 9:30 – 11:00[4], 8:00-9:00[5]	10:04	8:25	10:12
Exothermic Temperature (°C)	90°C max.	71.9	76.9	77.5
Exothermic Setting Time (Min: sec)	CMW specifications 07:00-12:00[4], 06:30-10:00[5]	10:07	7:58	11:25
Compressive Strength (MPa) (graph 4)	70 minimum	105.4	120.5	93.5
Flexural Strength (MPa) (graph 4)	50 minimum	72.5	78.9	75.7
Flexural Modulus (MPa) (graph 4)	1800 minimum	3409	3479	2306

(1) Taken from report R744, on file at DePuy CMW
(2) Taken from report R743, on file at DePuy CMW
(3) Taken from report R064, on file at DePuy CMW (Palacos specifications unknown)
(4) SmartSet GHV Gentamicin Bone Cement Specification
(5) CMW 1 Gentamicin Bone Cement Specification

The results of the testing (summarised in Table 9) show that the physicomechanical properties of SmartSet GHV Gentamicin and SmartSet HV Bone Cements are equivalent to those of other commercially available bone cements and comply with the requirements of the international standard for acrylic bone cements, ISO 5833:2002. The data for compressive strength, flexural strength and flexural modulus has also been depicted in graphical format for ease of viewing. Refer to graph 4 shown overleaf.

Graph 4: Compressive, Flexural Strength and Flexural modulus

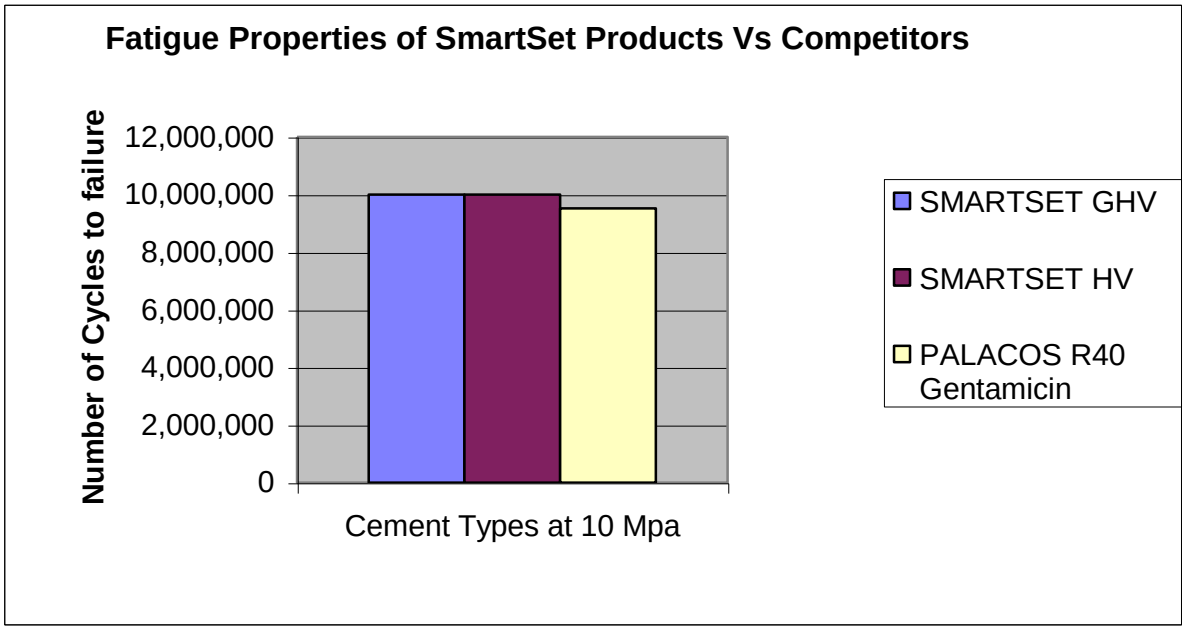


9.4 Fatigue Life

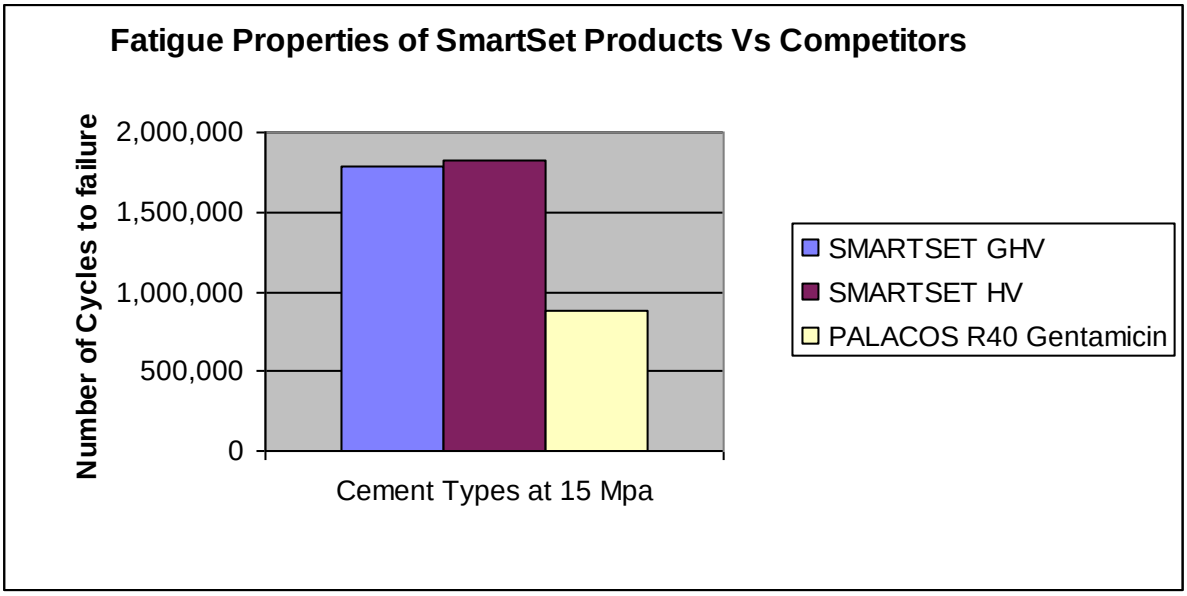
Clinically, failure or loosening of a total joint arthroplasty may be often attributed to mechanical failure of the acrylic bone cement surrounding the prosthesis. The loading imposed on the cement during normal patient activity indicates fatigue as the most probable mode of failure. Therefore the fatigue performance of the cement is very important.

Fatigue testing on SmartSet GHV Gentamicin and SmartSet HV Bone Cements was conducted and compared directly with another commercially available bone cement, Palacos R40 with Gentamicin. Testing was completed at 10 MPa and 15 MPa. The results can be seen overleaf in graphs 5 and 6 respectively.

Graph 5: Fatigue testing at 10 MPa



Graph 6: Fatigue testing at 15 MPa



The results presented show that the fatigue properties of both SmartSet GHV Gentamicin Bone Cement and SmartSet HV Bone Cement are statistically better than Palacos R40 Gentamicin at the 15MPa loading level and are comparable at the 10MPa loading level.

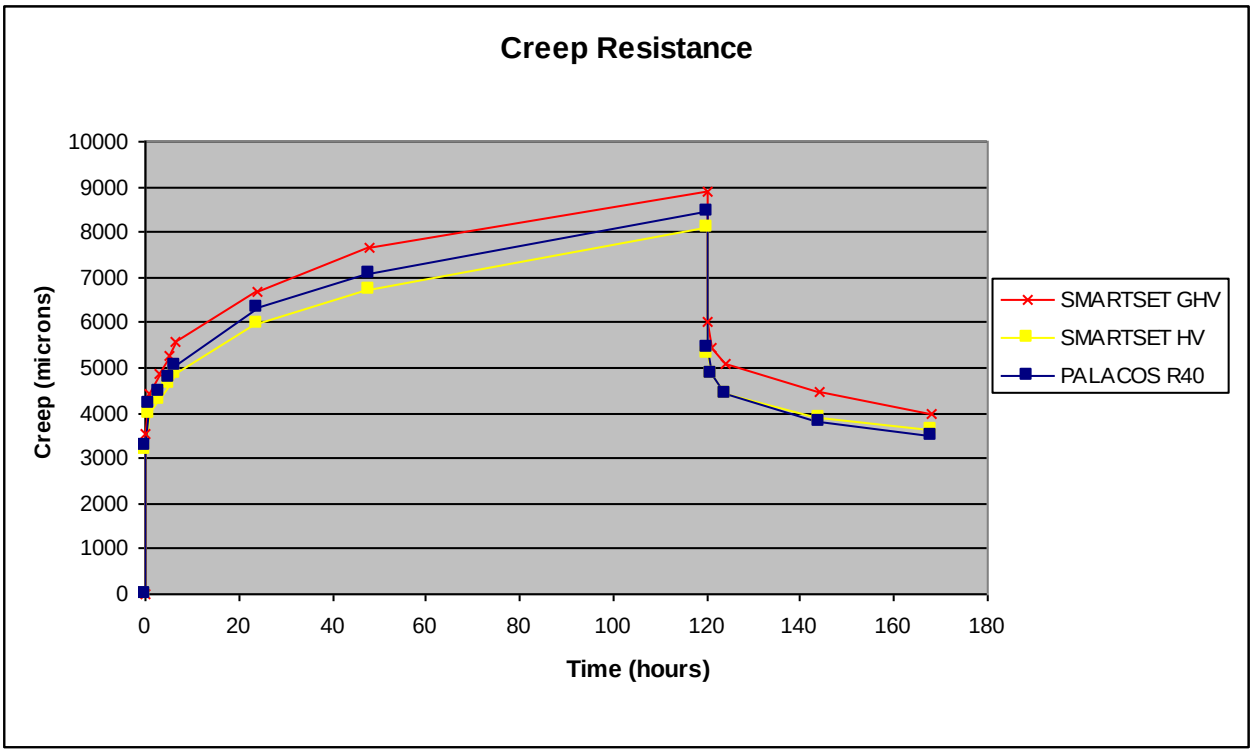
In addition, DePuy International Ltd has carried out hip simulator work on SmartSet GHV Gentamicin Bone Cement. The results of this testing demonstrated that after 10 million cycles no visible signs of cracking or fracture of cured SmartSet GHV Gentamicin Bone Cement were observed. This data will also support the SmartSet HV Bone Cement. The full report of this study is held on file at DePuy CMW.

9.5 Creep Resistance

Creep characteristics of bone cements are an indication of the degree of movement or subsidence likely to occur under static load.

The creep resistance properties of SmartSet GHV Gentamicin and SmartSet HV Bone Cements have been investigated and compared to those of another commercially available bone cement, Palacos R40 Gentamicin. The results are shown in graph 7.

Graph 7: Creep data



SS GHV Data taken from report R744, on file at DePuy CMW
SmartSet HV Data taken from technical file at DePuy CMW
Palacos Data taken from report, R001, on file at DePuy CMW

The results show that both SmartSet GHV Gentamicin and SmartSet HV Bone Cements exhibit creep resistance performance similar to Palacos R40 Gentamicin bone cement.

9.6 Product Shelf life

Refer to the shelf life listed in table 1, Section 3.0. This is acceptable when the products are stored in their unopened packaging below 25°C and protected from light.

10.0 Biocompatibility / Toxicology Data

Biocompatibility and toxicity tests have been carried out on SmartSet GHV Gentamicin and SmartSet HV Bone Cements in accordance with ISO 10993: Biological Evaluation of Medical Devices.

The cements have been evaluated as a permanent implant device, which principally contacts tissue and bone.

The results of the tests show that SmartSet GHV Gentamicin Bone Cement demonstrate satisfactory biocompatibility and toxicity and are therefore considered safe in their intended use.

In addition to the above testing, an expert review report has been conducted which considers the pharmacodynamics, pharmacokinetics and toxicology of SmartSet GHV Gentamicin Bone Cement, this report can be extended to cover all other DePuy CMW gentamicin bone cements. The review concludes that DePuy gentamicin bone cements are safe and effective with no foreseen dangers to either patients or the surgical team.

Summaries of the tests are listed below in table 12. Copies of all reports are on file at DePuy CMW.

Table 10 - Summary of Biocompatibility Testing Performed on SmartSet GHV Gentamicin Bone Cement

Test	**Standard**	**Results**
Tissue Implantation	10993-6	Pass
Sensitisation (Maximisation test)	10993-10	Pass
Genotoxicity (Ames test)	10993-3	Pass
In-vitro Cytotoxicity	10993-5	Pass
Acute Systemic Toxicity	10993-11	Pass

11.0 Clinical Evidence

11.1 SmartSet GHV Gentamicin Bone Cement (and prefilled systems)

SmartSet GHV Gentamicin Bone Cement was designed and developed to have both and an extended working time with mechanicals properties that are at least equivalent when compared to other commercially available bone cements (including DePuy CMW bone cements). The longer working time allows for more flexibility in the time that can be taken during the surgical implantation of the prostheses.

Palacos R40 with gentamicin and DePuy CMW 1 Gentamicin Bone Cements have been commercially available throughout the world for over thirty years and fourteen years respectively. Consequently, documentation is available to demonstrate their clinical safety and efficacy. Since the composition of SmartSet GHV Gentamicin Bone Cement is similar to both DePuy CMW 1 Gentamicin and Palacos R40 with gentamicin, the clinical safety and efficacy of SmartSet GHV Gentamicin Bone Cement can also be inferred.

11.1.1 Clinical Studies

Taking in account the wealth of clinical data and experience available on gentamicin bone cements and in particular DePuy CMW gentamicin bone cements, it was concluded that it was not necessary to conduct a clinical investigation for SmartSet GHV Gentamicin Bone Cement.

In-vitro test data provided on SmartSet GHV Gentamicin Bone Cement has shown that the elution profiles and the physicomechanical properties to be similar to other commercially available gentamicin bone cements. Refer to section 9.0.

Previous clinical trials on DePuy CMW gentamicin bone cements (DePuy CMW 1 Gentamicin) have demonstrated that *in-vivo* elution profiles of gentamicin can be correlated to those of *in-vitro* profiles. As the *in-vitro* elution of gentamicin from SmartSet GHV Gentamicin Bone Cement is similar to other commercially available gentamicin bone cements (DePuy CMW 1 Gentamicin and Palacos R40 Gentamicin) then the clinical safety and efficacy of SmartSet GHV is expected to be similar.

A review of the published literature for SmartSet GHV Gentamicin Bone Cement has been undertaken, along with the biocompatibility and toxicity testing in accordance with ISO 10993. The information together provides data to prove the safety, efficacy and performance of SmartSet GHV Gentamicin Bone Cement and its prefilled systems.

11.1.2 Review of published literature

DePuy CMW conduct regular reviews of the published literature relating to the use of DePuy CMW gentamicin bone cements in joint arthroplasty procedures. This includes SmartSet GHV Gentamicin Bone Cement. The reviews include the abstracts from the literature search that includes papers supporting the long-term use of bone cement containing antibiotic.

Each review concludes that SmartSet GHV Gentamicin Bone Cement can be considered to confer a comparably favourable risk-benefit profile to that of its essentially similar brands of Palacos R40 Gentamicin and DePuy CMW 1 Gentamicin Bone Cements.

11.1.3 Post Marketing Surveillance Studies

DePuy CMW undertakes a systematic review of information relating to its products once they have been placed on the market. Two recent post marketing clinical studies supporting SmartSet GHV Gentamicin Bone Cement are summarised in the following sections. Recent publications relevant to the use of the product are summarised in the literature reviews covered in section 11.1.2.

<u>Study 1 - Wrightington Hospital, Wigan, UK</u>

This ongoing single centre, prospective, 10-year study is designed to compare the clinical performance of SmartSet GHV Gentamicin Bone Cement with that of DePuy CMW 1 Gentamicin Bone Cement in primary hip and knee arthroplasty.

The primary objective of the investigation was to evaluate the safety of levels of gentamicin in serum, urine and wound drainage fluid, eluted from SmartSet GHV Gentamicin Bone Cement when used in primary total hip and knee arthroplasty.

The secondary objective of the investigation is to further evaluate the safety and performance of SmartSet GHV Gentamicin Bone Cement when used in primary hip arthroplasty when compared to DePuy CMW 1 Gentamicin and also to evaluate the safety and performance when used in primary knee arthroplasty.

A total of 27 patients were recruited into the study. Patients undergoing hip arthroplasty received either SmartSet GHV Gentamicin Bone Cement (11 patients) or DePuy CMW 1 Gentamicin (8 patients) for the femoral component, DePuy CMW 2 Gentamicin for the acetabular component. SmartSet GHV was used in 8 patients undergoing knee arthroplasty.

An interim report of the results at 3 months post surgery show the following:
- Radiographic results show that a stable, well-positioned prosthesis has been achieved in all subjects
- Therapeutic, non toxic levels of gentamicin were achieved in wound drainage, serum and urine of all patients

• The usual pattern of gentamicin clearance via the kidneys was seen in all patients, with urine concentration reaching a maximum between 6 and 24 hours post operatively, then declining to low levels by the time of patient discharge

The results demonstrate equivalent performance of SmartSet GHV Gentamicin Bone Cement to DePuy CMW 1 Gentamicin Bone Cement, at 3 months post surgery when used for fixation of prosthetic hip and knee implants.

Study 2 - University Hospital of Trondheim, Norway

This ongoing single centre, prospective, radiostereometric analysis (RSA) study is designed to compare the clinical performance of the unmedicated SmartSet HV Bone Cement with that of the unmedicated Palacos R Bone Cement in primary hip arthroplasty.

The primary objective of this investigation is to determine whether the stability of the Charnley femoral prostheses are equivalent when implanted with SmartSet HV or Palacos R Bone Cements.

A total of 35 patients were recruited into the study. SmartSet HV Bone Cement was used in 18 patients; Palacos R Bone Cement was used in 17 patients. A summary of the RSA results up to 12 months show only minor differences in rotations and translations between the two cements after one year.

The 2-year RSA data is currently being evaluated.

Although this study was performed with SmartSet HV Bone Cement, the results are considered equally applicable to SmartSet GHV Gentamicin Bone Cement, since the latter only differs from the former by the inclusion of Gentamicin Sulphate; both SmartSet HV and SmartSet GHV Gentamicin have been shown, through *in vitro* testing, to have similar physicomechanical properties.

11.2 SmartSet HV Bone Cement (and prefilled systems)

11.2.1 Clinical Studies

SmartSet HV Bone Cement was designed and developed at DePuy CMW, Blackpool to be a high viscosity bone cement with a fast pick-up, long working time and mechanical properties similar to Palacos R40 Bone Cement. Palacos R40 Bone Cement has been commercially available worldwide for over thirty years, and as such there is clinical documentation demonstrating its safety and efficacy. Since the composition of the cements are similar, the safety and efficacy of Palacos R40 can be inferred to SmartSet HV Bone Cement.

The safety of SmartSet HV Bone Cement has also been demonstrated by direct comparison to Palacos R40 for creep, fatigue, biocompatibility and toxicity testing. All results are comparable to Palacos R40.

11.2.2 Post Marketing Surveillance Studies

Study 1 - University Hospital of Trondheim, Norway

This ongoing single centre, prospective, radiostereometric analysis (RSA) study is designed to compare the clinical performance of the unmedicated SmartSet HV Bone Cement with that of the unmedicated Palacos R Bone Cement in primary hip arthroplasty.

The primary objective of this investigation is to determine whether the stability of the Charnley femoral prostheses are equivalent when implanted with SmartSet HV or Palacos R Bone Cements.

A total of 35 patients were recruited into the study. SmartSet HV Bone Cement was used in 18 patients; Palacos R Bone Cement was used in 17 patients. A summary of the RSA results up to 12 months show only minor differences in rotations and translations between the two cements after one year.

The 2-year RSA data is currently being evaluated.

11.3 Undesirable effects

The majority of orthopaedic surgical procedures are very invasive, and are often performed on elderly patients who are at a higher risk of complications including a number of severe complications. Those with fatal outcome associated with the use of bone cements include myocardial infarction, cardiac arrest, cerebrovascular accident, pulmonary embolism and anaphylaxis. The risks associated with the use of SmartSet GHV Gentamicin Bone Cement are the same as for any other bone cement containing Gentamicin; these risks are articulated in the instructions for use provided with each pack of SmartSet GHV Gentamicin Bone Cement. Literature searches and reviews regarding complications from using bone cement are detailed below.

- N D Watkins, Death and Serious Complications from Acrylic Bone Cements, A Literature Review
- Steffen J. Breusch, MD, Serious complications in total hip arthroplasty related to the use of bone cement

There is no specific undesirable side effects relating to the use of SmartMix Cemvac prefilled with SmartSet GHV Gentamicin or SmartSet HV Bone Cements. Providing the systems are stored and used correctly as intended in line with the instructions for use.

11.4 Conclusions

Post marketing clinical studies can demonstrate the clinical efficacy and safety of SmartSet GHV Gentamicin Bone Cement and its prefilled systems and SmartSet HV Bone Cement and its prefilled systems. Additionally, the clinical experience of DePuy CMW 1 Gentamicin and Palacos R with Gentamicin, and the results of non-clinical testing demonstrate that SmartSet GHV Gentamicin Bone Cement has equivalent elution results to Palacos Gentamicin Bone Cements and that both SmartSet GHV Gentamicin

Bone Cement and SmartSet HV Bone Cement have at least equivalent biocompatibility and physicomechanical properties to DePuy CMW 1 Gentamicin and Palacos R Gentamicin bone cements.

It is concluded that both SmartSet GHV Gentamicin Bone Cements and SmartSet HV Bone Cements are safe and effective for their intended use, and therefore can be considered to confer a favourable risk benefit profile in arthroplasty procedures.

12.0 References

1. Charnley J.
   Low friction arthroplasty.
   Clin. Orthop. Rel. Res. 72:7. (1970)

2. Charnley J. & Cupic F.
   The nine and ten year results of low friction arthroplasty of the hip.
   Clin. Orthop. 95:9. (1973)

3. Wroblewski BM. (1983)
   Instrumentation and practical approach of revision.
   Article in University of Sheffield Symposium on Revision Surgery

4. Chen X.X
   Influence of vacuum mixing on mechanical properties of homemade bone cement.
   Chung Hua Wai Ko Tsa Chih, 1992 Oct; 30(10):593-5, 635-6.

5. Alkire M.J., Dabezies E.J., Hastings P.R.
   High vacuum as a method of reducing porosity of polymethyl methacrylate
   Orthopaedia 1987 Nov 10(11):1533-9

6. Wang J.S.; Franzen H, Jonsson E, Lidgren L.
   Porosity of bone cement reduced by mixing and collecting under vacuum.
   Acta. Orthop. Scand., Apr 1993; 64(2): 143-6

7. Wixson R.L.
   Do we need to vacuum mix or centrifuge cement?
   Clin. Orthop., Dec 1992 (285): 84-90.

8. Linden U, Gillquist J
   Air inclusion in bone cement. Importance of the mixing technique.
   Clin. Orthop., Oct 1989 (247): 148-51.

9. Linden U
   Fatigue properties of bone cement. Comparison of mixing techniques.
   Acta. Orthop. Scand., Aug. 1989; 60(4): 431-3.

10. Schreurs B.W., Spierings P.T., Huiskes R, Sloof T.J.
    Effects of preparation techniques on the porosity of acrylic cements.
    Acta. Orthop. Scand., Aug 1988; 59(4): 403-9.

11. Lidgren L, Drar H, Moller J.
    Strength of polymethyl methacrylate increased by vacuum mixing.
    Acta. Orthop. Scand., Oct 1984; 55(5): 536-41.

12. Wixson R.L., Lautenschlager E.P., Novak M.A.
Vacuum mixing of acrylic bone cement.
J Arthroplasty 1987; 2(2): 141-9.

13. Norman T L, Kish V, Blaha J D, Gruen T A, Hustosky K
Creep characteristics of hand and vacuum mixed acrylic bone cement at elevated stress levels.

14. Askew M J, Kufel M F, Fleissner Dr Jr, Gradisar I A, Salstrom S J, Tan J S
Effect of vacuum mixing on the mechanical properties of antibiotic impregnated polymethyl methacrylate bone cement.
J. Biomed Mater Res., May 1990; 24(5): 573-80

15. Health & Safety Executive, UK
EH40/2000 Occupational Exposure Limits
Pub: HMSO, London.