HELSINN HEALTHCARE	Medical Device Division	Number: HHC-MDD/FT01/A11/r04

Issued: 28/04/2016 Subject: **Technical File – Annex 11 - Revision 04: Biocompatibility – Clinical –Safety Data** **GEL FOR TREATMENT OF ORAL MUCOSA**	Edited by: RA Reviewed by: QA Approved by: Management 29.04.16

Changes from previous revision:

Date	Rev	Document Status
25-Aug 2009	01	First emission (a new TF was prepared, after reclassification of product).
31-Jan 2013	02	Integration of new clinical data available, by means of a Clinical Evaluation Report covering the period 20.05.2009 – 2.10.2012. The original Expert Report dated 15.07.09 is included as Appendix n° 1.
31-Mar 2015	03	Integration of new clinical data available, by means of a Clinical Evaluation Bridging Report and a Postmarketing Safety Data Report, both covering the period 3.10.2012 – 31.12.2014. Addition of experts' CV.
28-Apr 2016	04	Addition of a Clinical Evaluation Bridging Report and a Postmarketing Safety Data Report, both covering the period 1.01.2015 – 31.12.2015. Update of relating experts' CV.

Table of contents

Efficacy and Safety Evaluation

"Clinical Evaluation Bridging Report (from January 1st to December 31 2015)
Gel for treatment of oral mucosa - Gelclair®"
dated 25.04.2016, by Fabio Macchi

Fabio Macchi's CV

"Postmarketing Safety Data - Gelclair®" - January 1, 2015 to December 31, 2015",
Dated 14.03.2016, by Diana Koprivec

Diana Koprivec's CV

"Clinical Evaluation Bridging Report (from 3 October, 2012 to 31 December, 2014)
Gel for treatment of oral mucosa - Gelclair®"
dated 19.02.2015, by Fabio Macchi

"Postmarketing Safety Data - Gelclair®" - October 3, 2012 to December 31, 2014",
dated 2.03.2015, by Diana Koprivec

"Clinical Evaluation Report - Gelclair® - May 20, 2009 to October 2, 2012 – Bridging document"
dated 31.01.2013, by Fabio Macchi

Enclosure:
"Postmarketing Safety Data of Gelclair® from May 20, 2009 to October 2, 2012"

Appendix 1:
"Gel for Treatment of Oral Mucosa – Expert Report" dated 15.07.2009,
by Dorothy Keefe

Dorothy Keefe's CV

Issued on : 29/09/2011 Object: **Model 29 – rev. 01:** **Clinical Evaluation Report**	Edited by : DD Reviewed by: QA Approved by : Management Date:

Clinical Evaluation Bridging Report

(From January 1st to December 31st 2015)

GEL FOR TREATMENT OF ORAL MUCOSA

GELCLAIR®

Helsinn Healthcare SA

This report was prepared according to:

MEDDEV 2.7.1. rev. 3 **December 2009**	**CLINICAL EVALUATION:** **A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES**

Table of Contents

1. General details

Name of the Device:	**Gelclair**
Formulation:	**Water-based oral rinse gel**
Use:	**Oral rinse**
Packaging (primary)	**15 ml Sachet Concentrated Oral Gel** **180ml Bottle Concentrated Oral Gel**
Medical Device Class:	**IIa**
Intended Use:	Gelclair® helps the management of painful symptoms of mucositis of the oropharyngeal cavity. Gelclair®, used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, traumatic ulcers caused by dental braces and dentures and ageing.
Instruction for Use:	**15 ml Sachet and 180 ml Bottle** Gelclair® should be used 3 times a day or as needed. Avoid eating or drinking for at least 30-60 minutes following treatment. Pour the entire contents of the single-dose Gelclair® sachet into a glass and add approximately 40ml of water (3 table spoon full). Stir mixture well and use at once. Rinse around the mouth for at least one minute or as long as possible to coat tongue, palate, throat, inside of cheeks and all oral tissue thoroughly. Gargle and spit out. Discard any unused mouthwash. Do not swallow. In patients which are not able to rinse and gargle (e.g. young children) it is suggested to apply the product directly into the mouth by using a sponge or swab.
Manufacturer:	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Pazzallo – Lugano – Switzerland

2. Description of the device and its intended application

GELCLAIR is a non-sterile, non-invasive, non-implantable, water-based gel for oral rinse; it can be used on intact or damaged oral mucosa.
GELCLAIR (180 ml Bottle) can be used after the first opening as allowed according to the validity date reported on the packaging.
Gelclair (15 ml sachet) is designed for single dose use.
The device is intended to be used as oral rinse in contact with oral mucosa, with or without minor trauma or ulcers, for a short term use (continued use: more than 30' but less than 30 days).

GELCLAIR must not be swallowed.

GELCLAIR is a gel that, when applied to the oral mucosa, forms a protective film, exerting a protective action in relation to damaged areas.
The components responsible for the formation of this film are mainly: polyvinylpyrrolidone (PVP) and hyaluronic acid.
PVP exert a filming action.
Hyaluronic acid is a bio-polymer with a very large molecular weight; hyaluronic acid plays a fundamental role in maintaining the homeostasis of the tissues thus promoting hydration, plasticity, viscosity and mucosa wellness.
The complete list of ingredients is reported in Table 1

Table1: GELCLAIR ingredients

AQUA, PVP, MALTODEXTRIN, PROPYLENE GLYCOL, PEG-40 HYDROGENATED CASTOR OIL, HYDROXYETHYLCELLULOSE, AROMA, DISODIUM EDTA, SODIUM HYALURONATE, SODIUM SACCHARIN, GLYCYRRHETINIC ACID, PRESERVATIVES (POTASSIUM SORBATE, SODIUM BENZOATE, BENZALKONIUM CHLORIDE)

GELCLAIR does not contain drugs, products of animal origin, or any other component extracted or derived from blood.

3. Intended therapeutic and/or diagnostic indication and claims

Gelclair® helps the management of painful symptoms of mucositis of the oropharyngeal cavity. Gelclair®, used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, traumatic ulcers caused by dental braces and dentures and ageing.

4. Scope of the document

Scope of the document is to verify, and, in case, integrate, scientific data available on the product Gelclair® between January 1st and December 31st 2015.

5. Data analysis

Literature review

Literature was evaluated according to SOP P17 Rev.02 and related annexes and the final results are summarized in the following references identified:

(1) Casale, M., Moffa, A., Sabatino, L. *et al.* Hyaluronic acid: Perspectives in upper aero-digestive tract. A systematic review. PLoS One 2015; 10.

(2) Caramella, C. M., Bonferoni, M. C., Sandri, G. *et al.* Medical devices for oral mucosal applications. Advances in Delivery Science and Technology 11, 225-245. 2015.

For these references, based on their contents, the potential relevance for the product, both in terms of efficacy and safety, was defined.

In Table 2, references are classified according to identified relevance.

	Relevance			
Ref.	***Performance***	***Safety***	***Both***	***Significant (Y/N)***
1	YES	NO	NO	NO
2	YES	NO	NO	NO

Table 2: evaluation of identified references

None of the 2 literature references identified was considered significant for the safety and/or performance of the device under evaluation (Gelclair).

6. Conclusions

A periodic check of new information relating to the period from January 1st to December 31st 2015 and potentially leading to the efficacy and/or safety of the medical device Gelclair was carried out.
Few articles were identified (n=2) and none of them was relevant, neither in terms of safety nor in terms of efficacy in relation to Gelclair.
In conclusion, it is possible to confirm the efficacy and safety profile of Gelclair.

Fabio Macchi, MSc

Helsinn Healthcare SA
Integrative Care Division - Head of Scientific & Clinical Portfolio Development
Medical Device Division - Corporate Design and Development Manager

Signature: .....

Date: 25 APR 2016 .....

CURRICULUM VITAE

PERSONAL DATA

Name	MACCHI FABIO
Address	C/O HELSINN HEALTHCARE SA
Phone	Office: +41 91 9852121
	Mobile +41 79 3752302
Fax	–
E-mail	fabio.macchi@helsinn.com

Nationality	Italian
Birth Date	APRIL 1ST, 1964

WORKING EXPERIENCES

• Date	From 2014 up to now
• Employer Name and Address	Helsinn Integrative Care Business unit of Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Pharmaceutical and Chemical
• Kind of job	Managerial, Head of scientific and clinical development
• Main duties and responsibilities	Identification of new products (supplements, food supplements, medical food, herbals) or ingredients useful in the management of symptoms related to chemo and/or radiotherapy Coordinate and realize regulatory, clinical, and technical activities related to products Responsible for scientific communication Keep the relationships with external KOLs, partners or suppliers in relation to products under development
• Date	From 2012 to 2014
• Employer Name and Address	Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Pharmaceutical and Chemical
• Kind of job	Managerial, a)Medical Device Division (MDD) b)Complementary products in cancer care c)OncoQOL International Division
• Main duties and responsibilities	Identification of new products (supplements, food supplements, medical food, herbals) or ingredients useful in the management of symptoms related to chemo and/or radiotherapy Coordinate and realize regulatory, clinical, and technical activities related to products Keep the relationships with external KOLs, partners or suppliers in relation to products under development

• Date	From 2010 to 2012
• Employer Name and Address	Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Chemical-Pharmaceutical
• Kind of job	Managerial, Medical Device Division (MDD) responsible for : a) Medical Devices Design and Development b) Clinical Investigation c) Project Management
• Main duties and responsibilities	Person in charge for the promotion of Design and Development of new Medical Devices (MD) as well as life cycle management and product already "in house" Organization and coordination of scientific activities related to the development of new MDs in compliance with EU and FDA requirements Creation of requested technical documentation both for US and UE markets Responsible for the clinical investigation activities related to MDs Coordination of the entire MD team through project management techniques Evaluation of unmet medical needs Development of new indications for already available MD Development of new products that will cover specific medical needs
• Date	From 2008 to 2010
• Employer Name and Address	Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Chemical-Pharmaceutical
• Kind of job	Managerial, Medical Development Department
• Main duties and responsibilities	Research and development of Unmet Medical Needs in cancer supportive care Responsible for the Medical Device Design & Development Department, related to Medical Devices (Risk Assessment & Management Techniques, ISO13485) Development of related Quality System, SOPs, Quality Manual, and Technical Documents
• Date	From 2007 to 2008
• Employer name and address	Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Chemical-Pharmaceutical
• Kind of job	Managerial; responsible for the Anti-inflammatory & Gastroenterology Medical Marketing activities
• Main duties and responsibilities	Person in charge for the promotion of scientific activities. As responsible for the Department promotion and management of the different activities aimed at supporting from a scientific point of view the licensing companies (WW) and/or the Opinion Leaders who work with our Company Coordination and organization, through collaborators and agencies, of scientific events related to product launch and/or support in marketing countries Pre-clinical and clinical study promoter Responsible for the experimental design of Phase IV clinical studies, with consequent editorial activities (scientific papers for product support) Project Leader of different activities of the Company, especially related to product life-cycle-management Evaluation of new therapeutical opportunities; search of new indications for the molecules which are already present in our Company Responsible for medical and scientific communication towards regulatory European (EMEA-CHMP) and international (AIFA, KFAD, Thai MoH..) agencies, in relation to regulatory activities aimed at "defending" our products, especially during revision procedures of benefit/risk profiles (Art. 31 and 107)
• Date	From 2001 to 2007
• Employer name and address	Boheringer-Ingelheim/Pharmaton SA Via Mulini , 6934 CH-Bioggio
• Kind of Company	Pharmaceutical

2

• Kind of job	Managerial; for: a) Quality Assurance Department (QA) b) Computer System Validation (CSV) c) Regulatory activities d) Pharmacovigilance
• Main duties and responsibilities	Validation, according to good manufacturing practices (GMP), of the productive processes. Analysis, development and implementation of specific processes related to the implementation of required good laboratory practices (GLPs) Local responsible for the Computer System Validation (CSV) activities with direct relationship to Boheringer-Ingelheim Head Quarters Development of specific procedure to assure the compliance of the Unit both to the Boheringer-Ingelheim rules as well as to the FDA & EU requirements related to the Computerized Systems Development, training and maintenance of specific SOPs related to CSV, and QA Implementation, updating, training and monitoring of the quality system Responsible for GMP, GLP, and CSV inspections to third parties Part of the e-CTD Team with the specific aim to implement a computerized system to fulfill the regulatory requirements related to the common technical documents Responsible for the identification and implementation of a computerized system related to the Pharmacovigilance needs according to the Vol. 9A of the EU, and related Quality System
• Date	From 1998 to 2001
• Employer name and address	Helsinn Healthcare SA CH-Pambio Noranco
• Kind of Company	Chemical-Pharmaceutical
• Kind of job	Managerial; Medical Marketing
• Main duties and responsibilities	Responsible for the scientific support to Helsinn Marketing Department and affiliated companies world-Wide Responsible for the scientific support towards the Medical Department of the Company Coordinator and planner of specific scientific activities related to product launch in different new countries (> 80 countries in the world) Pre-clinical and clinical study promoter to be conducted according to the required quality standards (GLP, GCP, GMP) Responsible for Phase IV studies
• Date	From 1993 to 1998
• Employer name and address	Zambon Group Bresso (MI)
• Kind of Company	Chemical-Pharmaceutical
• Kind of job	Technical-managerial; responsible for the pharmacokinetics laboratory
• Main duties and responsibilities	Responsible for GLP activities related to the laboratory of pharmacokinetics analysis Develop and implementation of a specific quality plan for the laboratory to achieve the GLP recognition from the Italian MoH Development, implementation and validation of the systems for the computerized management of critical analytical data Development and validation of new analytical methods, with different qualitative and quantitative techniques Pharmacokinetics modeling Pharmacokinetics of pre-clinical studies Pharmacokinetics studies related to Phase I, II and III clinical studies Consultant for WHO, concerning GLP e GCP rules
• Date	From 1991 to 1993
• Employer name and address	Inpharzam Ricerche CH-Taverne
• Kind of Company	Research and Development (R&D); responsible for the biological models laboratory
• Kind of job	Technical/analytical

3

• Main duties and responsibilities	Responsible for the screening activities related to new molecules under evaluation (NCE) in animal models (vitro-vivo) Development and validation of analytical methods with most common techniques (i.e. HPLC-UV, HPLC-GC, HPLC-MS)

EDUCATION AND TRAINING

• Date	From 1989 to 1991
• Name and kind of the education/training institute	Università degli Studi di Milano, post-degree training
• Main subjects / professional skills of the study	Purification and characterization of a serine-proteinase from the extreme thermophilus *S.solfataricus*
• Achieved title	Doctor in Biological Sciences, with a specialization in Biochemistry
• Date	From 1983 to 1988
• Name and kind of the education/training institute	Università degli Studi di Milano , Degree in Biological Sciences
• Main subjects / professional skills of the study	Enzimology
• Achieved title	Doctor in Biological Sciences
• Date (from – to)	From 1978 to 1983
• Name and kind of the education/training institute	Istituto Tecnico Superiore Statale "L.Cobianchi", Diploma in Biological Chemistry
• Main subjects / professional skills of the study	Chemistry, Biology, Biochemistry
• Achieved title	Chemical-Biological degree

NATIVE SPEAKER: ITALIAN

OTHER LANGUAGES

	ENGLISH
• Reading skills	very good
• Writing skills	very good
• Speaking skills	very good

RELATIONAL SKILLS AND COMPETENCES

Reflexive and well-judging, with good empathy, technical-scientific conversations are my favorite; but I am also interested in other daily subjects, like politics, sport and social matters.

I am very interested in the cultures of other countries and, when it is possible during my travels, I like broadening these subjects with my local interlocutors.

As Project Manager, I think that I am able to transmit to the team the importance of sharing objectives; I strongly believe that the team play is a "winning weapon", especially in today scientific and commercial field.

I think I better express my expertise when I am engaged in important matters, which are often of high criticality for the Company.

Of my job, I especially like the possibility to manage different activities in the same time: I find it very stimulating, because it makes me improve and optimize my skills, times and execution ways of my projects.

ORGANIZING SKILLS AND COMPETENCES

I coordinate the work of colleagues who help me in the daily activities and I am the operative interface with the direct superior.

As Project Manager, I use all the available instruments and techniques for the achievement of the identified objectives.

I had the opportunity to develop a "global vision" of the Pharma-world, which helps me a lot to frame the different problems and, as a result, to find the best solutions.

Specific skills can be summarized as follow:

a) Basic research
b) Pharmacokinetics
c) Pharmaceutical technology
d) Pharmaceutical production
e) Quality (GMP, GLP, GCP, ISO)
f) Regulatory aspects related to Drugs, Medical Devices, Medical food, and Food-supplements (EU & FDA)
g) Scientific and medical marketing
h) Computer System Validation.
i) Medical Devices (UE/US)
j) Food supplements, Medical Food

TECHNICAL SKILLS AND COMPETENCES	Microsoft Office suite (Excell, Word, Access, Visio, Front Page) Win NonLin Microsoft Project Calibration Manager Power Point Microcal Origin End Notes Reference Manager SaS (user) Webex Scientifc databases normally used
DRIVING LICENCE	"B"

I authorize the treatment of my personal data.

POSTMARKETING SAFETY DATA

GELCLAIR®

January 1, 2015 to December 31, 2015

Helsinn Healthcare SA

Introduction

Gelclair® is a Medical Device (MD) intended to help the management of painful symptoms of mucositis and stomatitis of the oropharyngeal cavity.
Gelclair® used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions and ulcers, including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces, dentures and ageing.
Over a period of time of about fifteen years about 24.4 million of single doses were supplied worldwide and only 45 post-marketing non-serious cases, none classified as incident/reportable adverse event, were collected in the manufacturer's safety database.

Aim of the document

The aim of this document is to integrate post marketing safety data previously reported (2000 to May 19, 2009; May 20, 2009 to October 2, 2012; October 3, 2012 and December 31, 2014) in Gelclair Technical File with data collected between January 1, 2015 and December 31, 2015.

Data collection

All relevant data coming from suppliers, pharmacists, physicians, patients and from all possible sources, concerning any real or potential safety problem related to the use of Gelclair®, are collected in the Manufacturer's Safety Database ARGUS.

Table 1: Post marketing data

ISSUE		PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4	TOTAL	COMMENT (Description, cause, consequence, etc.)
		2000 – 19.5.2009	20.5.2009-2.10.2012	3.10.2012-31.12.2014	01.01.2015-31.12.2015	2000 – 31.12.2015	
Preferred term (main event)	**Incident (Yes/No)**						
Gastrointestinal disorders SOC							
Abdominal pain upper	No	--	1	--	--	1	patient with chronic gastritis and oral fungal infection
Constipation	No	--	1	--	--	1	cancer patient
Dental caries	No	1	--	--	--	1	cancer patient
Hypoaesthesia oral	No	1	--	--	--	1	pre-existent Herpes simplex oral infection
Lip swelling	No	2	--	--	--	2	1 cancer patient, 1 unknown indication
Mouth ulceration	No	1	--	--	--	1	plasma cell stomatitis
Dry mouth	No	--	--	--	1	1	associated with oral pain
Nausea	No	1	--	--		1	cancer patient
Vomiting	No	--	--	--	1	1	no info on medical history provided
Oral discomfort	No	3	3	--	--	6	3 cancer patients, 1 stomatitis of unknown origin, 2 unknown indication
Oral mucosal blistering	No	--	1	--	--	1	end stage cancer
Oral mucosal discolouration	No	1	--	--	--	1	cancer patient
Oral mucosal erythema	No	--	1	--	--	1	diabetes patient with mouth ulcers and discomfort
Oral pain	No	2	--	--	1	3	1 unknown indication, 1unknown stage of mucositis, 1 unclear temporal relationship
Stomatitis	No	1	1	--	--	2	1 cancer patient, 1 medical history of lichen planus of mouth
Tongue discolouration	No	1	--	1	--	2	1 graft vs host disease, 1 on multiple unspecified medications

ISSUE		PERIOD 1 2000 – 19.5.2009	PERIOD 2 20.5.2009-2.10.2012	PERIOD 3 3.10.2012-31.12.2014	PERIOD 4 01.01.2015-31.12.2015	TOTAL 2000 – 31.12.2015	COMMENT (Description, cause, consequence, etc.)
Preferred term (main event)	**Incident (Yes/No)**						
Tooth discolouration	No	2	--	--	--	2	1 mouth lymphoma, 1 cancer patient with externsive denture and fillings
Total cases		**16**	**8**	**1**	**3**	**28**	
General disorders and administration site conditions SOC							
Device ineffective	No	--	1	2	--	3	1 unknown product indication and medical history, 1 sample sachets only used, 1throat cancer (unknown stage) patient under radio and chemotherapy
Device misuse	No	--	3	--	--	3	swallowing, no adverse event reported
Accidental Device ingestion	No	--	--	1	--	1	swallowed accidentally, no adverse event reported
Mucosal inflammation	No	--	--	--	1	1	no detail on mucositis stage and radiotherapy duration, no details on underlying cancer
Total cases		--	**4**	**3**	**1**	**8**	
Immune system disorders SOC							
Hypersensitivity	No	1	--	--	--	1	cancer patient with known hypersensitivity to penicillin
Total cases		**1**	--	--	--	**1**	
Injury, poisoning and procedural complications SOC							
Gingival injury	No	1	--	--	--	1	unknown indication
Total cases		**1**	--	--	--	**1**	
Nervous system disorders SOC				--			
Burning sensation	No	2	--	--	1	3	1 squamous cell carcinoma of mouth, 1 tonsilar lymphoma, 1 transitory burning sensation
Burning sensation mucosal	No	1	--	--	--	1	unknown indication
Total cases		**3**	--	--	**1**	**4**	

ISSUE		PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4	TOTAL	COMMENT (Description, cause, consequence, etc.)
		2000 – 19.5.2009	20.5.2009- 2.10.2012	3.10.2012- 31.12.2014	01.01.2015- 31.12.2015	2000 – 31.12.2015	
Preferred term (main event)	**Incident (Yes/No)**						
Respiratory, thoracic and mediastinal disorders SOC							
Dyspnoea	No	1	--	--	--	1	history of asthma in cancer patient, concomitant mucosal inflammation
Total cases		**1**	**--**	**--**	**--**	**1**	
Skin and subcutaneous tissue disorders SOC							
Rash	No	1	1	--	--	2	1 unknown indication, 1 cancer patient
Total cases		**1**	**1**	**--**	**--**	**2**	
Overall total cases		**23**	**13**	**4**	**5**	**45**	

Data analysis

Between 2000 and May 19, 2009 (Period 1) **23** reports were collected and evaluated, and about 12 million single doses were supplied worldwide. None of these cases was classified as incident/reportable adverse event.

In the period of time between May 20, 2009 and October 2, 2012 (Period 2) further **13** reports were collected and about 5.4 million of single doses supplied worldwide. As for the previous ones, no incidents/reportable adverse events were identified.

Between October 3, 2012 and December 31, 2014 (Period 3), **4** reports were collected and about 4.8 million of single doses supplied worldwide. No incidents/reportable adverse events were received.

From January 1, 2015 to December 31, 2015 (Period 4), **5** reports only were collected and about 2.2 million single doses supplied worldwide. None of the reports referred to incidents/reportable adverse events.

Overall, **45** post-marketing reports (Table 1) were collected in the Safety Database. None of them was assessed as incident. The distribution of the reported cases by System Organ Class (SOC) and Preferred Term (main event) shows a prevalence of Gastrointestinal disorders SOC adverse events (25) and are mainly regarding cancer patients (14). It is to be noted that Gelclair is indicated for the treatment of chemotherapy and radiotherapy-induced mucositis, therefore the underlying disease, often severe at the time of Gelclair application, may determine or influence the reaction to the product. Cases of hypersensitivity, rash, dyspnoea, gingival injury and burning sensation were also described (8). One case 2008AU004275 described dyspnoea associated with burning sensation, mucosal inflammation and dysphagia in a colon cancer patient; the patient had an underlying asthma which confounded the causality assessment, it is unclear if the patient received chemo or radiotherapy and for which duration. It did not meet incident criteria and was assessed possibly related due to temporal relationship only.

During the period between May 20th, 2009 and October 2nd, 2012 a total of **13** reports were received, including the cases of lack of efficacy and device misuse.
None was assessed as incident. One case 2012DE006847 (Oral discomfort, oral mucosal erythema, dysphagia) was assessed as incident by the German Regulatory Authority due to the lack of information with regard to the case assessment elements, however, based on the Manufacturer investigation and internal evaluation, the case did not meet the incident criteria. No safety concerns arise from the in-depth analysis of this single case or from the overall analysis of other cases collected in the Safety Database.
It is to be noted that starting from 2010, upon internal decision to monitor the correct use of the product, all cases of device misuse were collected. These cases (3) referred to accidental swallowing of the product and did not lead to adverse events. Additionally, 1 case of reported lack of efficacy was received.

The distribution by SOC and main event's Preferred Term is similar to the previous analysed period, showing the prevalence of Gastrointestinal disorders SOC (8). As previously mentioned, 3 cases of misuse and 1 lack of efficacy were also reported. Additionally, 1 case of rash in a cancer patient was reported in this last period.

The previous update refers to the period between October 3, 2012 and December 31, 2014; a total of **4** reports were collected, including 1 case of tongue discoloration, 2 cases of lack of efficacy and 1 accidental device ingestion. None was assessed as incident/reportable adverse event.

The current update considered the time interval between January 1, 2015 to December 31, 2015; **5** reports were received from various sources, including 1 case of dry mouth, 1 oral pain, 1 vomiting, 1 mucosal inflammation and 1 referring to burning sensation. None was assessed as incident/reportable adverse event.

Conclusion

No safety concern was identified so far from the separate and cumulative analysis of the post-marketing reports. The well-known Gelclair® benefit-risk balance remains favourable and unchanged over the time. No change in the Product's Instructions for Use is deemed necessary in this regard.

HELSINN HEALTHCARE SA

Diana Koprivec, MD PhD
Safety, Medical Device Division

Pazzallo-Lugano, 14th March 2016

CURRICULUM VITAE

DIANA KOPRIVEC, MD PhD

Personal data

Adress:	Via San Gottardo 80, 6900 Massagno (Lugano), Switzerland
Telephone N.:	+41 79 220 10 94
Citizenship:	Romania, Slovenia
Birth date:	30.07.1967

Education

Universitary:	*M.D. degree* (1992 University of Medicine, Craiova, Romania)
Postuniversitary:	*Endocrinology Specialist degree* (2000 Bucharest, Romania) *Ph.D. degree* (2006 University of Milan, Italy)

Professional Career

1992-1993:	Endocrinology training (pre-specialization), Craiova
1993-2000:	Specializing in Endocrinology and Metabolic Diseases, Bucharest
2001-2004:	Clinical research for Ph.D. degree, Milan
2003:	Assistant MD for Clinical Trials at Dr. P.Gerber Clinic, Lugano
2004-2005:	Assistant MD for Clinical Trials at Cardiocentro Ticino
From 09.01.2006:	**Drug Safety Manager**, Helsinn Healthcare SA.

Memberships

International Society of Pharmacovigilance (ISOP)
Ordine dei Medici del Cantone Ticino (OMCT)
Società Italiana dell'Obesità
Società Lombarda dell'Obesità (founding member)
Romanian Society of Psychoneuroendocrinology
Associazione Farmaceutici Ticinese AFTI (member of the Directive Committee)

Lugano, 14 March 2016

Issued on : 29/09/2011 Object: **Model 29 – rev. 01:** **Clinical Evaluation Report**	Edited by : DD Reviewed by: QA Approved by : Management Date:

Clinical Evaluation Bridging Report

(From 3.10.2012 to 31.12.2014)

GEL FOR TREATMENT OF ORAL MUCOSA

GELCLAIR®

Helsinn Healthcare SA

Lugano, 19/02/2015

This report was prepared according to:

MEDDEV 2.7.1. rev. 3 December 2009	CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Table of Contents

1. General details

Name of the Device:	**Gelclair**
Formulation:	**Water-based oral rinse gel**
Use:	**Oral rinse**
Packaging (primary)	**15 ml Sachet Concentrated Oral Gel** **180ml Bottle Concentrated Oral Gel**
Medical Device Class:	**IIa**
Intended Use:	Gelclair® helps the management of painful symptoms of mucositis of the oropharyngeal cavity. Gelclair®, used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, traumatic ulcers caused by dental braces and dentures and ageing.
Instruction for Use:	**15 ml Sachet and 180 ml Bottle** Gelclair® should be used 3 times a day or as needed. Avoid eating or drinking for at least 30-60 minutes following treatment. Pour the entire contents of the single-dose Gelclair® sachet into a glass and add approximately 40ml of water (3 tablespoonfuls). Stir mixture well and use at once. Rinse around the mouth for at least one minute or as long as possible to coat tongue, palate, throat, inside of cheeks and all oral tissue thoroughly. Gargle and spit out. Discard any unused mouthwash. Do not swallow. In patients which are not able to rinse and gargle (e.g. young children) it is suggested to apply the product directly into the mouth by using a sponge or swab.
Manufacturer:	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Pazzallo – Lugano – Switzerland

2. Description of the device and its intended application

GELCLAIR is a non-sterile, non-invasive, non-implantable, water-based gel for oral rinse; it can be used on intact or damaged oral mucosa.

GELCLAIR (180 ml Bottle) can be used after the first opening as allowed according to the validity date reported on the packaging.

Gelclair (15 ml sachet) is designed for single dose use.

The device is intended to be used as oral rinse in contact with oral mucosa, with or without minor trauma or ulcers, for a short term use (continued use: more than 30' but less than 30 days).

GELCLAIR must not be swallowed.

GELCLAIR is a gel that, when applied to the oral mucosa, forms a protective film, exerting a protective action in relation to damaged areas.

The components responsible for the formation of this film are mainly: polyvinylpyrrolidone (PVP) and hyaluronic acid.

PVP exerts a filming action.

Hyaluronic acid is a bio-polymer with a very large molecular weight; hyaluronic acid plays a fundamental role in maintaining the homeostasis of the tissues thus promoting hydration, plasticity, viscosity and mucosa wellness.

The complete list of ingredients is reported in Table 1

Table 1: GELCLAIR ingredients

AQUA, PVP, MALTODEXTRIN, PROPYLENE GLYCOL, PEG-40 HYDROGENATED CASTOR OIL, HYDROXYETHYLCELLULOSE, AROMA, DISODIUM EDTA, SODIUM HYALURONATE, SODIUM SACCHARIN, GLYCYRRHETINIC ACID, PRESERVATIVES (POTASSIUM SORBATE, SODIUM BENZOATE, BENZALKONIUM CHLORIDE)

GELCLAIR does not contain drugs, products of animal origin, or any other component extracted or derived from blood.

3. Intended therapeutic and/or diagnostic indication and claims

Gelclair® helps the management of painful symptoms of mucositis of the oropharyngeal cavity. Gelclair®, used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, traumatic ulcers caused by dental braces and dentures and ageing.

4. Scope of the document

Scope of the document is to verify, and, in case, integrate, scientific data which became available for the product Gelclair® as from the last version of the Clinical Evaluation Report dated 31/01/2013 (covering from 20/05/2009 to 02/10/2012) and 31/12/2014.

5. Data analysis

Literature review

Literature was evaluated according to SOP P17 Rev.01 and related annexes, and the final results are summarized in the following references identified:

(1) da Cruz Campos MI, Campos CN, Aarestrup FM, Aarestrup BJV. Oral mucositis in cancer treatment: Natural history, prevention and treatment (Review). *Mol.Clin.Oncol.* 2014;2:337-40.

(2) Martinez JM, Pereira D, Chacim S et al. Mucositis care in acute leukemia and non-Hodgkin lymphoma patients undergoing high-dose chemotherapy. *Supportive Care Cancer* 2014;22:2563-9.

(3) Pettit L, Sanghera P, Glaholm J, Hartley A. The use of MuGard(trademark), Caphosol(registered trademark) and Episil (registered trademark) in patients undergoing chemoradiotherapy for squamous cell carcinoma of the head and neck. *Journal of Radiotherapy in Practice* 2014;13:218-25.

(4) Rasero L, Marsullo M, Dal MA. [Assessing the effectiveness of Gelclair(R) in the prevention and therapy of stomatitis in patients undergoing hematopoietic stem-cell transplantation: a randomized trial]. *Prof.Inferm.* 2014;67:15-20.

(5) Ambrose N, Mehta P, Haskard DO. Treatment of oral and genital ulceration in behcnullet syndrome. *Ann.Rheum.Dis.* 2013;72.

(6) Lipp H-P, Bornmann L, Kunecki J, Terkola R. Prophylaxis and treatment of radio/chemotherapy-associated mucositis: Revised international guidelines and critical considerations in respect to case series and published mixtures ready-to-use. *Krankenhauspharmazie* 2013;34:541-9.

(7) Pereira D, Chacim SP, Martinez J et al. Mucositis in patients with hematologic malignancies: Prophylaxis or treatment-that is the question! *Blood* 2013;122.

(8) Brasil CMV, Serpa MS, de Franca TRT, de Castro JFL. Management of oral mucositis. *Arch.Oncol.* 2012;20:57-61.

(9) Satheesh Madhav NV, Semwal R, Semwal DK, Semwal RB. Recent trends in oral transmucosal drug delivery systems: An emphasis on the soft palatal route. *Expert Opin.Drug Deliv.* 2012;9:629-47.

From these references, according to their contents, it was possible to define the potential interest for the product both in relation to efficacy and safety.

In Table 2, references are classified according to the identified relevance.

	Relevance			
Ref.	***Performance***	***Safety***	***Both***	***Significant (Y/N)***
1	YES	NO	NO	NO
2	YES	NO	NO	NO
3	YES	NO	NO	NO
4	YES	NO	NO	YES
5	YES	NO	NO	NO
6	YES	NO	NO	NO
7	YES	NO	NO	NO
8	YES	NO	NO	NO

Table 2: evaluation of identified references

Out of the 8 relevant literature references identified, 1 (Ref. 4) reports citations of clinical results obtained by Rasero et al. and will therefore be further considered.

Of the remaining 7 articles, 1 (Ref. 1) refers to a previously considered paper and 6 (Ref. 2, 3, 5, 6, 7, 8) report Gelclair only as a possible effective tool for Oral Mucositis management, without any specific clinical data, neither in terms of efficacy nor in terms of safety.

Ref. 4: Rasero L, Marsullo M, Dal MA. Assessing the effectiveness of Gelclair® in the prevention and therapy of stomatitis in patients undergoing hematopoietic stem-cell transplantation: a randomized trial]. Prof.Inferm. 2014;67:15-20.

The aim of this randomized controlled study was to assess the effectiveness of Gelclair® in patients undergoing hematopoietic stem-cell transplantation in terms of reducing the incidence of oral mucositis.

Fifty-seven patients (28 control group and 29 experimental group) used a mouthwash 3 times a day and were evaluated by means of a specially-tailored form containing the following assessment items:

a) stomatitis evaluation scale (WHO),

b) VAS for pain

c) Likert-Scale for agreement.

Of the 57 patients, 35 (61%) presented stomatitis, no difference was observed between the two groups with regard to stomatitis grade throughout the observation period. Painful symptoms were observed in 54% subjects. No differences were observed in terms of average pain perception before the use of mouthwashes throughout the period of observation (p=0.06).

Results showed a pain-relieving effect in the experimental group after using the mouthwash (p=0.04).

Conclusions: Although Gelclair® had no influence on the onset and severity of stomatitis in transplanted patients, a significant benefit was observed in terms of pain control. Our study suggests the possibility to implementation the use of Gelclair® in clinical practice.

6. Conclusions

A periodic check of the new information on the efficacy and/or safety of the medical device Gelclair® between 2012 and 2014 was carried out.

Few new articles were identified (n=8) and only one of them was relevant to the efficacy of Gelclair® in terms of pain control.

In conclusion it is possible to confirm the efficacy and safety profile of Gelclair®.

Fabio Macchi, MSc

Helsinn Healthcare SA

Integrative Care Division - Head of Scientific & Clinical Portfolio Development

Medical Device Division - Corporate Design and Development Manager

Signature: ..... MACCHI FABIO

Date: FEB, 19TH - 2015

POSTMARKETING SAFETY DATA

GELCLAIR®

October 3, 2012 to December 31, 2014

Helsinn Healthcare SA

Introduction

Gelclair® is a Medical Device (MD) intended to help the management of painful symptoms of mucositis and stomatitis of the oropharyngeal cavity.
Gelclair® used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions and ulcers, including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces, dentures and ageing.
Over a period of time of about fifteen years about 24 million of single doses were supplied worldwide and only 40 post-marketing non-serious cases, none classified as incident/reportable adverse event, were collected in the manufacturer's safety database.

Aim of the document

The aim of this document is to integrate post marketing safety data previously reported (2000 to May 19, 2009 and May 20, 2009 to October 2, 2012) in Gelclair Technical File with data collected between October 3, 2012 and December 31, 2014.

Data collection

All relevant data coming from suppliers, pharmacists, physicians, patients and from all possible sources, concerning any real or potential safety problem related to the use of Gelclair®, are collected in the Manufacturer's Safety Database ARGUS.

Table 1: Post marketing data

ISSUE		PERIOD 1	PERIOD 2	PERIOD 3	TOTAL	COMMENT (Description, cause, consequence, etc.)
		2000 –19.5.2009	20.5.2009-2.10.2012	3.10.2012-31.12.2014	2000 – 31.12.2014	
Preferred term (main event)	**Incident (Yes/No)**					
Gastrointestinal disorders SOC						
Abdominal pain upper	No	--	1	--	1	patient with chronic gastritis and oral fungal infection
Constipation	No	--	1	--	1	cancer patient
Dental caries	No	1	--	--	1	cancer patient
Hypoaesthesia oral	No	1	--	--	1	pre-existent Herpes simplex oral infection
Lip swelling	No	2	--	--	2	1 cancer patient, 1 unknown indication
Mouth ulceration	No	1	--	--	1	plasma cell stomatitis
Nausea	No	1	--	--	1	cancer patient
Oral discomfort	No	3	3	--	6	3 cancer patients, 1 stomatitis of unknown origin, 2 unknown indication
Oral mucosal blistering	No	--	1	--	1	end stage cancer
Oral mucosal discolouration	No	1	--	--	1	cancer patient
Oral mucosal erythema	No	--	1	--	1	diabetes patient with mouth ulcers and discomfort
Oral pain	No	2	--	--	2	unknown indication
Stomatitis	No	1	1	--	2	cancer patient
Tongue discolouration	No	1	--	1	2	1 graft vs host disease, 1 on multiple unspecified medications

ISSUE		PERIOD 1	PERIOD 2	PERIOD 3	TOTAL	COMMENT (Description, cause, consequence, etc.)
		2000 –19.5.2009	20.5.2009-2.10.2012	3.10.2012-31.12.2014	2000 – 31.12.2014	
Preferred term (main event)	**Incident (Yes/No)**					
Tooth discolouration	No	2	--	--	2	mouth lymphoma
Total cases		**16**	**8**	**1**	**25**	
General disorders and administration site conditions SOC						
Device ineffective	No	--	1	2	3	1 unknown product indication and medical history, 1 sample sachets only used, 1throat cancer (unknown stage) patient under radio and chemotherapy
Device misuse	No	--	3	--	3	swallowing, no adverse event reported
Accidental Device ingestion		--	--	1	1	swallowed accidentally, no adverse event reported
Total cases		--	**4**	**3**	**7**	
Immune system disorders SOC						
Hypersensitivity	No	1	--	--	1	cancer patient with known hypersensitivity to penicillin
Total cases		**1**	--	--	**1**	
Injury, poisoning and procedural complications SOC						
Gingival injury	No	1	--	--	1	unknown indication
Total cases		**1**	--	--	**1**	
Nervous system disorders SOC				--		

ISSUE		PERIOD 1	PERIOD 2	PERIOD 3	TOTAL	COMMENT (Description, cause, consequence, etc.)
		2000 –19.5.2009	20.5.2009-2.10.2012	3.10.2012-31.12.2014	2000 – 31.12.2014	
Preferred term (main event)	**Incident (Yes/No)**					
Burning sensation	No	2	--	--	2	cancer patient
Burning sensation mucosal	No	1	--	--	1	unknown indication
Total cases		**3**	--	--	**3**	
Respiratory, thoracic and mediastinal disorders SOC						
Dyspnoea	No	1	--	--	1	cancer patient
Total cases		**1**	--	--	**1**	
Skin and subcutaneous tissue disorders SOC						
Rash	No	1	1	--	2	1 unknown indication, 1 cancer patient
Total cases		**1**	**1**	**--**	**2**	
Overall total cases		**23**	**13**	**4**	**40**	

Data analysis

Between 2000 and May 19, 2009 (Period 1) **23** cases were collected and evaluated, and about 12 million single doses were supplied worldwide. None of these cases was classified as incident/reportable adverse event.

In the period of time between May 20, 2009 and October 2, 2012 (Period 2) further **13** cases were collected and about 5.4 million of single doses supplied worldwide. As for the previous ones, no incidents/reportable adverse events were identified.

This last update considers the period of time between October 3, 2012 and December 31, 2014 (Period 3), when **4** cases were collected and about 4.8 million of single doses supplied worldwide. No incidents/reportable adverse events were received.

Overall, **40** post-marketing cases (Table 1) were collected in the Safety Database. None of them was assessed as incident. The distribution of the reported cases by System Organ Class (SOC) and Preferred Term (main event) shows a prevalence of Gastrointestinal disorders SOC adverse events (25) and are mainly regarding cancer patients (14). It is to be noted that Gelclair is indicated for the treatment of chemotherapy and radiotherapy-induced mucositis, therefore the underlying disease, often severe at the time of Gelclair application, may determine or influence the reaction to the product. Cases of hypersensitivity, rash, dyspnoea, gingival injury and burning sensation were also described (8).

During the period between May 20th, 2009 and October 2nd, 2012 a total of **13** cases were reported, including the cases of lack of efficacy and device misuse.
None was assessed as incident. One case 2012DE006847 (Oral discomfort, oral mucosal erythema, dysphagia) was assessed as incident by the German Regulatory Authority due to the lack of information with regard to the case assessment elements, however, based on the Manufacturer investigation and internal evaluation, the case did not meet the incident criteria. No safety concerns arise from the in-depth analysis of this single case or from the overall analysis of other cases collected in the Safety Database.
It is to be noted that starting from 2010, upon internal decision to monitor the correct use of the product, all cases of device misuse were collected. These cases (3) referred to accidental swallowing of the product and did not lead to adverse events. Additionally, 1 case of reported lack of efficacy was received.

The distribution by SOC and main event's Preferred Term is similar to the previous analysed period, showing the prevalence of Gastrointestinal disorders SOC (8). As previously mentioned, 3 cases of misuse and 1 lack of efficacy were also reported. Additionally, 1 case of rash in a cancer patient was reported in this last period.

The current update refers to the period between October 3, 2012 and December 31, 2014; a total of 4 cases were reported, including 1 case of tongue discoloration, 2 cases of lack of efficacy and 1 accidental device ingestion. None was assessed as incident/reportable adverse event.

Conclusion

No safety concern was identified so far from the separate and cumulative analysis of the post-marketing cases. The well-known Gelclair® benefit-risk balance remains favourable and unchanged over the time. No change in the Product's Instructions for Use is deemed necessary in this regard.

HELSINN HEALTHCARE SA

Diana Koprivec, MD PhD
Manager, Corporate Drug Safety

Pazzallo-Lugano, 2nd March 2015

Issued : 29/09/2011 Subject: **Model 29 – rev. 01:** **Clinical Evaluation Report**	Edited by: DD
	Reviewed by: QA
	Approved by : Management Date:

Clinical Evaluation Report

GELCLAIR®

May, 20st 2009 to October, 2nd 2012

Bridging document

Helsinn Healthcare SA

Lugano, 31/01/2013

This report was prepared according to:

MEDDEV 2.7.1. rev. 3 **December 2009**	**CLINICAL EVALUATION:** **A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES**

Table of Contents

1. Aims of the document

Aims of this document are:

1- To collect relevant scientific data produced between May 1st 2009 and September 30th 2012 on Gelclair®

2- To analyze such evidences

3- To confirm adequate, positive benefit/risk ratio observed for the medical device (MD) Gelclair®.

The present report is based on the original document "Gel for treatment of oral mucosa - Expert Report" by Prof. Dr. Dorothy Keefe issued on 15/07/2009, that has been included in Gelclair® Technical File (Annex 11) since its first emission on 06/08/2009.

According to Procedure HHC-MDD/P17/02, it is responsibility of the manufacturer to collect, analyze and report any scientific document available in the international scientific literature, as well as from data on file, at least every three years. To this purpose, by integrating new available data on the medical device Gelclair®, this document is an update to Prof. Keefe's report, which is hereto included as Appendix 1.

2. General details

Name of the Device:	**Gelclair®**
Formulation:	**Water-based gel**
Use:	**Oral application**
Packaging (primary)	**15 ml Sachet**
	180 ml Bottle
Medical Device Class:	**IIa**
Intended Use:	**Gelclair®** is intended to help the management of painful symptoms of mucositis and stomatitis of the oropharyngeal cavity.
	Gelclair® used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions and ulcers,

	including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces and dentures and ageing.
Instructions for Use:	**Gelclair**® should be used 3 times a day or as needed. Avoid eating or drinking for at least 30-60 minutes following treatment. Pour the entire contents of the single-dose sachet or 15ml (1 tablespoonful) into a glass and add approximately 40ml of water (3 tablespoonfuls). Stir mixture well and use at once. Rinse around the mouth for at least one minute or as long as possible to coat tongue, palate, throat, inside of cheeks and all oral tissue thoroughly. Gargle and spit out.
Manufacturer:	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Pazzallo – Lugano – Switzerland.

3. Description of the device and its intended application

Gelclair® is a non-sterile, non-invasive, non-implantable, water-based gel for topical use on intact or damaged oral mucosa.

Gelclair® is available both as 15 ml Sachet (enough for a single application) or as 180 ml Bottle (enough for at least 12 applications).

The device is not intended to be swallowed.

Gelclair® is a gel that, when applied to the damaged oral mucosa, forms a protective film, that helps to provide pain relief, soothing mouth lesions and ulcers, including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces and dentures and ageing.

The complete list of Gelclair® ingredients, according to INCI classification, is reported in Table 1.

Table 1: List of ingredients used in Gelclair® (INCI classification)

AQUA, PVP, MALTODEXTRIN, PROPYLENE GLYCOL, PEG-40 HYDROGENATED CASTOR OIL, HYDROXYETHYLCELLULOSE, AROMA, DISODIUM EDTA, SODIUM HYALURONATE, SODIUM SACCHARIN, GLYCYRRHETINIC ACID, PRESERVATIVES (POTASSIUM SORBATE, SODIUM BENZOATE, BENZALKONIUM CHLORIDE)

Gelclair® does not contain drugs, ingredients of animal origin, nor components extracted or derived from blood.

4. Intended therapeutic and/or diagnostic indications and claims

Gelclair® is a device not intended for diagnostic purposes; it is a topical gel that, when applied to the oral mucosa, helps to provide pain relief, soothing mouth lesions and ulcers, including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces and dentures and ageing.

5. Summary of the preclinical, clinical data and appraisal collected between May, 20th 2009 and October, 2nd 2012

During the period of time between May, 1st 2009 and September, 30th 2012 a lot of new scientific information related to Gelclair® became available, as summarized in Table 2.

This information was not included in the previous version of Gelclair® Clinical Evaluation (the "Biocompatibility – Clinical Safety Data" report) and therefore, according to the Procedure HHC-MDD/P17/02, a new edition of the document is required.

The relevance to the benefit/risk ratio of the device will then be evaluated.

Table 2: Scientific data on Gelclair® identified and/or collected between May, 1st 2009 and September, 30th 2012

Source	**Number of results or sources**
Preclinical studies	2
Literature	19
Adverse Events (AEs) databases	2
Manufacturer's Post Marketing Safety Data report	1

Preclinical studies

Preclinical data refer to two specific studies:

a) Evaluation of the mucoadhesive properties of Gelclair® as it is (undiluted) using the tensile tests

b) Evaluation of the washability properties of Gelclair® as it is and diluted from porcine buccal mucosa

Both tests were conducted by Prof. Carla Caramella and Prof. Silvia Rossi from the University of Pavia, Department of Pharmaceutical Science, Faculty of Pharmacy.

Clinical trial

According to the official clinical trial register of the FDA (www.clinicaltrial.gov) in the analyzed period of time one clinical trial was conducted using Gelclair® as test article.

One study was identified and results are already reported in the literature retrieved (Gibson 2010)

Clinical literature data

Clinical data regarding Gelclair® used in the management of oral mucositis were identified in peer reviewed clinical journals.

Literature search aimed at identifying published clinical data was carried out according to SOP P17 Rev.01 and related annexes.

As per the adopted internal quality system, main evaluation criteria related both to efficacy and safety of Gelclair® were defined and reported in Modello 27 "Clinical data search strategy" and a specific literature survey was conducted.

All clinical information related to the treatment of cancer patients undergoing chemio and radiotherapy with Gelclair® were searched.

Furthermore general information on any possible adverse event related to the use of the product was evaluated.

As a general result, 19 relevant papers were identified.

All of them were related to the use of Gelclair® according to the intended use of the device, no specific adverse events related to topical application of Gelclair®.

Identified papers are:

(1) Bey A, Ahmed SS, Hussain B, Devi S, Hashmi SH. Prevention and management of antineoplastic therapy induced oral mucositis. National Journal of Maxillofacial Surgery 2010;**1**:127.

(2) Clarkson JE. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews 2010.

(3) Di Lorenzo G, Scagliarini S, Di Napoli M et al. Targeted Therapy in the Treatment of Metastatic Renal Cell Cancer. Oncology 2009;**77**:122.

(4) Epstein J, Hong C, Logan R et al. A systematic review of orofacial pain in patients receiving cancer therapy. Supportive Care in Cancer 2010;**18**:1023.

(5) Gibson F. International Society of Paediatric Oncology SIOP XXXXII Congress Boston, United States October 21-24, 2010 SIOP Abstracts. Pediatric Blood & Cancer 2010;**55**:775.

(6) Kantardzic N, Smajlbegovic V, Kazic N, Cardzic A. Efficacy of Gelclair oral gel in the treatment of oral mucositis in patients with head and neck tumours treated with chemotherapy and /or radiotherapy. Internet Journal of Oncology 2009;**6**:7.

(7) Kapoor P, Sachdeva S, Sachdeva S. Topical hyaluronic acid in the management of oral ulcers. Indian Journal of Dermatology 2011;**56**:300.

(8) Autore/i: L.J.Pomper, A.Ostojic, R.Jakovac, S.Zemljak, M.Vukelic, I.Zivotic et al. Data di pubblicazione 2-4-2011

(9) Loren Godfrey, Cermella Cuccurullo, ohn Theuer. Analysis Of Mucositis-Associated Health Outcomes In Patients Treated With Image-Guided Imrt For Head And Neck Cancer: Should Caphasol Be Included. Support Care Cancer 2010;**18**:S107.

(10) Lori Johnson. A randomized trial comparing Gelclair to standard care for radiation therapy related oral mucositis and associated oral pain: progress and challenges. Oncology Nursing Forum 2010;**37**:E198-E279.

(11) Pedro DD, Juan SLn. Review: Oral cancer pain. Oral Oncology 2010;**46**:448-451.

(12) Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Annals of Oncology 2011;**22**:vi78.

(13) Pilotte A, Hohos M, O., Huftalen T, Treister N. Managing Stomatitis in Patients Treated With Mammalian Target of Rapamycin Inhibitors. Clinical Journal of Oncology Nursing 2011;**15**:E83-E89.

(14) Rodriguez-Caballero A, Torres-Lagares D, Robles-Garc+¡a M et al. Review Paper: Cancer treatment-induced oral mucositis: a critical review. International Journal of Oral & Maxillofacial Surgery 2012; **41**:225-238.

(15) Samuel V, Jana S, Michal K et al. Letter: Oropharyngeal Mucositis Pain Treatment with Transdermal Buprenorphine in Patients After-áAllogeneic Stem Cell Transplantation. Journal of Pain and Symptom Management 2010;**39**:e4-e6.

(16) Sankar V, Hearnden V, Hull K et al. Local drug delivery for oral mucosal diseases: challenges and opportunities. Oral Diseases 2011;**17**:73.

(17) Vanessa H, Vidya S, Katrusha H et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Advanced Drug Delivery Reviews 2012;**64**:16-28.

(18) Vokurka S, Skardova J, Hruskova R et al. The effect of polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair) on oral microbial colonization and pain control compared with other rinsing solutions in patients with oral mucositis after allogeneic stem cells transplantation. Medical Science Monitor: International Medical Journal Of Experimental And Clinical Research 2011;**17**:CR572-CR576.

(19) Wolf-Oliver Jordan. Oropharyngeal mucositis prophylaxis in combined radioimmunochemotherapy. Annals of Oncology 2010;**21**:viii314.

Each document was evaluated and the obtained information is collected in Table 3

Table 3 : search results.

References(s)	Type of information	Relevant Information	Comment
1, 3, 7, 9, 11, 12, 13, 15, 16, 17	Gelclair® is only mentioned as possible remedy for the intended use of the device	No	No data on safety or efficacy are available in these papers
2,4,14	Data from Barber et al, 2007	No	Already evaluated
5, 6, 8, 10, 18, 19	Direct experience with the product	Yes	--

Adverse Events Databases

According to SOP P17 Rev.01 and related annexes, the following official databases were consulted in order to verify if any incident related to the use of Gelclair® was reported in the period of time analyzed in this document.
Consulted databases and results are reported in Table 3.

Table 3: Official databases consulted

Database	**MoH**	**Reported AE(S)**	**Note**
Maude http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm	FDA	0	The entire period of commercialization of the product was considered
IRIS http://www.tga.gov.au/safety/problem-device-iris.htm	TGA	0	No alerts for Gelclair® were reported

Manufacturer's Post Marketing Safety Data

All events reported are analyzed and classified, in the period between May 20th 2009 and October, 2nd 2012, 13cases were collected and analyzed.

This analysis is reported in the specific document Postmarketing Safety Data of Gelclair (Enclosure 7.1)

Data analysis

A) Preclinical Data

<u>Evaluation of the mucoadhesive properties of Gelclair as it is (undiluted) using the tensile tests</u>

Aim of the study

The aim of the study was to evaluate, using tensile testing, the mucoadhesive properties of the "as it is" (undiluted) Gelclair® formulation.

The test was conducted using different biological substrates (rat esophagus, porcine buccal mucosa and porcine gastric mucin suspension).
In particular, the main aim was to define the minimum contact time of the product needed to form a stable and effective adhesion to the oral mucosa.
Specifically, the influence of the duration of the application on this property was investigated.

Experimental conditions

The mucoadhesion measurements were carried out at 37° C (water bath) using a tensile stress tester. This system consists of a support A and a probe B. The support A is made up of two concentric cylinders held together by four screws. The upper cylinder has a hole in the center for the sample chamber. The probe is cylindrical in shape and has a diameter lower than that of the cylinder.
The mucoadhesion test involves measuring the force required to detach the sample from a biological substrate in relation to the displacement occurring on the mucoadhesive interface. The maximum force of adhesion (Fmax) was taken as the parameter for mucoadhesion.
The measurements were carried out using different biological substrates (i.e. rat oesophagus, porcine buccal mucosa and commercial mucin).

Results

A set of three different experiments were prepared, each one with a different substrate (rat esophagus, porcine buccal mucosa and porcine gastric mucin suspension).

Here below the three sets of results are reported in graphic form; the complete report in enclosed in Enclosure 1.

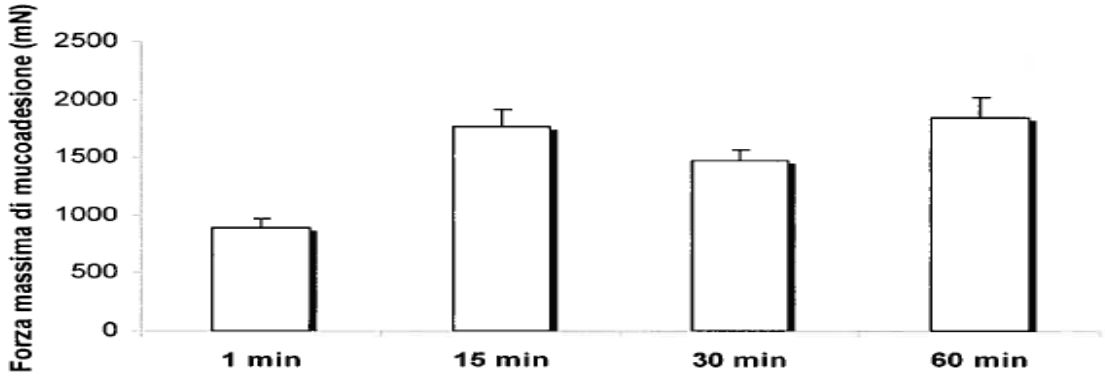


Figure 1 - Maximum mucoadhesive force values obtained for Gelclair® formulation for increasing contact times/preload with rat esophagus (mean values ± SE; n = 9; see annexed raw data [Mann-Whitney test: Significant ($p < 0.05$) for 1 min vs. 15 min, 1 min vs. 30 min, 1 min vs. 60 min]

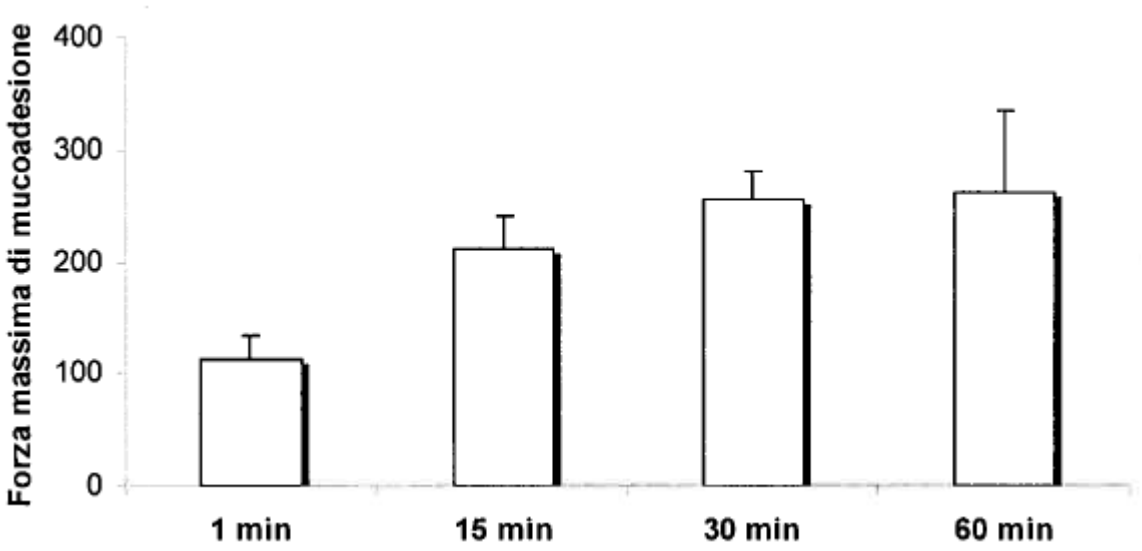


Figure 2 - Maximum mucoadhesive force values obtained for Gelclair® formulation for increasing contact times/preload with porcine buccal mucosa (mean values ± SE; n = 4-6; see annexed raw data)[Mann-Whitney test: Significant ($p < 0.05$) for 1 min vs. 15 min, 1 min vs. 30 min, 1 min vs. 60 min]

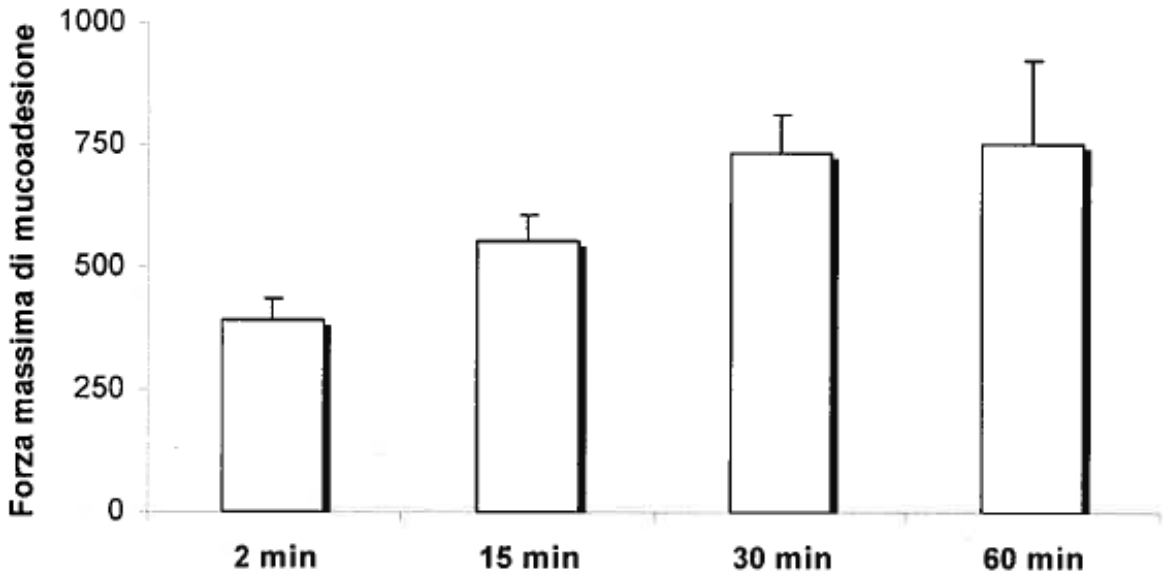


Figure 3 - Maximum mucoadhesive force values obtained for Gelclair® formulation for increasing contact times with mucin suspension (mean values ± SE; n = 4-7; see annexed raw data) [Mann-Whitney test: Significant ($p < 0.05$) for 2 min vs. 30 min, 2 min vs. 60 min]

As evidenced by the results, it is possible to appreciate that, after a short time (about 15 minutes) from the application of Gelclair® onto the ex-vivo or in-vitro model of oral or gastric mucosa the product creates a strong and stable binding with the substrate, forming a mechanical protection of the mucosa. This confirms:

1- the capability of this device to establish a stable connection with biological substrates
2- that the time to create the film is evaluated in 15-30 minutes .

Evaluation of the washability properties of Gelclair as it is and diluted from porcine buccal mucosa

Aim of the study

This experiment investigated the capacity of diluted Gelclair® and its "as it is" formulation to remain adherent to the surface of porcine buccal mucosa after washing with water. Specifically, the influence of the time of application on this capacity was studied.

Experimental conditions

Preparation of the samples

Fluorescein-isothiocyanate dextran PM 4000 (FD4) was added to the "as it is" Gelclair® formulation and diluted in accordance with Gelclair® product leaflet at a concentration of 0.06% (w/w).

The reference used was a solution of FD4 in distilled water at a concentration of 0.06% (w/w).

Washability measurements

The washability measurements were carried out using strips of porcine buccal mucosa. Mucosal strips measuring 1x1 cm were glued to optical microscope slides using cyanoacrylate glue and then placed inside Petri dishes.

50 mg of the formulation loaded with FD4 (Gelclair® as it is or diluted according to package insert) was placed on the mucosal strips and left in contact with it for increasing times (2, 15, 30 and 60 min) in 100% humidity conditions at a temperature of 37° C. After these pre-set times had elapsed, 5 ml of distilled water was added by automatic pipetting machine to the Petri dishes next to the mucosa ensuring that it wet the sample. After 1 minute, the water was collected and analyzed by fluorimetry for the dosage of the fluorescent probe.

Similar measurements were carried out in the absence of fluorescent probe, using the diluted and undiluted formulations, without FD4 (blank measurements). In this case, the contact times considered were 30 and 60 minutes. Measurements were also carried out using the aqueous solution of FD4 (reference) on its own, held in contact with the mucosa for 15 and 30 minutes.

Results

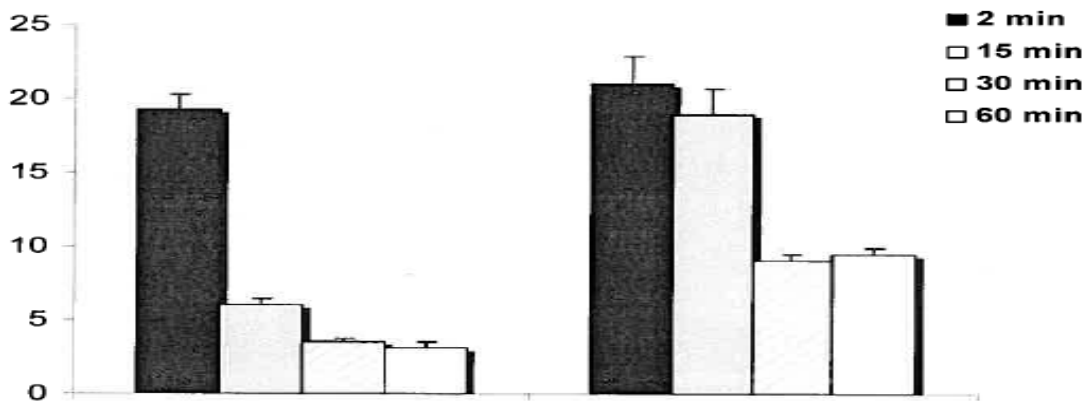


Figure 1 - Quantity (μg) of fluorescent probe washed away from the mucosa in the presence of Gelclair® formulation (diluted and undiluted) (average value ± SE, n = 5-6; see annexed raw data)

Mann-Whitney test:

UNDILUTED: Significant ($p<0.05$) for 2 min vs. 15 min, 2 min vs. 60 min, 15 min vs. 30 min, 15 min vs. 60 min - Not significant for 30 min vs. 60 min

DILUTED: Significant ($p<0.05$) for 2 min vs. 30 min, 2 min vs. 60 min, 15 min vs. 30 min, 15 min vs. 60 min - Not significant for 2 min vs. 15 min, 30 min vs. 60 min; UNDILUTED vs. DILUTED: 2 min: Not significant; 15 min: Significant ($p <0.05$) 30 min: Significant ($p<0.05$); 60 min: Significant ($p <0.05$)

The values of non-specific binding of the fluorescent probe (FD4) to porcine mucosa were measured and they are negligible if compared to those observed both for concentrated and diluted Gelclair®+FD4.

Conclusions

Results confirm the mucoadhesive properties of Gelclair®. Under the experimental conditions employed, these properties are more manifest when contact time with the mucosa is 15 and 30 minutes, depending on whether the diluted or undiluted solution is used. A further extension of the contact time (60 min) does not result in a significant increase of the product capacity to interact with the mucosa.

In conclusion, on the basis of the experimental data obtained, undiluted and diluted Gelclair® shows good mucoadhesive properties occurring within a short time (15-30 minutes) when put in contact with the mucosa.

B) Literature review

In 10 (ref. 1, 3, 7, 9, 11, 12, 13, 15, 16, 17) of the 19 relevant literature identified, Gelclair® is mentioned only as possible remedy for the intended use of the device, no further scientific information on safety and/or efficacy is present. Therefore these are not relevant for the purpose of the present document.

In 3 papers, the only reference is made to the paper from Barber 2007 that was already considered in the Expert Report document from Prof. Dr. Dorothy Keefe.

In 2 papers (ref. 8and 10) no enough data to evaluate the performances or the safety of Gelclair are available.

The remaining 4 articles (Ref. 5, 6, 18, and 19) mainly focus on the performance of Gelclair®.

Ref 5: Gibson F. International Society of Pediatric Oncology SIOP XXXXII Congress Boston, United States October 21-24, 2010 SIOP Abstracts. Pediatric Blood & Cancer 2010; 55:775.

The prospective, open, uncontrolled pilot study was conducted to examine the feasibility and acceptability of Gelclair® for use in children and young people experiencing pain with oral mucositis.

Children and young people aged between 4-19 years, admitted to an in-patient unit following any chemotherapy anticipated to cause oral mucositis were recruited. Data were collected at baseline and at key defined points over a 48-hour period to record oral pain (faces scale), condition of the oral mucosa (oral assessment scale [OAG] and WHO scale), ability to eat and drink, pain medication taken, and acceptability of Gelclair®. Data analysis were performed to identify any possible relationship between patients' mean and baseline pain scores, with the covariates; age, gender, baseline neutrophil count and the administration of opiate medication.

Of the screened patients, forty-eight were eligible for analysis. The median OAG score was 15 and the median WHO score was 3.

79.2% of the patients reported a lower pain score than at baseline at one of the assessment times post administration, and 60.4% of the patients reported their lowest pain score within the first 6 hours.

52.1% of patients showed an improvement in their ability to eat and drink over the study period with 17 patients showing improvement within the first 6 hours.

At least 82.4% of the patients who were assessed reported that their mouth felt nice and more than 50% of the patients reported that they liked the taste of Gelclair® at every assessment time.

In conclusion the study has found evidence that Gelclair® is tolerable to children and young people who develop oral mucositis.

Some patients had an improvement in their ability to eat and drink and most of the patients had some relief from pain.

NOTE: This study is reported in the web site www.Clinicaltrial.gov

Ref 6: Kantardzic N, Smajlbegovic V, Kazic N, Cardzic A. Efficacy of Gelclair oral gel in the treatment of oral mucositis in patients with head and neck tumours treated with chemotherapy and /or radiotherapy. Internet Journal of Oncology 2009;6:7.

This is nonrandomized prospective study, 15 patients were included and treated with radiotherapy and/or chemotherapy and proven head and neck tumors.

During their oncology therapy they were treated with Gelclair® oral gel and checked every day for severity of their symptoms.

Of the enrolled patients, 13 had a significant improvement in the management of pain was observed, and 11 patients had improvement in food and fluid intakes. There were no delays in treatment, caused by severity of oral mucositis.

These data indicate that Gelclair® is a safe and efficient agent in the treatment of oral mucositis, one of most common complication of radiotherapy and/or chemotherapy in patients with head and neck tumors.

Ref 18: Vokurka S, Skardova J, Hruskova R et al. The effect of polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair) on oral microbial colonization and pain control compared with other rinsing solutions in patients with oral mucositis after allogeneic stem cells transplantation. Medical Science Monitor: International Medical Journal Of Experimental And Clinical Research 2011; 17:CR572-CR576.

In this study the efficacy, tolerability and impact on oral cavity microbial colonization in patients with OM after allogeneic hematopoietic stem cells transplantation were evaluated.

Gelclair® was administered in a group of 22 patients with active OM. A control group of 15 patients used other rinsing solutions (chlorhexidine, benzydamine, salvia).

Tests with oral cavity swabs for microbiology analysis were performed once a week.

The characteristics of OM in both groups were comparable, and rinsing solutions had satisfactory tolerability. There was no difference in the median improvement of oral intake and OM-related pain relief, which was assessed mostly as “slight effect”.

In the Gelclair® group, the effect duration was longer (median 3 [0–5] vs. 1 [0–3] hours, p=0.001). There was significant increase of *Enterococcu faecalis* and *Candida sp*. colonization of the oral cavity over the course of the hospitalization and significantly reduced incidence of such colonization in patients with OM in the Gelclair® group: 1/22 (5%) vs. 6/15 (40%), p=0.01.

In vitro tests showed inhibited growth of *Enterococcus faecalis* and *Candida sp.* colonies within the area of the Gelclair® application.

Results indicate that Gelclair® may be individually helpful in the management of OM and pain in patients after allogeneic stem cells transplantation. Its use did not lead to worsened oral bacterial and yeast colonization and probably even helped to protect mucosa from Enterococcus and Candida.

Ref 19: Wolf-Oliver Jordan. Oropharyngeal mucositis prophylaxis in combined radioimmunochemotherapy. Annals of Oncology 2010;21:viii314.

129 patients received the oral gel as a mouth rinsing solution (15 ml) 4 times daily 10 min after antimycotics (1ml containing 100 mg amphotericin B) and panthenol solution(10 ml containing 500 mg Dexpanthenol).

The treatment started simultaneously with radiotherapy and was discontinued 4 weeks after the end of the radiotherapy.

In consequence 117 patients were evaluable. Under this treatment we observed in 96 patients only mild cases of oropharyngeal mucositis. In 16 patients we observed a grade III mucositis and in 5 patients a grade IV mucositis.

There were no specific side effects of the oral gel observed and all patients were mostly compliant. In 14 cases therapy had to be interrupted because of a severe mucositis (grade III/ IV). 11 patients had therapy interruptions or discontinuation for other reasons.

A prophylactic treatment of head & neck cancer patients receiving a combined radioimmunochemotherapy with Gelclair® additionally to antimycotics / panthenol seems to effectively reduce most commonly observed mucositis and leads to an improved patient compliance and increases their QoL.

Rates of infections and pain symptoms decrease significantly.

C) Postmarketing Safety Data

Between 2000 and May 19th, 2009 (Period 1) 23 cases were collected and evaluated meanwhile about 12 million single doses were supplied worldwide. None of these cases was classified as incident/reportable adverse event.

In the period covered by this analysis (May 20th, 2009 -October 2nd, 2012) further 13 cases were collected and about 5.4 million of single doses supplied worldwide. As for the previous ones, no incidents/reportable adverse events were identified.

Overall, 36 postmarketing cases (Table 1, Enclosure 1) were collected in the Safety Database. None of them was assessed as incident. The distribution of the reported cases by System Organ Class (SOC) and Preferred Term (main event) shows a prevalence of Gastrointestinal disorders SOC adverse events (n=24) and are mainly regarding cancer patients (n=14). It is to be noted that Gelclair is indicated for the treatment of chemotherapy and radiotherapy-induced mucositis, therefore the underlying disease, often severe at the time of Gelclair application, may determine or influence the reaction to the product. Cases of hypersensitivity, rash, dyspnoea, gingival injury and burning sensation were also described (n=8).

Starting from 2010, upon internal decision to monitor the correct use of the product, all cases of device misuse were collected. These cases (n=3) referred to accidental swallowing of the product and did not lead to adverse events. Additionally, 1 case of reported lack of efficacy was received.

During the period between May 20th, 2009 and October 2nd, 2012 a total of 13 cases were reported, including the cases of lack of efficacy and device misuse.

None was assessed as incident. It is to be noted that one case 2012DE006847 (Oral discomfort, oral mucosal erythema, dysphagia) was assessed as incident by the German Regulatory Authority due to the lack of information with regard to the case assessment elements, however, based on the Manufacturer investigation and internal evaluation, the case did not meet the incident criteria. No safety concerns arise from the in-depth analysis of this single case or from the overall analysis of other cases collected in the Safety Database.

The distribution by SOC and main event's Preferred Term is similar to the previous analyzed period, showing the prevalence of Gastrointestinal disorders SOC (8). As previously mentioned 3 cases of misuse and 1 lack of efficacy were also reported. Additionally, 1 case of rash in a cancer patient was reported in this last period.

In conclusion No safety concern was identified so far from the separate and cumulative analysis of the postmarketing cases. The benefit-risk of Gelclair remains favourable and unchanged over the time. No change in the Product's Instructions for Use is deemed necessary in this regard.

6. Conclusions

According to available information and based on experimental results obtained with Gelclair® in vitro, and considering the literature information available and based on the postmarketing safety data, it is possible to conclude that:

1- The benefit-risk of Gelclair remains favorable and unchanged over the time and, therefore, no change in the Product's Instructions for Use is deemed necessary in this regard.

2- Based on the available experimental information it is possible to conclude that the requested time for the barrier formation after the application can be defined in 30-60 minutes. This particular aspect is considered very important for the patient's compliance and therefore it will be entered in the Product's Instructions for Use.

MACCHI FABIO

Signature: ..

Date: 31/01/2013

7. Enclosures

7.1 Postmarketing Safety Data of Gelclair from May, 20th 2009 to October, 2nd 2012

Enclosure 7.1

Postmarketing Safety Data of Gelclair from May, 20th 2009 to October, 2nd 2012

POSTMARKETING SAFETY DATA

GELCLAIR®

May, 20th 2009 to October, 2nd 2012

Helsinn Healthcare SA

Introduction

Gelclair® is a Medical Device (MD) intended to help the management of painful symptoms of mucositis and stomatitis of the oropharyngeal cavity.
Gelclair® used as a mouthwash, forms a protective film that helps to provide pain relief, soothing mouth lesions and ulcers, including those caused by medication, disease, radiotherapy, chemotherapy, oral surgery, dental braces, dentures and ageing.
Over a period of time of about thirteen years about 19 million of single doses were supplied worldwide and only 36 postmarketing non-serious cases, none classified as incident/reportable adverse event, were collected in the manufacturer's safety database.

Aim of the document

The aim of this document is to integrate post marketing safety data previously reported (2000-May, 19th 2009) in the Gelclair Technical File with data collected between May, 20th, 2009 and October 2nd, 2012.

Data collection

All relevant data coming from suppliers, pharmacists, physicians, patients and from all possible sources, concerning any real or potential safety problem related to the use of **Gelclair**®, are collected in the Manufacturer's Safety Database ARGUS.

Table 1: Post marketing data

ISSUE		**PERIOD 1**	**PERIOD 2**	**TOTAL**	**COMMENT** (Description, cause, consequence, etc.)
		2000 – 19.5.2009	20.5.2009– 2.10.2012	2000 – 2.10.2012	
Preferred term (main event)	**Incident (Yes/No)**				
Gastrointestinal disorders SOC					
Abdominal pain upper	No	--	1	1	patient with chronic gastritis and oral fungal infection
Constipation	No	--	1	1	cancer patient
Dental caries	No	1	--	1	cancer patient
Hypoaesthesia oral	No	1	--	1	pre-existent Herpes simplex oral infection
Lip swelling	No	2	--	2	1 cancer patient, 1 unknown indication
Mouth ulceration	No	1	--	1	plasma cell stomatitis
Nausea	No	1	--	1	cancer patient

Oral discomfort	No	3	3	6	3 cancer patients, 1 stomatitis of unknown origin, 2 unknown indication
Oral mucosal blistering	No	--	1	1	end stage cancer
Oral mucosal discolouration	No	1	--	1	cancer patient
Oral mucosal erythema	No	--	1	1	diabetes patient with mouth ulcers and discomfort
Oral pain	No	2	--	2	unknown indication
Stomatitis	No	1	1	2	cancer patient
Tongue discolouration	No	1	--	1	graft vs host disease
Tooth discolouration	No	2	--	2	mouth lymphoma
Total cases		**16**	**8**	**24**	
General disorders and administration site conditions SOC					
Device ineffective	No	--	1	1	unknown product indication and medical history
Device misuse	No	--	3	3	swallowing, no adverse event reported
Total cases		--	**4**	**4**	
Immune system disorders SOC					
Hypersensitivity	No	1	--	1	cancer patient with known hypersensitivity to penicillin
Total cases		**1**		**1**	
Injury, poisoning and procedural complications SOC					
Gingival injury	No	1	--	1	unknown indication
Total cases		**1**	--	**1**	
Nervous system disorders SOC					
Burning sensation	No	2	--	2	cancer patient
Burning sensation mucosal	No	1	--	1	unknown indication
Total cases		**3**	--	**3**	
Respiratory, thoracic and mediastinal disorders SOC					
Dyspnoea	No	1	--	1	cancer patient

Total cases		**1**	--	**1**	
Skin and subcutaneous tissue disorders SOC					
Rash	No	1	1	2	1 unknown indication, 1 cancer patient
Total cases		**1**	**1**	**2**	
Overall total cases		**23**	**13**	**36**	

Data analysis

Between 2000 and May 19th, 2009 (Period 1) **23** cases were collected and evaluated meanwhile about 12 million single doses were supplied worldwide. None of these cases was classified as incident/reportable adverse event.

In the period of time between May 20th, 2009 and October 2nd, 2012 (Period 2) further **13** cases were collected and about 5.4 million of single doses supplied worldwide. As for the previous ones, no incidents/reportable adverse events were identified.

Overall, **36** postmarketing cases (Table 1) were collected in the Safety Database. None of them was assessed as incident. The distribution of the reported cases by System Organ Class (SOC) and Preferred Term (main event) shows a prevalence of Gastrointestinal disorders SOC adverse events (24) and are mainly regarding cancer patients (14). It is to be noted that Gelclair is indicated for the treatment of chemotherapy and radiotherapy-induced mucositis, therefore the underlying disease, often severe at the time of Gelclair application, may determine or influence the reaction to the product. Cases of hypersensitivity, rash, dyspnoea, gingival injury and burning sensation were also described (8).

Starting from 2010, upon internal decision to monitor the correct use of the product, all cases of device misuse were collected. These cases (3) referred to accidental swallowing of the product and did not lead to adverse events. Additionally, 1 case of reported lack of efficacy was received.

During the period between May 20th, 2009 and October 2nd, 2012 a total of **13** cases were reported, including the cases of lack of efficacy and device misuse.
None was assessed as incident. It is to be noted that one case 2012DE006847 (Oral discomfort, oral mucosal erythema, dysphagia) was assessed as incident by the German Regulatory Authority due to the lack of information with regard to the case assessment elements, however, based on the Manufacturer investigation and internal evaluation, the case did not meet the incident criteria. No safety concerns arise from the in-depth analysis of this single case or from the overall analysis of other cases collected in the Safety Database.
The distribution by SOC and main event's Preferred Term is similar to the previous analyzed period, showing the prevalence of Gastrointestinal disorders SOC (8). As previously mentioned 3 cases of misuse and 1 lack of efficacy were also reported. Additionally, 1 case of rash in a cancer patient was reported in this last period.

Conclusion

No safety concern was identified so far from the separate and cumulative analysis of the postmarketing cases. The benefit-risk of Gelclair remains favourable and unchanged over the time. No change in the Product's Instructions for Use is deemed necessary in this regard.

Appendix 1

Prof. Dr. Dorothy Keefe, “Gel for Treatment of Oral Mucosa – Expert Report”
dated 15.07.2009

Annex 11

BIOCOMPATIBILITY – CLINICAL – SAFETY DATA

Helsinn Healthcare SA

via Pian Scairolo 9

6912 Pazzallo - Lugano – Svizzera

Verified by
G. CALDERARI

GEL FOR TREATMENT OF ORAL MUCOSA

Expert report

Prof. Dr. Dorothy Keefe

Clinical Director RAH Cancer Centre

Royal Adelaide Hospital

North Terrace

Adelaide SA 5000 Australia

TABLE OF CONTENTS

1. INTRODUCTION

Oral mucositis is a frequent and disabling side effect of chemotherapy, targeted anti-cancer therapies and radiotherapy, with negative consequences both from the pharmacological/economical standpoint and that of the patient's quality of life. This pathological condition, in fact, increases the need for total parenteral nutrition, increases the administration of opiate analgesics, exposes the patient to greater risk of infections, compromises the possibility of completing antineoplastic therapy properly and within the expected time frame, and may extend the patient's hospital stay with consequent increases in healthcare expenses (Sonis et al., 2001, 2004a, 2004b). Treatment guidelines were developed by MASCC/ISOO (Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology), and later reviewed and updated in 2005 (http://www.mascc.org/ktml2/images/uploads/Resource_centers/Guidelines; Keefe et al., 2007). Despite the usefulness of these guidelines, the methods for evaluating and managing mucositis remain less than satisfactory. There is no gold standard treatment for mucositis, resulting in the need for use of palliative symptom control measures, which by definition are not successful in treating the mucositis itself (Köstler et al., 2001). In fact, the current therapeutic approach is based mostly on the use of several topical and systemic symptom-alleviating treatments. Recently there has been development of growth factors that have a protective effect on the epithelium of the oral mucosa; although their use is reserved for particularly high-risk conditions. Therefore, in the absence of therapies aimed towards preventing and controlling the clinical symptoms of mucositis, such as inflammation and ulcerations, it is extremely important to have treatments available that control painful symptoms and their consequent functional impairment.

Gelclair® mode of action

Within the above scenario, the so-called "barrier products" have a particularly important

role. To this product class belongs Gelclair®, which is presented as an innovative product characterized by a special action mechanism. Gelclair® concentrated oral gel has been shown to provide good pain relief and improved functionality (eating, drinking, etc) for oral mucositis in different symptom-response studies, which are summarized in the present document.

Gelclair® is presented as a concentrated oral gel for managing the painful symptoms of mucositis. It contains the barrier-forming ingredients PVP (polyvinylpyrrolidone) and sodium hyaluronate. When Gelclair® is used as an oral solution, these ingredients adhere to the mucosa to form a protective barrier.

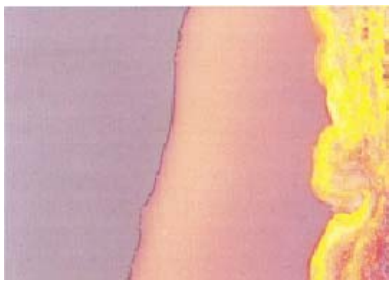
Oral lesions cause pain because the exposed nerve endings, or those surrounded by inflammation, are overstimulated. Mechanical or chemical stimuli within the mouth such as

that caused by eating, drinking or speaking, stimulate these receptors further and can be extremely painful.

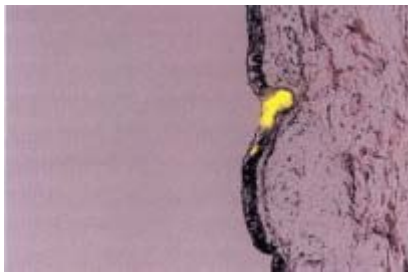
The physical barrier over the surface of the oral mucosa that is formed by Gelclair® shields these receptors from overstimulation. In this way Gelclair® can reduce the pain of oral mucositis and can also enable patients to eat and drink more easily while they have the condition.

Figure 1 shows an adherent layer of Gelclair® (left), compared to control (right). The barrier can be seen here at 0, 15, 30, 45 and 60 minutes. This figure helps understanding the mechanism of action of Gelclair®.

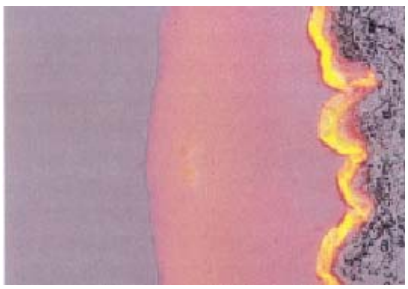
Figure 1: Adherence of Gelclair® vs control using fluorescent marker tetramethylrhodamine isothiocyanate and fluorescence microscopy.



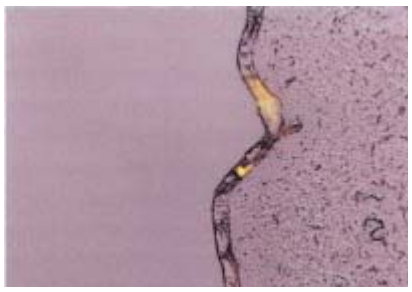
Gelclair® barrier at t=0



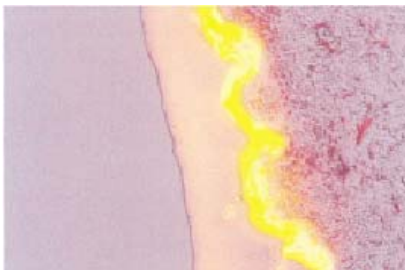
control (no Gelclair) at t=0



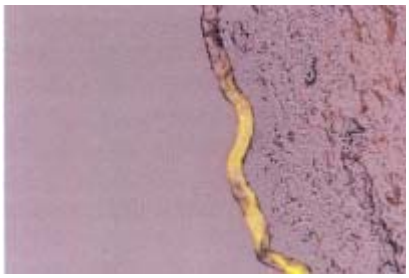
Gelclair® barrier at t=15 mins



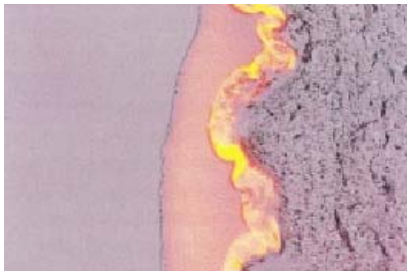
control (no Gelclair) at t=15 mins



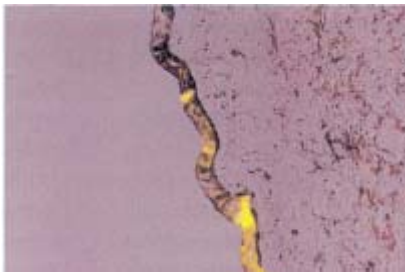
Gelclair® barrier at t=30 mins



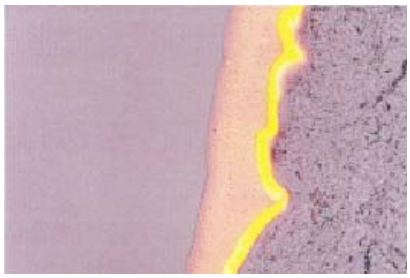
control (no Gelclair) at t=30 mins



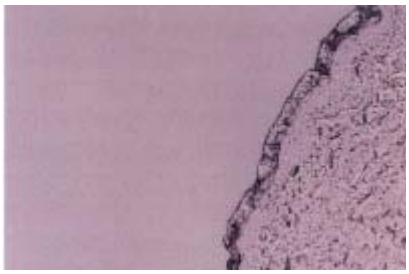
Gelclair® barrier at t=45 mins



control (no Gelclair) at t=45 mins



Gelclair® barrier at t=60 mins



control (no Gelclair) at t=60 mins

2. PRECLINICAL SECTION

2.1. EXECUTIVE SUMMARY

Gelclair® consists of widely-used ingredients that can be recognised as safe. There are no references in the peer-reviewed scientific literature to indicate that unexpected toxicity might arise when the product is used for the proposed indication.

The product has been investigated in a battery of biocompatibility tests to evaluate the potential cytoxicity and the irritation and /or sensitisation that might occur after topical administration. The results showed that Gelclair® induced limited irritation but demonstrated a certain degree of cytotoxicity .

In relation to the topical use of the product for the proposed indication, and specifically for the length of the treatment, it appears that the risk-benefit balance for Gelclair® is positive and the results of the preclinical biocompatibility test support the use of the product.

2.2. REVIEW OF THE PRECLINICAL SAFETY DATA OF GELCLAIR®

Gelclair® is the brand name of a product that consists of well known and widely used ingredients that have been used for a long time in food and pharmaceutical products with most of the ingredients generally recognised as safe. This product is used orally as a mouthwash to create a physical barrier which protects the mucosa from the irritation thus reducing pain caused by the exposure of pain fibres in lesions caused by chemotherapeutics. This picture is well described as mucositis.

The quali-quantitative composition of Gelclair® is reported in the following table:

Table 1: Composition of concentrated Gelclair

Ingredient	% in finished product before dilution	Function
Maltodextrin	6.00	Thickener / flavour carrier
Propylene glycol	2.94	Solvent / vehicle
Polyvinylpyrrolidone (PVP)	9.00	Film-forming agent
Sodium hyaluronate[1]	0.10	Film-forming agent
Potassium sorbate	0.30	Preservative
Sodium benzoate	0.30	Preservative

Hydroxyethylcellulose	0.25	Thickening agent
PEG-40 hydrogenated castor oil	1.50	Stabiliser
Disodium edetate	0.10	Antioxidant
Benzalkonium chloride	0.25	Preservative
Aroma[2]	0.16	Aroma, flavouring
Saccharin sodium	0.10	Sweetener
Glycyrrhetinic acid	0.06	Flavouring /sweetener
Water	To 100	Diluent

1) Sodium hyaluronate produced by fermentation

2) Aroma = methylcyclopentenolone (US CFR 21, 172.515, GRAS)

The formula includes 13 components, of which the most important are the film-forming agents PVP and Sodium Hyaluronate. While the first is used also as an excipient in many pharmaceutical preparations, the second is a natural constituent of the cellular membranes and is widely distributed throughout connective, epithelial and neural tissue. Also it is largely used in cosmetic products. The other Gelclair® components are preservatives, flavouring , sweeteners and additives used in the food industry. Of note, Glycyrrhetinic acid is considered a sweetener in this formulation since the low concentration utilized does not reflect any pharmacological activity.

Gelclair® is licensed in the USA using a section 510(k) notification procedure (Reference Product: Carrington Laboratories Radiacare®). The product is also marketed in some EU countries:

Biocompatibility testing was performed at NAMSA (Northwood, Ohio, USA) using modified ISO methods for testing devices applied to breached or compromised surfaces with limited exposure (category A)

The ISO10993 Part 1 indicated that initial biocompatibility testing can be limited to cytotoxicity, sensitisation and irritancy or intracutaneous reactivity (the test method was a standard ISO method modified for chemical solutions). It should be noted that the intracutaneous test is generally applied for biocompatibility testing of plastics (USP).

The following tests were performed under GLP conditions:

Cytotoxicity testing

Two methods were utilized to investigate the potential cytotoxicity of the product. The first utilitzed the Agarose Overlay Method (liquid). The second test utilized the tritration method (1X MEM dilution). Both methods are in compliance with ISO procedures that use positive and negative control.

In the study V0015-20 the potential of the reference compound Radiacare® in inducing cytotoxicity has been evaluated on L-929 mouse fibroblast cells. A solution of saline (NaCl

0.9%) USP was used as a negative control. After incubating at 37º C in 5% CO2 for 24 hours the cell culture was examined macroscopically for cell decoloration around the test article and controls to determine the zone of cell lysis. Under these experimental conditions Radiacare showed no evidence of cell lysis.

Gelclair® was evaluated in the same experimental conditions as described. The test article showed a toxicity of grade 4 whereas the negative control and the filter disc control showed no cell lysis.

In another experiment (Study V0006-131 NAMSA) the cytotoxicity of Gelclair® was investigated by using the end-point titration method (1x MEM solution at 72 hours exposure). A series of 5 dilutions was prepared. The stabilized polyvinylchloride was used as a positive control for determination of a cytotoxic end-point. In this test, a monolayer of L-929 mouse fibroblast cells was grown to confluency in the presence of 5% CO2 and exposed to the test article dilutions. Observation for the test wells and the positive control wells were conducted at 24 hours of incubation. Scoring for cytotoxicity was based on the criteria of three different end-points, i.e. non toxic, intermediate and toxic. Under these experimental conditions, Gelclair® exhibited cell lysis at all dilution tested.

There are some possible explanations for the observed cytotoxicity exhibited by Gelclair® in the above experimental conditions. The first is related to the assumption that the standard ISO toxicity tests employed in testing biocompatibility are designed to be extremely sensitive and are biased towards showing even the slightest degree of cytotoxic potential in L-929 fibroblast. Secondly, the cells utilized in the present investigation are mammalian but not human cells, therefore differences in the sensitivity to the cytotoxic agents cannot be ruled out. Recent publications (abstracts presented at the 2009 Society of Toxicology Annual meeting, Lehmann et al., 2009; Loftin et al., 2009) have pointed out that assay selection and protocol design often depend on a specific testing standard rather than on the specific form and function of the medical device. The chemical and/or physical characteristics of some medical devices may predispose them to false positive results in certain cytotoxicity assays.

The results demonstrated that Radiacare® has the potential to cause slight cytotoxicity whereas Gelclair® has the potential to induce moderate to severe cytotoxocity in the Agarose Overlay test and was found to be cytotoxic in the MEM dilution step. As a retest has been done on Gelclair® and because the controls have performed as expected the results cannot be attributed to problems with the method utilized.

A modified ISO acute intracutaneous reactivity study in rabbit (modified for chemical solution) has been used to investigate the possible irritative effects of the test article. The rabbit is an appropriate animal model for evaluating potential skin irritants by the current ISO testing standard. In the first study Gelclair® (TI251-804) and control article (saline) were injected s.c. in the right and left side of the back of the animals, respectively. The sites of injections were graded for erythema and edema up to 72 hours after the administration.

Under these experimental conditions there was evidence of irritation or toxicity from the

test article. It should be noted that not all components of Gelclair® have been evaluated for systemic administration. Following these results, and taking into consideration the type of application of Gelclair® in the clinical settings, it was determined that it would be more appropriate to conduct additional tests after topical administration.

In this study (TI262-809) 0.5 ml of the test articles (Radiacare® and Gelclair®) and control (saline solution) were topically applied to the skin of three rabbits and left in place for 24 hours. The sites were graded for erythema and edema up to 72 hours after the removal of the sample application. The results showed that Radiacare® showed no irritation whereas Gelclair® exhibited a slight irritation (Primary Irritation Index 1.6).

An additional irritation study on intact skin was further evaluated in the guinea pig (Study T1260-300). In this evaluation Gelclair® was occlusively patched for 6 to 8 hours to the intact skin of 10 guinea pigs, three times a week, for a total of nine treatments over a 3 week period. The control article was similarly patched to 5 guinea pigs. All sites were observed for evidence of dermal reactions up to 72 hours after patch removal. The results showed that Gelclair® did not induce a delayed irritation phenomenon nor sensitisation on the skin of guinea pig.

2.3. CONCLUSIONS PRECLINICAL SECTION

The results obtained in the experiments described above support the use of Gelclair® for the proposed indication. The product ingredients are considered generally safe on the basis of their large use, and, additional application outside the pharmaceutical field. Some are GRAS materials and there are no references in the peer-reviewed scientific literature to indicate that unexpected toxicity may arise.

The results of the relevant *in vivo* tests indicate that Gelclair® might cause some mild irritation, of similar severity as that seen with many marketed consumer products. The results also support the fact that there is no evidence of any delayed contact sensitisitation.

The results obtained in the experiments for the evaluation of cytotoxicity and biocompatibility tests might indicate some concerns over the safety profile. This is related to the results from the Agarose Overlay method and the MEM dilution method which show evidence for toxicity in a very sensitive cell assay that is designed to indicate the slightest degree of cytotoxic potential in mouse L-929 fibroblasts.

However, the high sensitivity of this test needs to be considered in relation to the chemical class of compounds that constitute the ingredients of Gelclair®. Further, the discriminatory nature of the test is considered poor when it comes to predicting cytotoxic effects after exposure of mucous membrane according to some authors in the peer-reviewed literature (Earl et al., 1996; Wilhelm et al, 2001). In light of recent data presented at SOT 2009, the routine *in vitro* cytotoxicity tests are not able to predict *in vivo* toxicity (Lehmann et al,

2009, Loftin et al., 2009). Further experiments should be performed to elucidate if the observed results are relevant to the clinical situation. So far, on the basis of the clinical experience and for the use of the products in human there is no evidence of toxicity related to the mucosal cells.

In relation to the topical use of the product for the proposed indication, and specifically for the length of the treatment, it appears that the risk-benefit balance for Gelclair® is positive and the results of the preclinical biocompatibility test support the use of the product.

3. CLINICAL

3.1. EXECUTIVE SUMMARY OF ALL STUDIES

The effectiveness of Gelclair™ has been evaluated in 16 clinical trials involving 672 patients affected by oral mucositis and other inflammatory or ulcerative lesions of the oral cavity of which 459 were treated with Gelclair®.

All 16 completed clinical trials have been included in this assessment. A summary table is presented at the end of the section.

The majority of the studies (13 studies) were carried out in patients with oral mucositis, either induced by chemotherapy, by radiotherapy or by both. Three further studies conducted in patients with painful lesions of the mouth of different origin are also presented. Among these three studies, for the purpose of this document, the study in "painful lesions of mouth" (Innocenti et al., 2002) will be included in the analysis together with the ones in oral mucositis, since it included a vast majority of patients with cancer therapy induced oral mucositis. The study in subjects under CO_2 laser surgery (Hita-Iglesis et al., 2006) and the one on recurrent aphtae will be described separately (Marzatico 1999).

Moreover, the oral mucositis studies are separated into different sections depending if they were uncontrolled (8 studies) or controlled (4 studies) and according to the patient population included (2 uncontrolled studies were in pediatric patients).

In the various studies the effectiveness of Gelclair® was evaluated in terms of the reduction of pain and recovery of functionality, intended as the ability to eat and drink (Innocenti et al., 2002, DeCordi et al., 2001, D'Andrea et al., 2003, Flook et al., 2005, Hita-Iglesias et al., 2006, Gibson et al., 2008). Some studies also addressed the reduction of the severity of mucositis (Del Mar Sabater et al., 2006). The impact of Gelclair® on quality of life and acceptability of the product by patients was also evaluated (D'Andrea et al., 2003, Del Mar Sabater et al, 2006).

Eight out of thirteen studies are open-label, uncontrolled trials. All of the remaining four were open-label, but including a control arm, varying from standard hospital care (Del Mar Sabater et al., 2006), to "Institutional Standard Magic Mouthwash" (McKenzie et al., 2006) to benzydamine (Flook et al., 2005), and to sucralfate+mucaine (Barber et al., 2006). The daily dose used in most cases was 3 sachets/day, while the duration of treatment varies between one day, 7 and 21 days. In the majority of the studies conducted, the primary endpoint was "Pain", recorded by the patients on a visual-analog scale (VAS) or visual-numeric scale (VNS).

In at least 3 studies on mucositis, the reduction in the grade of disease, usually measured via the WHO severity scale, was also considered as an endpoint.

3.2. CLINICAL STUDIES

3.2.1. Non-controlled studies in adult patients

1) Efficacy of Gelclair® in Reducing Pain in Palliative Care Patients with Oral Lesions: Preliminary Findings from an Open Pilot Study

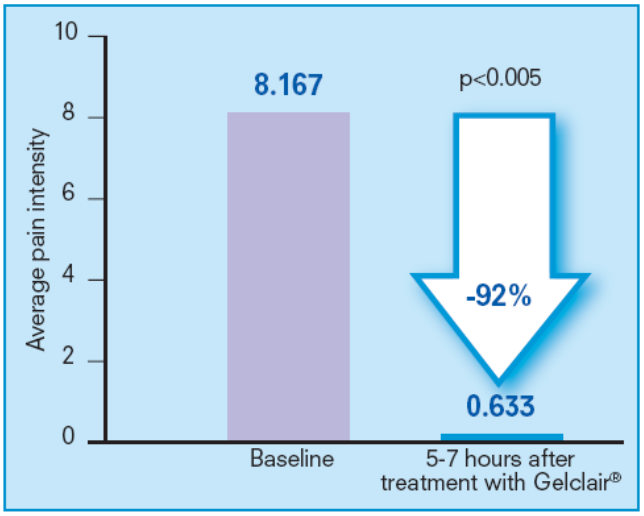
Innocenti M. et al.

J Pain Symptom Manag. 24(5): 456-7, 2002

This prospective, open, uncontrolled, pilot study evaluated the efficacy of Gelclair® in reducing oral pain. Thirty patients suffering from painful oral lesions of various aetiologies (mucositis and stomatitis, severe diffuse aphthosis and post-surgical pain) were enrolled and evaluated. Patients included oncology patients as well as for example 10 AIDS patients. Gelclair® was administered three times daily. Pain and functionality (ability to eat and drink) levels were evaluated by the patients using a visual numerical scale (VNS, 0 = no pain to 10 = maximum pain) at baseline, 5-7 hours after first application of Gelclair® and after 7 to 10 days of continuous daily administration. These time periods are considered valid for a symptom response study for patients with oral mucositis in a palliative care setting.

The results showed a significant 92% reduction of total oral pain in the short-term 5-7-hour period following administration of Gelclair® compared with baseline measurements (mean scores: 8.167 at baseline and 0.633, 5-7 hours post Gelclair, $p<0.005$; Fig 2).

Figure 2: Reduction in spontaneous pain 5 to 7 hours post treatment with Gelclair



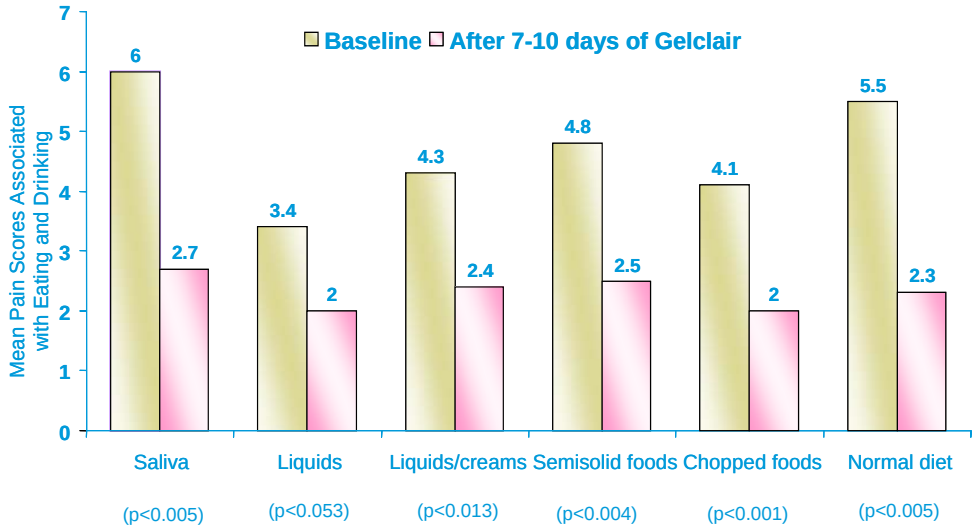
After one week of using Gelclair™ 87% of patients reported overall significant improvements from baseline scores related to pain on swallowing food, liquids and saliva. A statistically significant 50 % pain reduction on eating was observed in the evaluation performed 7 to 10 days after treatment ($p<0.005$; Fig 3, Table 2). Meals included normal diet with solid food. This interesting result sets the basis for a controlled study in a more homogeneous patient population with a well defined course of the disease. Such a study may include for example only patients who underwent radiotherapy and for which oral mucositis is know to last for several weeks. This could confirm the good results obtained also after 7-10 days of Gelclair® eliminating the confounding variable of the natural healing history of the oral condition, which can last from 5 days, in case of aphtous ulcers, to several weeks in case of radiotherapy induced oral mucositis.

No patients reported side effects with Gelclair®.

Table 2: Efficacy of Gelclair® on pain on the ingestion of food after 7 to 10 days of treatment (mean ± standard deviation), N=30

	Baseline	**7-10 days after Gelclair**	**P value**
Pain on swallowing	6.0±2.6	2.7±2.3	<0.005
Pain on ingesting liquids	3.4±3.0	2.0±2.5	0.053
Pain on ingesting liquids and creams	4.3±2.9	2.4±2.5	0.013
Pain on ingesting semisolid foods	4.8±3.1	2.5±2.4	0.004
Pain on ingesting chopped food, rice and pasta	4.1±3.1	2.0±2.2	0.001
Pain on ingesting a normal diet, 3 times daily	5.5±2.9	2.3±2.1	<0.005
Total pain score	28.3±14.3	14.0±10.5	<0.005

Figure 3: Efficacy of Gelclair® on pain on ingesting food after 7 to 10 days of treatment, N=30



2) Gelclair: potentially an efficacious treatment for chemotherapy-induced mucositis.

De Cordi D. et al.

Abstract: Italian Tumour League III congress for professional oncology nurses, Conegliano, Italy, 10-12 October 2001.

This was an open label, uncontrolled study in oral mucositis following chemo and/or radiotherapy.

Thirty-three ≥30 year old patients with breast, colorectal, lung, stomach cancer, cancer to the oral cavity and non-hodgkin lymphoma were included in the study. Thirty patients whom completed the study, received 3 sachets of Gelclair/day for 3 days. Evaluations were carried out on day 0, 1 and 3, considering the following parameters:

- Pain intensity, on a visual numerical scale from 0 to 10;

- Severity of mucositis according to the WHO scale (from grade 1 to grade 4)

- Functionality understood as the ability to consume solid foods or liquids and concomitant presence of pain, on a scale from 1 to 10;

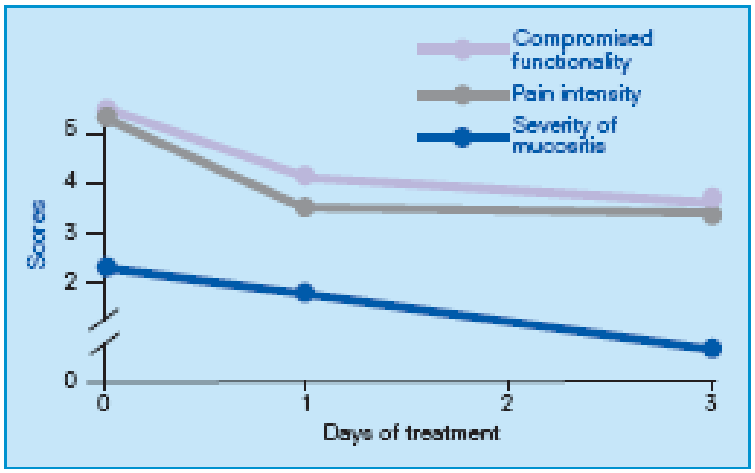
The results obtained are encouraging, both in terms of diminution in the grade of mucositis (43%) and a reduction in the level of pain (51%) as well as improved functionality in the ability to take food (41%) (Table 3).

Table 3: Efficacy of Gelclair® in chemotherapy-induced mucositis

	Baseline	**After 1 day**	**After three days**
Spontaneous pain	4.68	3.38	2.27
Ability to feed oneself	4.72	3.88	2.77
Severity of mucositis - WHO grade	2.18	2.02	1.52

For all three evaluation parameters the percentage of patients who benefited from treatment was high: 25 patients (83%) reported reduction of pain, in 25 patients (83%) an improvement of functionality and in 17 patients (57%) an improvement in the grade of mucositis was observed (Fig. 4).

Figure 4: Improvement in the course of treatment with Gelclair®



Hence, in this uncontrolled study, the treatment with Gelclair® is effective in decreasing the severity of mucositis by reducing pain and improving ability to consume foods; all aspects that significantly improve the patient's quality of life.

3) A Preliminary Study of Orassist (Gelclair) in the management of Oral Mucositis.

Berndtson M.

Svensk Sjukhustandlakartidning (Swedish Hospital Dentistry) Nr 3 (Argang 26) pp17-21, 2001

This was an open label, uncontrolled pilot study in oral mucositis following chemo- or radiotherapy.

Ten patients with malignant tumors (9 patients with solid tumors to mouth or head and neck and 1 lymphoma patient) and 3 patients with GVH (graft versus host disease) were treated and evaluated. Oral mucositis pain (measured by VAS, 1-10), grade (WHO) and the use of analgesics were monitored.

All 13 patients included in this open study were treated with 3 daily applications of Gelclair®. Acceptance (taste, consistency, pain on application), and side effects of Gelclair® were evaluated.

The results showed that during their radiotherapy all patients developed grade 3 mucositis and all except one had intense pain and made some use of analgesics.

All patients tolerated the taste and consistency of Gelclair, whose application was not painful.

One patient did not wish to continue the rinses because she thought that they generated increased secretion of saliva, which made her nauseous.

The majority of patients attributed to Gelclair® a soothing effect on lesions.

4) Treatment with Gelclair® in patients suffering grade III-IV oral mucositis: efficiency and impact on quality of life

Bonassi L. et al.

Annals of Oncology;14(supplement 4): E38, 2003

This was an open-label, uncontrolled study including 15 patients with polychemotherapy-induced oral mucositis of grade III and IV.

All patients were treated with Gelclair®, 3 applications per day, for 4 months. Evaluation parameters were:

- Pain, evaluated on a visual – analog scale;

- Severity of mucositis;

- Presence of local ulcerations evaluated on days 1, 3, 7 and 14.

Five patients needed hospitalization as they were completely unable to feed themselves. The remaining 10 patients showed a substantial improvement after the third day of treatment with Gelclair, and by the seventh day their mucositis had almost completely disappeared. By day 19 all patients had recovered from their mucositis.

Initially all patients showed aversion toward certain foods because of the pain caused by their ingestion and dysguesia, symptoms that disappeared as mucositis improved.

It was demonstrated that Gelclair® gave consistent relief from pain associated with mucositis, allowing patients to overcome food refusal and improving their well-being.

5) Oral pharyngeal mucositis: nursing assessment on the efficacy of a new treatment.

D'Andrea N. et al.

Annals of Oncology 14(supp. 4): 97 (Abstract N2), 2003

This was an open label, uncontrolled study including 53 patients which developed oral mucositis following chemotherapy (50), radiotherapy (1) or supportive therapy (2). Patients were 50-69 years old and most of them had breast, colorectal, or lung cancer.

Mucositis symptoms were evaluated at the baseline (upon onset of the disease) and after 1 and 3 days of treatment with Gelclair®. Evaluation parameters were as follows:

- Intensity of pain, on a numerical scale from 0 to 10;

- Ability to eat and drink (a high score indicated damage);

- Severity of mucositis according to the WHO scale.

The results showed a trend towards an improvement in pain from baseline (4.58) to the third day of therapy with Gelclair® (2.04). A similar finding was observed for the ability to ingest foods or drinks (baseline value = 4.10, after 1 day = 3.2, after 3 days = 2.36). In addition, the median severity of mucositis on the WHO scale was 1 grade lower after 3 days of Gelclair® (grade 1) than at baseline (grade 2).

6) Gelclair® for the treatment of chemotherapy-induced stomatitis in transplant and hematology patients: an interim analysis.

Liewer SE. et al.

Blood (ASH Annual Meeting Abstracts) 2004 104: Abstract 5317

This open label, single-arm study evaluated the effectiveness of Gelclair® administered every 8 hours to relieve pain associated with treatment-induced stomatitis in patients with hematological malignancies.

Efficacy was determined by obtaining hourly pain scores on a 10-point scale for the first 8 hours, then every 6 hours until resolution of symptoms, while controlling for stomatitis severity and opioid consumption. Secondary endpoints included quality of life [functional living index-cancer (FLIC)], ability to consume a soft diet, and ability to take oral medications. Fifteen of 30 planned patients have been enrolled, with 12 being transplant patients (8 auto, 4 allo). Melphalan was the most common therapy received and multiple myeloma was the most common patient diagnosis.

The median time on study was 5 days. The median stomatitis severity was grade 2 with a range of 1 to 3 (NCI criteria). The mean pain score at baseline was 5.8 +/– 0.6, which declined to 3.8 +/– 0.6 one hour after Gelclair® application and remained below baseline for 8 hours. Over the first 72 hours, average daily pain scores, stomatitis severity, and opioid consumption all increased, while WBC decreased. The average FLIC score at baseline was essentially unchanged on day 1, 7 or at the end of study (102, 102, 98, and 101, respectively). Oral medications were administered and soft diet tolerated during 93% and 85% of treatment days. Adverse events were limited to nausea with or without vomiting in 2 patients. Interim analysis suggested Gelclair® improves pain scores quickly while allowing patients to continue oral medications. This improvement was sustained throughout the dosing interval.

7) An Audit of the Efficacy of Gelclair® for Mouth Pain in Patients Undergoing Radiotherapy or Chemotherapy

McLean M.

Presented at British Association of Head and Neck Oncology Nurses (BAHNON)

National Study Day on Sharing Good Practice in Head and Neck Cancer

Nursing, 12 June 2009, Leeds, UK.

This audit aimed at assessing the efficacy of Gelclair® in terms of symptom relief for patients with radiotherapy or chemotherapy induced oral mucositis.

The audit included 26 patients with head and neck cancer (n=20), ovarian cancer (n=1), oesophageal cancer (n=3) and anal cancer (n=2) who developed grade II oral mucositis. The first 20 patients underwent radiotherapy, the remaining patients chemotherapy.

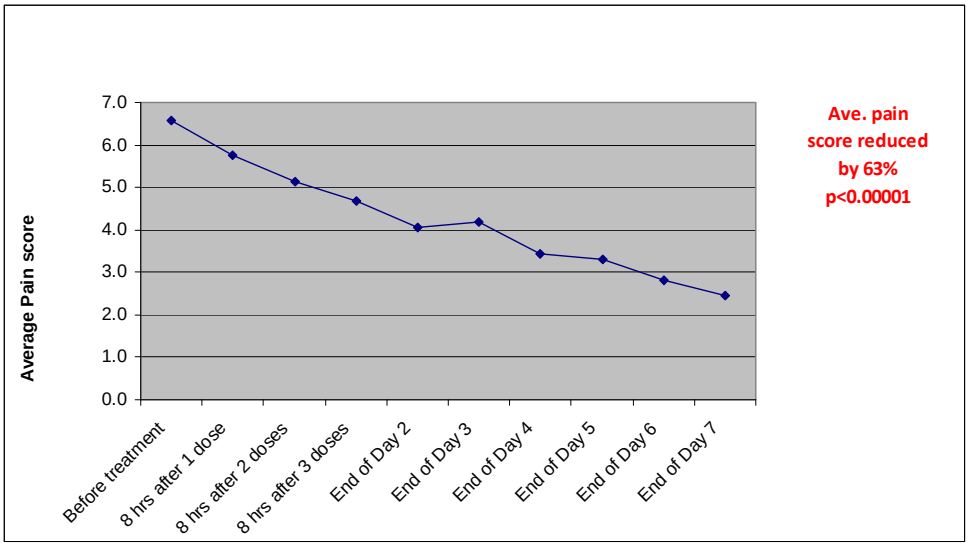
Patients received Gelclair® 3 times daily for a period of 7 days. Patients were allowed to receive pain and infection-control medications at the discretion of the radiotherapy/chemotherapy healthcare professional.

Each day patients recorded pain (primary endpoint, recorded on a visual numerical scale, 0-10), functionality score (based on the ability to eat and drink/swallow different foods/only saliva, score based on 6 questions) and their analgesic consumption in a specific assessment sheet. It is noteworthy that in the assessments a decrease in functionality score, meant an increase in functionality (or the ability to eat more solid foods). Moreover, the patients were evaluated by a member of radiotherapy/ chemotherapy department staff at a first review assessment with a second follow up review 3-7 days later.

Of the 26 patients, which were included in the study, complete results for each day exist for 16 patients.

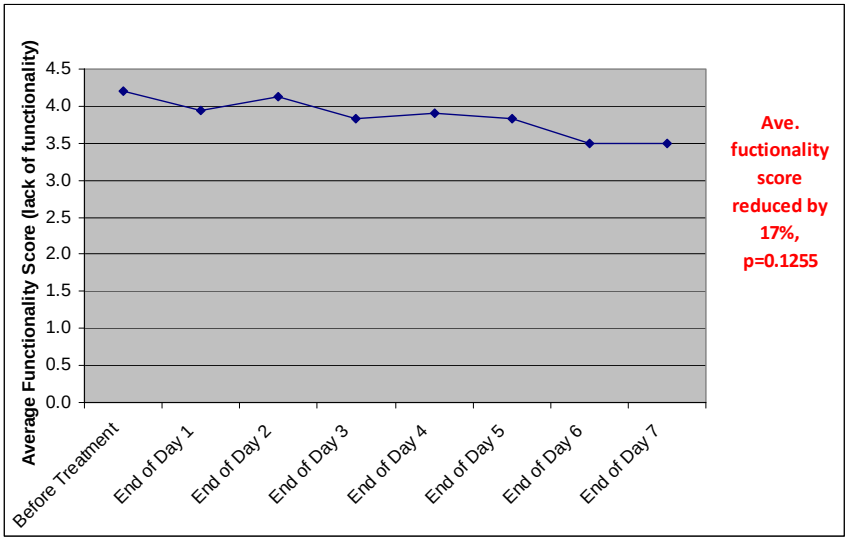
By the end of day 1, for these 16 patients the average pain score had reduced from 6.6 to 4.7. By the end of day 7, the average score had decreased from 6.6 to 2.4, signifying an average reduction of 63% at the end of the 7 day assessment period (Fig. 5).

Figure 5: Average pain over 7 days



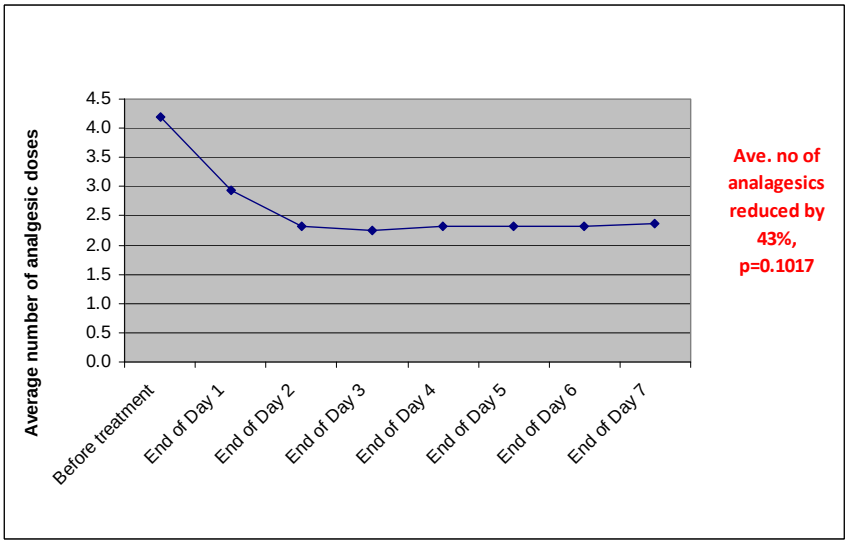
By the end of day 7, the average functionality score (or lack of functionality) had reduced from 4.2 to 3.5, which means that there has been an average increase in functionality of 17% (Fig. 6).

Figure 6: Average lack of functionality over 7 days



By the end of day 7, the average number of analgesic doses taken by patients had reduced from 4.2 to 2.4, an average reduction of 43% (Fig. 7).

Figure 7: Average use of analgesics over 7 days



The above results were calculated on the 16 patients, out of 26, for which complete data on each day were available. However, on day 3 there were complete data for respectively 25, 24 and 26 patients out of the 26 and the results confirm the trend observed on 16 patients:

pain was reduced from 6.4 before treatment to 4.2 on day 3 (35% difference, p=0.0003); lack of functionality from 4.0 before treatment to 3.8 on day 3 (6% difference, p = 0.3285), and analgesics consumption from 3.2 before treatment to 2.3 on day 3 (27% difference, p = 0.1996)

No serious adverse events were observed that were judged to be connected to the study substances.

Hence, Gelclair® was well tolerated and significantly reduced mouth pain associated with oral mucositis in cancer patients undergoing radiotherapy or chemotherapy. The treatment also resulted in a reduced analgesic consumption and enabled a more comfortable intake of food and fluids.

8) The clinical effectiveness of Gelclair® in the management of oral mucositis.

Lindsay, G, , Rushton, R., Harris, T., et al.,

Aust Nurs J. 2009 Apr;16(9):30-3

This open label, single-arm study evaluated the effect of Gelclair® on pain scores in head and neck cancer patients undergoing radiotherapy, which developed oral mucositis. The study included 33 patients with a confirmed oral mucositis.

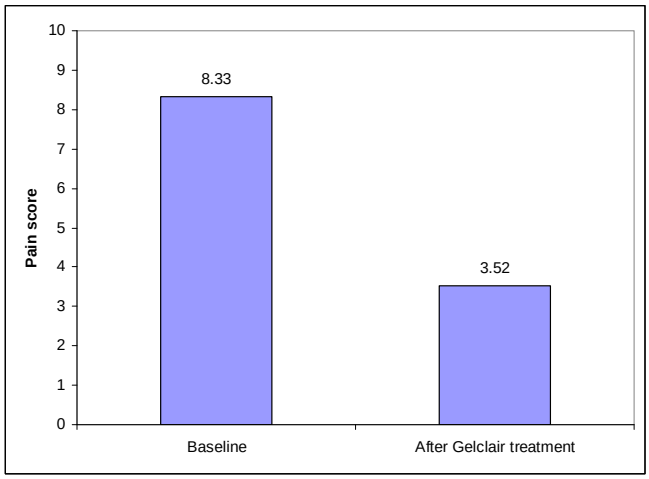
Patients received standard oral care as well as soluble paracetamol or aspirin, local anesthetics or morphine or phentanyl, if required. Patients whose pain exceeded 5 on a 0-10 visual analog scale (VAS) received Gelclair®. Gelclair® was used diluted in 40 ml of water, three times per day, 1 hour before meals. Pain was evaluated at baseline and 1 hour after treatment with Gelclair®.

Gelclair® was used by the patients for an average of 2.29 days with the maximum treatment being 4 days.

The results showed an improvement in pain scores in 85% of the patients who used Gelclair®. It is of note that prior to the use of Gelclair® 88% of patients presented with a severe oral mucositis pain, grade (VAS scale) of 7 or higher.

The average pain score at baseline was 8.33, which was reduced to 3.52 after treatment (Figure 8). Anecdotal patient comments showed also an improvement in the patients' ability to eat and drink. The power of the positive results could possibly have been enhanced if the study had been designed as a blinded and placebo-controlled study.

Figure 8: Pain score at baseline and after Gelclair



3.2.2. Controlled studies in adult patients

1) Gelclair® vs benzydamine in a randomised controlled study in patients with oral mucositis due to radical radiotherapy.

Flook C. et al.

Supportive Care in Cancer, 13 (6): 443-444 (Abstract 15-098), 2005

This was an open-label, controlled study in patients with oral mucositis following chemo- or radiotherapy, where the control group received the drug benzydamine. The study included 65 patients of whom 61 developed grade 2 and 3 mucositis and were included in the effectiveness analysis.

In total 29 patients were treated with Gelclair® and 32 with benzydamine. Patients were evaluated on the day of the first dose of radiotherapy and weekly for the entire period of radiotherapy treatment.

Evaluation parameters were:

- Pain at rest and when swallowing saliva, liquids, soft and solid

foods; through the use of a visual – numerical scale from 1 to 10;

- Pain when speaking (scale from 1 to 10);

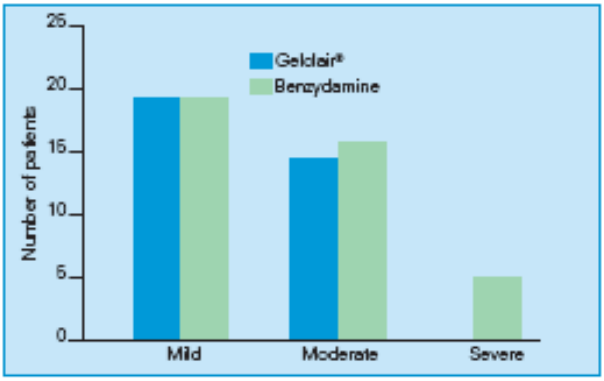
- Pain when applying (on a 4 point scale, from 1, least acceptable, to 4, most acceptable;

- Need to use enteral or parenteral feeding, upon being admitted to the hospital, naso-gastric tube for nutritional support;

- Use of additional pain medication.

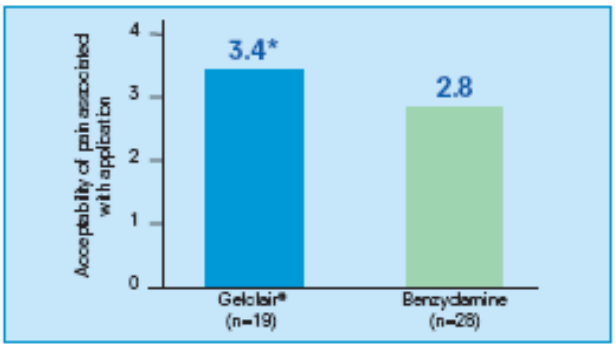
The results showed that Gelclair® is at least as effective as benzydamine, the only agent currently recommended for the treatment of oral mucositis, in all outcomes except acceptability of smell. A trend in favor of Gelclair® was observed since no patient treated with Gelclair® reported severe pain when speaking (Fig. 9).

Figure 9: Pain associated with speaking after developing oral mucositis.



Gelclair® demonstrated significantly lower pain on application (2.8 vs 3.4, p = 0.012, Fig. 10).

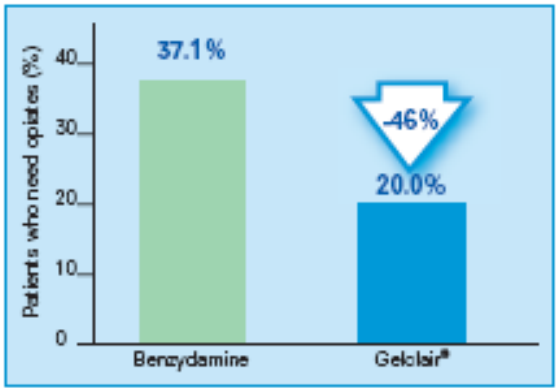
Figure 10: Acceptability of pain associated with application (1= least acceptable, 4= most acceptable)



In patients treated with Gelclair® a lower incidence (>8%) of pain in swallowing food was observed (Table). None of the patients treated with Gelclair® needed artificial feeding by means of nasogastric tube, unlike what was observed with benzydamine: respectively 0% compared to 12.5%.

A lower number of patients needed opiates in the Gelclair® group compared to the Benzydamine group (20% vs. 37.1%) (Figure 11).

Figure 11: Gelclair® reduces use of opiates with respect to benzydamine



The lower need for opiate medication and artificial feeding with NG tubes may contribute to maintaining an acceptable quality of life. Hence Gelclair® represents a beneficial and effective alternative compared to benzydamine for patients suffering from radiotherapy induced mucositis.

Safety evaluation showed no serious adverse events that were judged to be related with the study substances. This is an interesting study, and would have been more powerful if results had been correlated with OM scores using a scale such as the WHO scale which combines symptoms, signs and function to ascribe a score.

2) Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis.

Barber C. et al.

Supp Care Cancer, 15 (4): 427-440, 2007

This was an open-label, controlled study in oral mucositis following radio- and/or chemotherapy, where the control group received sucralfate+mucaine. Twenty Head and neck cancer patients (10 in each group) were enrolled and evaluated. Patients were eligible for the trial when they felt that they were no longer receiving adequate pain control via simple analgesia (i.e. approaching third rung of WHO analgesic ladder). Study medication and control were administered 4 times in 24 hours. Evaluations were performed via patients questionnaires at baseline (before treatment start) and at 1, 3 and 24 hours after initiation of the treatment. The endpoints included general pain and pain on speaking (primary outcome measure, measured on visual analog scale, with endpoints ‘0 = no pain’ and ‘10= most pain imaginable’) and pain on swallowing (secondary outcome, recorded on self-recorded

swallowing scales).

Pain assessments did not reach any statistically significant difference between intervention and control groups across the time intervals (F= 1.512; df=1, 17; p=0.236), although Gelclair® has shown improved pain-reduction in 4 patients already 1 hour after its first application, while this was observed in only 1 patient in the control group. However, the small sample of patients included is one of the limitations of the present study and does not allow drawing any further conclusions. As the authors state, 'a potential difference in the effectiveness of Gelclair® and standard therapy may not have been identified because too few patients took part in the research'.

Regarding safety, in one patient Gelclair® was found to cause mild inflammation and stinging to the oral cavity 30 minutes after use, although no serious anaphylactic event occurred.

3) Tratamiento de la mucositis oral con un protector de la mucosa.

Del Mar Sabater et al.

Dentum, 6(1): 36-41, 2006.

This was an open-label, controlled study in 97 hematological patients of which 79 developed oral mucositis following chemotherapy or a bone marrow transplantation conditioning regimen. Eigtheen patients received Gelclair® 3 times per day, while the 41 patients in the control group received standard mouthcare and hospital standard mucositis treatment. The duration of treatment was 10 days. The endpoints considered were: improvement in pain and grade of mucositis.

The mean pain at baseline, before start of mucositis treatment (visit 1, 4 days after beginning of cancer therapy), was 2.75. At the second visit (day 9 from beginning of cancer therapy) pain was increased of 1.5 in the investigational arm and 2.4 points in the control group. These differences were not statistically significant (p=0.227). At visit 3 (15 days after beginning of cancer therapy), pain in both groups further increased of 0.5 points in the investigational arm and 1.9 in the control arm. These differences were still not statistically significant. Hence, a trend towards a smaller increase in pain was observed in the Gelclair® group, although the incremental differences did not reach statistical significance.

Also the results on the grade of mucositis and patients' ability to eat and drink did follow a similar trend, but did not reach statistical significance.

Regarding safety, 3 patients reported irritation and a burning sensation on application.

4) A randomized, open-label comparison with institutional standard magic mouthwash for the treatment of pain associated with radiation-chemotherapy induced mucositis

MacKenzie M.et al.

Supportive Care in Cancer 14(6): 641 (abstract 16-116), 2006

This was a multi-center open-label, controlled study in 115 patients with oral mucositis following chemo- and radiotherapy. Patients were randomly assigned (2:1 treatment ratio) to either Gelclair® (77 patients) or ISMM (38 patients, control group). Patients received Gelclair® or ISMM over 21 days.

Evaluation parameters were recorded in patient diaries and included the following primary and secondary outcomes.

Primary outcomes:

- Mean reduction in pain score measured on a 6 point pain assessment scale

- Mean increase in duration of pain relief

Secondary outcomes:

- Safety assessment

- Assessment of treatment preference and satisfaction

The results showed no statistically significant differences between treatments in Pain scores (P=0.1563), pain relief rates (P=0.2056), or number of treatments (P=0.0833).

However, in absolute terms, treatment with Gelclair® demonstrated a more favorable rate of pain relief vs ISMM, 71.4% vs 57.9% respectively.

Regarding safety, both treatments were well tolerated by patients. No related serious adverse events were reported, and only 1 patient experienced retching, which was considered related to the study substance.

3.2.3. Studies in pediatric patients

1) Clinical effectiveness of Gelclair® in the treatment of oral mucositis: a patient based questionnaire

Short L., Fung D.

Intl. J. Pediatric Dentistry 18 (suppl 1): 14 (abstract P25)

This was a questionnaire-based pilot study including 31 pediatric oncology/hematology patients. Of 19 patients suffering from oral/oesophagal mucositis 13 used Gelclair® and 10 found that it resolved their mucositis symptoms (pain, debility and ability to eat and drink).

Hence, Gelclair® appeared to be effective in reducing oral symptoms in young oncology patients.

2) Efficacy of Gelclair® in reducing the pain of oral mucositis in children and young people with cancer

Gibson F., Eden T.

Presented at Symposium on Oral care, SIOP Congress, Berlin, 2008

This was a multicenter, prospective, open, uncontrolled, pilot study to examine the feasibility of such a study and acceptability of Gelclair® in 50 pediatric patients (4-19 years old) who were experiencing oral pain from mucositis following cancer therapy. Cancer treatments included chemotherapy, radiotherapy, and bone marrow- or stem cell-transplantation regimens. The most frequent tumor types were Non-Hodgkin lymphoma, sarcoma, ALL, and AML. The study evaluated oral pain (measured with Wong and Baker pain faces scale, from No hurt=0 to hurts worst=5, reference Wong and Baker 1988), ability to eat, drink and speak, and acceptability of the product. Moreover, use of analgesics as well as grade of Oral mucositis (WHO and OAG) were recorded. Gelclair® was administered 3 times per day. Total study duration was 48 hours, with assessments before Gelclair® (baseline) and at 1, 3, 6, 12 24 and 48 hours after Gelclair®.

The study was recently presented at the International pediatric oncology society congress (SIOP, 2008). First results on 40 patients showed a reduction in the pain faces score, and a positive evaluation of its taste. Two case reports were presented. The first patient went from only taking sips of water to being able to eat anything and from a pain faces score of 3 to a score of 1. The second patient went from not being able to swallow saliva to taking small sips of water and a pain faces score of 5 to a score of 2.

Results analysis on the total 50 patients is ongoing.

3.2.4. Other studies in settings other than Oral mucositis

1) Evalauation of tolerability of a mouthrinse and of its power of keeping the oral bacterial load under control. Assessments through a test of use and microbiological evaluations.

Marzatico F.

Helsinn, data on file.

Open label study including 20 patients suffering from recurrent aphtosis. The study was performed over 30 days and product used at least twice per day. The main endpoints included the product agreeableness (included feeling of cleanness and freshness, taste, fragrance, color, texture, ease of use and rinsing), state of the mucosa and gums and microbial load.

The results show a very good agreeableness and tolerability, an improvement of the status of the oral mucosa and gums and a decrease of the bacterial load for at least 6 hours

2) Evaluacion del comportamento clinico de un gel concentrado de polivinilpirrolidona ehialuranato sodico, en pacientes sometidos a tratamento quirurgico con laser C02.

Hita Iglesias et al.

Medicina Oral (supplement): 79-80, 2003

This was an open-label, controlled study in patients with oral lesions subjected to surgical treatment with CO_2 laser, where the control group received ibuprofen and the investigational group received ibuprofen+Gelclair®. Sixty patients (30+30) were enrolled and evaluated. 30 patients carried out 3 local applications of Gelclair® per

day, for 7 consecutive days. Spontaneous pain and pain on swallowing were evaluated using a visual numeric scale (VNS 1-10)..

The results show that the treatment with Gelclair® reduces the perception of pain, compared to the control group, both in the short (day 1) and long term (day 7).

At 24 hours, the spontaneous pain was rated at 0.83 in the experimental group as opposed to 2.13 in the control group (P=0.000) and 0.67 against 1.17 (P=0.012) at 7 days. The pain on swallowing showed a mean of 3.73 as opposed to 4.70 from control group (P=0.029) at 24 hours, and 2.10 against 3.77 (P=0.000) at 7 days. The experimental group had a

statistically significant reduction in postoperative spontaneous and swallowing pain during the first 24 hours. This difference was maintained during the first week of postoperative follow up.

No hypersensitivity to Gelclair® ingredients was observed.

Hence, Gelclair®, whose effect occurs rapidly after the first application, allows an effective reduction, continued and lasting over time, of pain in patients undergoing surgical treatment with CO_2 laser.

3.3. SUMMARY TABLE

Author/ Investigator	Study Title	Study design	Patients treated with Gelclair/ total number of patients	Main results
Non-controlled studies				
1) Innocenti M. et al.	Efficacy of Gelclair® in Reducing Pain in Palliative Care Patients with Oral Lesions: Preliminary Findings from an Open Pilot Study	Open label descriptive study. Patients with painful lesions of the mouth. Evaluated pain at baseline, after 5-7 hours and 7-10 days (VNS 0-10).	30/30	Pain: -short term pain reduction from 8.167 at baseline to 0.633, 5-7 hours after use of Gelclair - medium term(7-10 days) reduction of pain upon ingestion of food No patients reported side effects with Gelclair®
2) De Cordi D. et al.	Gelclair: potentially an efficacious treatment for chemotherapy-induced mucositis.	Open label study. Patients underwent CT and/or RT. Evaluated pain (VNS 0-10), mucositis intensity (grade, WHO) and functionality at baseline, on days 1 and 3..	30/33	Pain: 4.68 (basal) > 3.38 (day 1) > 2.27 (day 3) Functionality: 4.72 (basal) > 3.88 (day 1) > 2.77 (day 3) WHO OM Grade: 2.18 (basal) > 2.02 (day 1) > 1.52 (day 3)
3) Berndtson M.	A Preliminary Study of Orassist (Gelclair) in the management of Oral Mucositis.	Open label study. Patients undergoing CT or RT. Evaluated pain (VAS 1-10) and mucositis grade (WHO). .	10/10	Patients developed high grade mucositis during RT, had intense pain and used some analgesics. Patients tolerated taste and consistency of Gelclair® well and application was not painful. Most patients attributed Gelclair® a

				soothing effect. One patient with impression of increased salivation.
4) Bonassi L. et al.	Treatment with Gelclair® in patients suffering grade III-IV oral mucositis: efficiency and impact on quality of life	Open label study. Patients with polychemotherapy-induced grade III-IV OM. Evaluated pain (VAS), mucositis severity and presence of local ulcerations on days 1, 3, 7, 19.	15/15	Substantial improvement in 10 patients after day 3 of treatment with Gelclair®.
5) D'Andrea N. et al.	Oral pharyngeal mucositis: nursing assessment on the efficacy of a new treatment.	Open label study. Patients with OM following CT, RT or supportive therapy. Evaluated pain intensity (VNS 0-10), ability to eat and drink, OM severity (WHO) at baseline, on days 1 and 3.	53/53	Pain: 4.58 (basal) > 2.04 (day 3) Functionality: 4.10 (basal) > 3.20 (day 1) > 2.36 (day 3) OM grade: lower at day 3 vs basal value
6) Liewer SE. et al.	Gelclair® for the treatment of chemotherapy-induced stomatitis in transplant and hematology patients: an interim analysis.	Open label study. Patients with treatment for hematological malignancies. Evaluated pain (10 point scale), ability to eat/swallow, severity of stomatitis and opioid consumption untill resolution of symptoms (median time on study: 5 days).	15/15	Pain: 5.8 (basal) > 3.8 (1 hour) Remains < baseline for 8 hours Over first 72 hours: average daily pain scores, severity of stomatitis and opioid consumption increased. Average FLIC score unchanged from baseline to end of study. Oral medications and soft diet tolerated. Adverse events limited to nausea with or without vomiting in 2 patients.
7) McLean M.	An Audit of the Efficacy of Gelclair® for Mouth Pain in Patients Undergoing Radiotherapy or	Open label audit. Patients with grade II (WHO) OM from CT or RT.	26/26	Significant pain reduction: 6.6 /(baseline) >4.2 day 3

	Chemotherapy	Evaluated pain (VNS 0-10), functionality (ability to eat and drink), and analgesic consumption over 7 days.		No serious adverse events were observed that were judged to be connected to the study substances.
8) Lindsay, G, , Rushton, R., Harris, T., et al.,	The clinical effectiveness of in the management of oral mucositis.	Open label study. HNC patients with OM from RT and presenting with a pain score >5 (VAS). Evaluated pain (VAS).	33/33	Pain: 8.33 (baseline)> 3.52 (1 h post-Gelclair). Patients anecdotally reported improvement in ability to eat and drink.
Controlled studies				
1) Flook C. et al.	Gelclair® vs benzydamine in a randomized controlled study in patients with oral mucositis due to radical radiotherapy.	Randomized, open label, controlled study. Active comparator: benzydamine. Patients with grade II-III OM from RT. Evaluated pain at rest, swallowing and speaking (VNSs 1-10); pain on Gelclair® application (4 point scale); use of enteral or parenteral feeding, use of pain medications. Pain evaluated weekly for 3 weeks.	29/64	Gelclair® was as effective as benzydamine in reducing pain. Gelclair® presented lower pain on application and higher acceptability. Lower need for opiate medication and NG tubes in Gelclair® group. No serious AEs judged to be related with the study substances.
2) Barber C. et al.	Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis.	Open label controlled study. Active comparator: sucralfate+ mucaine. HNC patients with OM approaching grade III. Evaluated pain, pain on speaking (VAS 0-10) and pain on swallowing (self recorded swallowing scales) at baseline, 1, 3 and 24 hours.	10/20	General pain: no significant difference between Gelclair® and comparator. Trend to initial improvement in Gelclair® arm. No significant difference in pain on speaking. Observed mild inflammation and stinging to the oral cavity after Gelclair®, no serious anaphylactic event.
3) Del Mar Sabater et al.	Tratamiento de la mucositis oral con un protector de la mucosa.	Open label controlled study. Patients with OM from CT or BMT conditioning	18/97	Pain at baseline: 2.75 Pain increment day 4: 2.4 (control) > 1.5

		regimens. Evaluated pain at baseline, on days 4 and 9.		(Gelclair®) Pain increment day 9: 1.9 (control) > 0.5 (Gelclair®) OM grade: similar trend. Differences were not statistically significant. Three patients reported irritation and a burning sensation on application.
4) MacKenzie M.et al.	A randomized, open-label comparison with institutional standard magic mouthwash for the treatment of pain associated with radiation-chemotherapy induced mucositis	Multi-center, randomized, open label controlled study. Active comparator: ISMM. Patients with OM from CT and RT. Evaluated pain scores (6 point scale) and duration of pain reduction, number of treatments, treatment preferences and patient satisfaction as well as safety.	77/115	Numerically in favor of Gelclair®, but no statistically significant difference in: pain scores, pain relief rates, duration of treatments. No serious AEs reported, 1 Gelclair® patient retching.
Studies in pediatric patients				
1) Short L., Fung D.	Clinical effectiveness of Gelclair® in the treatment of oral mucositis: a patient based questionnaire	Open label, non-controlled, questionnaire-based pilot study. Onco/hematology patienst with OM. Evaluated pain, debility, ability to eat and drink.	13/31	Of 61% (19 pts) of children who had OM, 13 used GC, 76.9% (10 patients) found that GC resolved their mucositis symptoms.
2) Gibson F., Eden T.	Efficacy of Gelclair® in reducing the pain of oral mucositis in children and young people with cancer	Multi-center open label, non-controlled study. Pediatric patients (4-19 years old) with OM from CT, RT, BMT, SCT regimens. Evaluated pain (0-5 pain faces scale), ability to eat, drink and speak,	50/50	First results on 40 patints show pain reduction and good acceptability of taste. Results analysis is ongoing.

		acceptability of the product. Recorded use of analgesics and OM grade (OAG, WHO). All measurements were performed at baseline, 1, 3, 6, 12 and 24 hours.		
Other studies (other indications than Oral mucositis)				
1) Marzatico F.	Evaluation of tolerability of a mouthrinse and of its power of keeping the oral bacterial load under control. Assessments through a test of use and microbiological evaluations.	Open label study. Patients with aphtosis. Evaluated product agreeableness, state of gums and microbial load.	20/20	Very good agreableness, Excellent tollerability, improvement of status of oral mucosa and gums,decrease of bacterial load for at least 6 hours
2) Hita Iglesias et al.	Evaluacion del comportamento clinico de un gel concentrado de polivinilpirrolidona ehialuranato sodico, en pacientes sometidos a tratamento quirurgico con laser C02.	Open label, controlled study. Control group: ibuprofen. Investigational group: ibuprofen + Gelclair®. Patients with oral lesions, subjected to CO2 laser therapy. Evaluated spontaneous pain and pain on swallowing (VNS 1-10).	30/60	Spontaneous pain: -24 hours: 2.13 (control) > 0.83 (Gelclair® group) -7 days: 1.17 (control) > 0.67 (Gelclair® group) Pain on swallowing: -24 hours: 4.70 (control) > 3.73 (Gelclair® group) -7 days: 3.77 (control) > 2.10 (Gelclair® group). Effect 2 to >3 hours. Gelclair: acceptable taste and smell; No hypersensitivity to Gelclair® ingredients was observed.

HNC: Head and Neck; OM: Oral Mucositis; CT: Chemotherapy; RT: Radiotherapy, VNS: Visual Numerical Scale; VAS: Visual Analogue Scale; All evaluations went from 0 or 1 = no pain to 10 = worst pain; NG tubes: Naso-Gastric tubes; ISMM: Institutinoal Standard Magic Mouthwash; Baseline: intended as 'before use of Gelclair'; Day 1, 3, ..: intended as 'after use of Gelclair'; AEs: adverse events.

3.4. CONCLUSIONS FROM CLINICAL STUDIES

Overall, 459 patients with oral complications have been treated with Gelclair® in a total of 16 studies. This is a considerable number of patients for a medical device such as Gelclair®. Given the numerous methodological differences existing across studies, and the lack of randomized controlled trials, a definitive judgment is probably impossible. However, an overall analysis of the efficacy results shows a trend in favor of Gelclair® in providing relief from pain, improvement in functionality and some reduction in severity of oral mucositis/oral lesions.

The results of the four controlled studies ranged from lack of demonstration of superiority in pain relief versus a comparator, to differences favoring Gelclair® in either relief from pain, pain on speaking or pain on swallowing, even if some of these did not reach statistical significance. Despite this, positive trends in pain relieve in the Gelclair® groups were observed in all four studies.

It should be noted that two studies were done in pediatric patients and both provided positive results. In this particular patient population the general medical need for an oral mucositis treatment is even more important, since, the weight loss associated with the decreased food intake due to pain may represent a particularly important issue. Hence, there is a definite need to provide these patients with the ability to have an acceptable food intake and, last but not least, a better quality of life.

In conclusion, a number of studies suggest the ability of Gelclair® to form a protective film that covers the exposed nerve endings, to reduce oral mucositis pain, and to restore functionality. In these already completed studies, tolerability, agreeableness, ease of use, and patient acceptability have been assessed. In addition, many studies evaluated the use of analgesics and the grade of oral mucositis during the Gelclair® treatment. Significant reductions in oral mucositis pain were reported in two studies. Most studies showed a positive trend in favor of Gelclair® for the above endpoints.

Considering the high overall number of patients enrolled, a meta-analysis would have been interesting to provide, but was not possible, because of the lack of homogeneity in study design, and the small number of patients enrolled in each single study, as well as due to the paucity of controlled trials.

Hence, there is still an ongoing need for larger, properly powered, randomized, controlled studies in this area. In order to confirm the positive trends observed, at the moment a large randomized, controlled study of 120 patients (60 in each study arm) is being set-up at the Royal Adelaide Hospital (RAH) Cancer Centre. This study will compare standard mouthcare + Gelclair® against standard mouthcare alone in managing the symptoms of chemotherapy and/or radiotherapy induced oral mucositis.

4. SAFETY

4.1. EXECUTIVE SUMMARY

Gelclair, a viscous bio-adherent oral gel especially formulated to aid in the management of lesions of the oral mucosa, is a relatively inexpensive medical device which acts as a topical analgesic barrier within the oral cavity, increasing the patient's ability to eat and drink. The lack of pharmacological action and interactions, together with the pain relief since its first application and a long mechanical protection (up to 7 hours), makes Gelclair® a potentially valuable element in the list of therapeutic approaches to Oral Mucositis.

This part summarizes the safety data received by the companies of the Helsinn group, Helsinn Healthcare SA (HHC) and Helsinn Birex Pharmaceuticals Ltd (HBP) for the device product Gelclair® from worldwide sources up to May 2009.

Gelclair® is marketed in USA, Europe, Latin America, Middle East and North Africa, Asia, Australia and New Zealand. From 2002 to March 2009 approximately 11.3 million single doses of 15 ml have been sold worldwide. Overall only minor complaints were reported, including oral discomfort, local burning sensation or hypersensitivity-like symptoms, which were all non-serious and all subsided. The medical review and evaluation of all the reported events resulted in no qualitative or quantitative safety concern for Gelclair, suggesting no change in the favorable benefit-risk profile of this product.

4.2. TYPE OF ADVERSE REACTION

Clinical Trials

The number of patients receiving Gelclair® in clinical trials between 2001 and 2009 was 459. No incidents or near-incidents were reported during this time frame from clinical trials. Few non-serious adverse events like nausea, stinging, retching and inflammation were collected (see Clinical Trial section).

Post-marketing survey

Prior to 19 May 2009, a total of 40 non-serious events were reported in a total of 23 patients. No incidents or near-incidents were reported.

The cases were classified as: Gastrointestinal disorders (15 cases), Nervous system disorders (4 cases), Immune system disorders, Injury, poisoning and procedural complications, Respiratory, thoracic and mediastinal disorders and Skin and subcutaneous

tissue disorders (1 case each).

The most frequently reported event was oral "burning sensation". 5 cases of non-serious "burning sensation" were reported. Six other cases associated with burning sensation were reported as follows: 2 "oral discomfort", 2 "oral pain", 1 "stomatitis" and 1 "hypersensitivity".

One case of "hypersensitivity" was reported. Five other cases containing events associated with hypersensitivity were reported ("lip swelling", "swollen tongue", "rash", "skin burning sensation).

Discoloration of tooth, tongue, oral mucosa and sputum were also reported in 4 cases.

4.3. CONCLUSIONS ON SAFETY

Until March 2009, about 11.3 million Gelclair® single doses of 15 ml were sold worldwide. At the same time point, 23 non-serious cases were collected from post-marketing safety survey and only few non-serious adverse events from clinical trials. No incidents or near-incidents were reported. No safety concern regarding Gelclair® emerged from the medical review of the cases reported worldwide.

The benefit-risk balance of Gelclair® is confirmed as favorable. Nevertheless, a continuous monitoring and re-evaluation of the Gelclair® safety profile is ongoing, in order to identify any potential safety concern related to Gelclair® administration.

5. GENERAL CONCLUSIONS

The present report reviews and comments the preclinical, clinical and drug safety data on Gelclair®.

In relation to the topical use of the product for the proposed indication, and specifically for the length of the treatment, it appears that the risk-benefit balance for Gelclair® is positive and the results of the preclinical biocompatibility test support the use of the product.

A number of studies suggest the ability of Gelclair® to form a protective film that, like a liquid bandage, covers the exposed nerve endings reducing oral mucositis pain from the first application, and restoring functionality. Many studies also evaluated the use of analgesics and the grade of oral mucositis. In addition, Gelclair® was considered agreeable and was very well accepted by the patients. These positive data obtained in the studies encourage the outline of new well designed controlled studies including a large number of patients.

The benefit-risk balance of Gelclair® is confirmed as favorable. In fact until March 2009, about 11.3 million Gelclair® single doses of 15 ml were sold worldwide. No incidents or near-incidents were reported. No safety concern regarding Gelclair® emerged from the medical review of the cases reported worldwide.

Many cancer treatments can lead to oral complications such as oral mucositis, which has been shown to significantly increase the burden of care, by increasing the number and length of hospitalizations, or reducing the compliance with cancer treatment regimens (Sonis et al., 2001). Gelclair® may, by its barrier effect, protect the oral mucosa and avoid further damage due to mechanical stimulation. The positive results obtained in the above-described studies as well as the good safety profile, suggest that Gelclair® may be useful in patients with chemotherapy and/or ratiotherapy induced oral mucositis.

6. REFERENCES

Barber C. et al. Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. Supp Care Cancer, 15 (4): 427-440, 2007

Berndtson M. A preliminary study of Orassist/Gelclair® in the management of oral mucositis. Svensk Sjukhustandlakartidning (Swedish Hospital Dentistry) 3(26): 17-21, 2001

Bonassi L. et al. Treatment with Gelclair® in patients suffering grade III-IV oral mucositis: efficacy and impact on quality of life (QOL). Annals of Oncology 14(4): 58 -(Abstract E38), 2003

D'Andrea N. et al. Oral pharyngeal mucositis: nursing assessment on the efficacy of a new treatment. Annals of Oncology 14(supp. 4): 97 -(Abstract N2), 2003

De Cordi D. et al. Gelclair®: potentially an efficacious treatment for chemotherapy-induced mucositis. III Congress of Professional Oncology Nurses -Italian Anti Tumor League-Conegliano, Italy. (Abstract), 2001

Del Mar Sabater, Tratamiento de la mucositis oral con un protector de la mucosa.

Dentum, 6(1): 36-41, 2006.

Earl, L.K. et al., Skin irritation potential of surfactant mixtures : using relevant doses in in Vitro system ; ATLA; Vol. 24: 249, abstract #73, 1996

Fleck J. et al. Novel use of Gelclair® in cancer patients with anal fistulas and excoriation. Supportive Care in Cancer, 12(6): abstract 104, 2004

Flook C. et al. Gelclair® vs benzydamine in a randomised controlled study in patients with oral mucositis due to radical radiotherapy. Supportive Care in Cancer, 13 (6): 443-444 (Abstract 15-098), 2005

Gelclair® - Information leaflet

Gibson F., Eden T., Efficacy of Gelclair® in reducing the pain of oral mucositis in children and young people with cancer, Presented at Symposium on Oral care, SIOP Congress, Berlin, 2008

Helsinn, Data on file

Hita-Iglesias P. et al. Evaluacion del comportamento clinico de un gel concentrado de polivinilpirrolidona e hialuranato sodico, en pacientes sometidos a tratamento quirurgico con laser C02. III Congresso de la Sociedad Espanola de Cirurgia Bucal, Valencia, Spain, Octubre 2003. Medicina Oral (supplement): 79-80, 2003

Innocenti M. et al. Efficacy of Gelclair® in reducing pain in palliative care patients with oral lesions: preliminary findings from an open pilot study. J Pain Symptom Manage 24(5): 546-547, 2002

Keefe D. et al. Updated Clinical Practice Guidelines for the prevention and treatment of mucositis, Cancer 109 (5): 820-831, 2007

Köstler et al. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. CA Cancer J Clin 51: 290-315, 2001

Lehmann D.M. et al., Impact of assay selection and Study design on the outcome of cytotoxicity testing of medical devices. SOT 48th Annual meeting, Baltimore Maryland , March 15-19, Abstract #496, 2009

Liewer SE. et al. Gelclair® for the treatment of chemotherapy-induced stomatitis in transplant and hematology patients: an interim analysis. Blood (ASH Annual Meeting Abstracts) 104: Abstract 5317, 2004

Lindsay, G, et al., The clinical effectiveness of Gelclair® in the management of oral mucositis. Aust Nurs J. 16(9):30-33, 2009

Loftin S. et al., Cytotoxicity of latex condom extracts in L929 fibroblast and raw macrophages. SOT 48th Annual meeting, Baltimore Maryland , March 15-19, Abstract #509, 2009

MacKenzie M.et al. A randomized, open-label comparison with institutional standard magic mouthwash for the treatment of pain associated with radiation-chemotherapy induced mucositis - final study results, Supportive Care in Cancer 14(6): 641 (abstract 16-116), 2006

McLean M., An Audit of the Efficacy of Gelclair® for Mouth Pain in Patients Undergoing Radiotherapy or Chemotherapy., Presented at British Association of Head and Neck Oncology Nurses (BAHNON) National Study Day on Sharing Good Practice in Head and Neck Cancer Nursing, 12 June 2009, Leeds, UK.

Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology. Summary of Evidence-based Clinical Practice guidelines for Care of Patients with Oral and Gastrointestinal Mucositis (2005 Update). http://www.mascc.org/ktml2/images/uploads/Resource_centers/Guidelines_table_12_Oct_05.doc

Short L., Fung D. Clinical effectiveness of Gelclair® in the treatment of oral mucositis: a patient based questionnaire. Intl. J. Pediatric Dentistry 18 (suppl 1): 14 (abstract P25), 2008

Sonis et al. Oral mucositis and the clinical and economic outcomes of Hematopoietic stem-cell transplantation, J Clin Oncol 19: 2201-2205, 2001

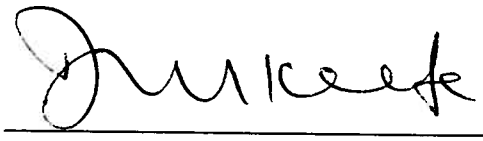
Sonis ST et al. Perspective on cancer therapy-induced mucosal injury. Cancer; 100 (9, supplement May 1): 1995 -2025, 2004a

Sonis ST et al. The Pathobiology of mucositis. Nat Rev Cancer 4 277-284, 2004b

Wilhelm K.P., Bottjer B., Siegers CP; Quantitative assessment of primary skin irritants in vitro in a cytotoxicity model: comparison with in vivo human irritation tests. Br. J. Dermatol.; 145 (5): 709-715, 2001.

7. EXPERT REPORT SIGNATURE PAGE

Expert Signature



15 July 2009

Prof Dr. Dorothy Keefe — Date

Clinical Director RAH Cancer Centre

Royal Adelaide Hospital

North Terrace

Adelaide SA 5000 Australia

Dorothy M K Keefe

Curriculum Vitae

2015

CAREER AND TRAINING HISTORY

NAME: Dorothy Mary Kate Keefe PSM
MBBS MD FRACP FRCP

CURRENT POSITIONS: Service Director, SA Cancer Service
SA Health
Medical Oncologist
Royal Adelaide Hospital
(Central Adelaide Local Health Network)
Professor of Cancer Medicine
University of Adelaide
Adjunct Professor, Sansom Institute for Health Research
University of South Australia
Clinical Ambassador
Transforming Health Project, SA Health

NATIONALITY: Australian/British

DATE OF BIRTH: 6th October 1961

PLACE OF BIRTH: Hornchurch, Essex, England

WORK ADDRESS: Level 4, Margaret Graham Building
Royal Adelaide Hospital
North Terrace
Adelaide SA 5000 Australia
Telephone: +618 8222 5577
Fax: +618 8222 5898
Email: dorothy.keefe@health.sa.gov.au

HOME ADDRESS: 34 Barnard St,
North Adelaide,
South Australia, 5006
Telephone: +618 8267 1224
Mobile phone: +61 417 861 157

SUMMARY: Dorothy Keefe has led the South Australian Cancer Clinical Network (CCN) and more recently the SA Cancer Service (SACS) for the past 6 years. She has an international reputation as a leader in Supportive Care in Cancer, and has recently completed her second term as President of MASCC (Multinational Association of Supportive Care in Cancer). Her research investigates mechanism, prevention and treatment of GI toxicity of cancer treatment and she has developed animal models for chemotherapy, radiotherapy and small molecule TKI- induced GI damage. She investigates links between toxicities and has been instrumental in the development of international, evidence-based guidelines in the area of mucositis. She also advices the Pharmaceutical Industry on the design and conduct of clinical trials in GI toxicity of Cancer treatment and participates in clinical trials of interventions, as well as in population studies of Burden of Illness of Regimen-related toxicity. This is true translation from bench to bedside, and population intervention.

She uses this to drive her policy and state-wide work: as Director SACS, Clinical Ambassador for Transforming Health SA and the SA representative for cancer on several national committees. Her role is all about improving health outcomes for the population of SA, in Cancer and all areas.

She is 2/3 way through a Master's in Organisational Psychology at Birkbeck, and her thesis will be on her work as Clinical Ambassador in the Transforming Health Project in SA.

EDUCATION:

1986	Bachelor of Medicine and Bachelor of Surgery (MBBS) University College and Middlesex Hospital Medical School University of London, London, UK
1996	Fellow of the Royal Australasian College of Physicians (FRACP) Royal Australasian College of Physicians
1999	Doctor of Medicine (by thesis) University of Adelaide The effect of cytotoxic chemotherapy of the mucosa of the small intestine

PROFESSIONAL APPOINTMENTS

2010 – 2011	Regional Clinical Director Adelaide Health Service Cancer Services
2009-2013	Chair, South Australian Cancer Clinical Network SA Health
2007 – 2010	Clinical Director RAH Cancer Centre
2007 - 2009	Deputy Chair South Australian Cancer Clinical Network
2007	Chair MBBS Curriculum Committee (Operations) Faculty of Health Sciences University of Adelaide
2006	Chair MBBS Curriculum Committee Faculty of Health Sciences University of Adelaide
2006-2007	Interim Clinical Director Royal Adelaide Hospital Cancer Centre Royal Adelaide Hospital
2005-2007	Associate Professor in Oncological Medicine Discipline of Medicine The University of Adelaide
2001-2011	Senior Consultant Medical Oncologist Department of Medical Oncology Royal Adelaide Hospital

2000-2004	Clinical Senior Lecturer Department of Medicine University of Adelaide
1999-2002	Consultant Medical Oncologist (Access appointment) Department of Gastroenterology The Queen Elizabeth Hospital (TQEH) Woodville Road Woodville South, SA 5011 Australia
1999	Associate Specialist Department of Haematology/Oncology The Queen Elizabeth Hospital
1996-2000	Consultant Medical Oncologist Department of Medical Oncology Royal Adelaide Hospital Cancer Centre
1996-1997	Anti-Cancer Foundation Research Associate Department of Gastroenterology The Queen Elizabeth Hospital
1996-1999	Clinical Lecturer Department of Medicine The University of Adelaide
1995	Gastroenterology Research Fellow The Queen Elizabeth Hospital
1992-1994	Medical Oncology/Haematology Registrar Department of Haematology/Oncology The Queen Elizabeth Hospital
1989-1992	Basic Physician Trainee The Queen Elizabeth Hospital
1988	Senior House Officer The Royal Cornwall Hospital (Treliske) Truro, Cornwall, UK
1987-1988	Medical Officer/Watch Officer STS Young Endeavour Britain Australia Bicentennial Schooner Trust
1986-1987	Medical and Surgical House Officer Royal Cornwall Hospital and West Cornwall Hospital Cornwall UK

HONOURS AND AWARDS

2014 MASCC Distinguished Service Award
For longstanding, devoted and exemplary service to the Multinational Association of Supportive Care in Cancer.

2013 Public Service Medal
Queen's Birthday Honours
For "Outstanding public service in the areas of Public Health, Medical Research and Oncology"

2009 Zonta International, Woman of Achievement Award

2009 Fellow of Royal College of Physicians (London)

1998 Clinical Research Prize
The Queen Elizabeth Hospital Research Day

1993 Clinical Research Prize
The Queen Elizabeth Hospital Research Day

1993 Best Physician Trainee
The Queen Elizabeth Hospital

HIGHER DEGREE SUPERVISION

PhD Students Current

01/03/2011 – 28/02/2015 Wan Noor I'zzah Wan Mohamad Zain
Thesis title: Mechanism of Lapatinib-Induced Gastrointestinal Toxicity in Breast Cancer Therapy.

30/12/2012-29/03/2015 Dr Bronwen Mayo
Thesis title: The effects of Elsiglutide on chemotherapy-induced mucositis.

Post-doctoral fellow Currently Mentoring

Dr Barbara Vanhoecke (Marie Curie International Outgoing Fellow)
Project Title: Development of a multidisciplinary platform for the screening of new preventive and therapeutic drugs against mucositis.

PhD Students Completed

2014 Dr Taryn Bessen
Thesis title: Optimising follow-up for women after primary treatment for early breast cancer.
Awarded Dean's commendation.

2012 Dr Siew Ping Lang
Thesis title: The Safe Administration of Rapid Rituximab Infusion: An Evidence-Based Approach.

2011 Dr Noor Al-Dasooqi
Thesis title: Chemotherapy-induced mucositis: the role of matrix metalloproteinases and the extracellular matrix.

2009 Dr Andrea Stringer
Thesis title: Chemotherapy-induced mucositis: the role of gastrointestinal microflora and mucins in the luminal environment.

2008 Dr Richard Logan
Thesis title: Alimentary Tract Mucositis: NF-kB and Pro-Inflammatory Cytokines in the Tissues and Serum Following Chemotherapy.

2006 Dr Joanne Bowen
Thesis title: Chemotherapy-induced intestinal mucositis: The role of apoptosis regulators.

2004 Dr Rachel Gibson
Thesis title: Chemotherapy-induced mucositis: mechanisms of damage, time-course of events and possible preventative strategies.

Doctorate of Clinical Dentistry Students (Coursework)

2013- Dr Gabrielle Allen – Paediatric Dentistry
Project title: Oral mucositis in a paediatric population.

2013- Narmin Nasr – Special Needs Dentistry
Project title: Management of oral toxicity of cancer treatment – a comparison between Australia and Oman.

Doctorate of Clinical Dentistry Students (HDR)

2010 – 2013 Dr Arlene Khaw – Periodontics
Project title: Influence of periodontitis on the experience of oral mucositis in cancer patients undergoing head and neck radiotherapy.

2009 – 2013 Dr Akram Qutob – Paediatric Dentistry
Project title: Assessment and Validation of a Diagnostic Scale, Oral Care Protocol and Prevention of Oral Mucositis in a Pediatric Population Receiving Cancer Therapy.

2009 - 2012 Dr Abdul Rahman Al-Azri – Oral Pathology
Project title: The role of matrix metalloproteinases in the pathology of mucositis.

TEACHING AND RELATED DUTIES
TEACHING AND TRAINING INNOVATIONS AND MATERIALS DEVELOPED

2011 - Chair, Board of Examiners Years 4 and 5, MBBS Curriculum, University of Adelaide

2006 Initiated and chaired the inaugural meeting of the Chairs of Australian Medical School Curriculum Committees.

2005 Developed and conducted the inaugural "Exam Setting Workshop" for the Year 5 final barrier exam for the new medical school curriculum.

2004-2005 Inaugural Co-ordinating Examiner for the Year 5 final barrier exam.

2003-2005 Chair of Common Program subcommittee of the MBBS Curriculum Committee. Developed common program for new medical school curriculum.

CURRICULUM DEVELOPMENT

2004-2005 Member Assessment Committee, MBBS Curriculum
2004-2005 Member of Year 6 Committee
2003-2005 Member of Year 4/5 Committee
2002-2005 Member MBBS Curriculum Committee during development of new curriculum
1999 Member of Oncology Concept Mapping Group for development of Curriculum 2000

CURRICULUM REVIEW

2006 Submission to the University of Adelaide review of the MBBS program on behalf of the curriculum committee.
2006 Member of working group developing submission to the Australian Medical Council regarding accreditation of the University of Adelaide MBBS program. Accreditation achieved until 2011.
2005 Royal Adelaide Hospital Physicians' Committee Curriculum Workshop. Developed and facilitated a review of medical student selection and assessment, as well as course structure, and generated a report for the University of Adelaide.

POST GRADUATE MEDICAL TEACHING

1999-2006 Intern Term Supervisor, Medical Oncology

1996-2007 Long-case FRACP trial examiner, Basic Physician Trainees, RAH

2006/2011 Re-accredited supervisor for Medical Oncology Trainees of the Royal Australasian College of Physicians

2006-2014 RACP State representative for assessment of overseas training in Medical Oncology.

COMMUNICATION SKILLS TRAINING

2006 NBCC Train the Trainers workshop
Training future facilitators for communications workshops in cancer

2006 Medical Oncology Group of Australia, Trainee Communications Workshop
Training Medical Oncology and Palliative Care Advanced Trainees in communication skills, and mentoring newly trained facilitators

2005 American Society for Clinical Oncology/Clinical Oncological Society of Australia (ASCO/COSA) communication skills workshop: Facilitator

ASSESSMENT

2008- Chair, MBBS, Year 4/5 Board of Examiners

2007 Member of Academic Progress Review Committee
Faculty of Health Sciences

2002-2006 OSCE Examiner for Medical School

2000-2010 Local Examiner for Royal Australasian College of Physicians

RESEARCH, SCHOLARSHIP AND CREATIVE ACTIVITY
RESEARCH COLLABORATIONS

International Academic

2004 - Triad Burden of Illness in Mucositis
Professor Stephen Sonis
Brigham and Womens' Hospital, Boston, MA, USA
Professor Linda Elting
MD Anderson Cancer Centre, Houston, TX, USA

2004 - 2011 The use of probiotics to prevent mucosal injury in the gut
Professor Claudio Simone
Rome, Italy

2001 - Guidelines for the management of mucositis
The Mucositis Study Group
The Multinational Association for Supportive Care in Cancer (MASCC)

RESEARCH CONSULTANCIES

International Pharmaceutical Industry

Helsinn Member of Advisory Board and research collaboration in field of oral and gastrointestinal mucositis

Merck Member of Advisory Board and research collaboration in Emesis

Consultant in gastrointestinal mucositis for multiple companies:

Pfizer, GSK, Inform Genomics, Entera Health, Procertus, Lactopharma

INVITED PRESENTATIONS
International

2014 Geriatric Oncology Workshop, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Canada
Invited Speaker, Reviewer and Panel Member

2014 M.Health Conference, University of Bocconi, Milan, Italy
Session Chair

2014 MASCC Annual Scientific Symposium, Miami, Florida, USA
Chair Presidential Plenary

2013 MASCC Annual Scientific Symposium, Berlin, Germany
Results of the PrACTICE Study
Chair and Speaker, Opening Plenary Session

2012 European Society for Medical Oncology, Annual Meeting, Vienna, Austria
Member of Program Committee, Invited Speaker, Session Chair
GI mucositis: Evolutionary Science

2012 American Society of Clinical Oncology, Scientific Meeting, Chicago, U.S.A.
Education Session: New Frontiers in Mucositis

2011 Clinical Oncology Society of Australia/Multinational Association of Supportive Care in Cancer, Workshop, Perth, Australia
Meeting President & Chair

2011 Japanese Society of Clinical Oncology, Nagoya, Aichi, Japan
Meeting Speaker
New developments in Supportive Care

2011 Korean Association of Clinical Oncology, Annual Meeting, Seoul, Korea
Updated perspective on Anti-emetics

2011 Asian Oncology Summit, Hong Kong
The management of mucositis

2011 MASCC/ISOO Annual Meeting, Athens, Greece
Mucosal injury from molecularly targeted agents; how does it fit?
Session Chair Plenary

2011 Pfizer Global Oncology Therapy Management Forum
Toxicity of targeted anti-cancer therapy

2010 European Society for Medical Oncology, Annual Meeting, Milan, Italy
Member of Program Committee
Session chair (x3)
Invited speaker: Gastrointestinal toxicity from targeted anti-cancer agents
Invited speaker: Summary of Supportive Care Track

2010 University of Iowa, Haematology/Oncology Grand Round
The pathobiology and management of mucositis

2009 World Lung Cancer Congress, San Francisco, USA
Mucositis and Lung Cancer
Invited speaker

2009 MASCC/ISOO Annual Scientific Meeting, Rome, Italy
GI Bleeding from Targeted Therapy
Co-chair and invited speaker

2009 MASCC/ISOO Annual Scientific Meeting, Rome, Italy
The Burden of Illness in Mucositis
Co-chair and invited speaker

2009 Oral Toxicities of Emerging Cancer Therapies, Bethesda, USA
The successes and challenges of targeted anticancer treatments
Invited speaker and session moderator

2007 MASCC/ISOO Annual Scientific Meeting, St Gallen, Switzerland,
Symposium: Toxicities Targeting Epithelium
Co-chair and invited speaker

2007 First World Congress of the International Academy of Oral Oncology, Amsterdam, The Netherlands
Symposium: MASCC/ISOO
Guidelines for the management of mucositis

2006 European Society for Parenteral and Enteral Nutrition, Istanbul, TURKEY
Satellite Education Symposium (sponsor: Nestle)
The Pathobiology of Mucositis

2006 Tandem Transplant Meeting, Honolulu, USA
Satellite Education Symposium (sponsor: Amgen)
Update of MASCC Mucositis Guidelines

2006 MASCC/ISOO Annual Scientific Meeting, Toronto, CANADA
Plenary Symposium
Mucosal injury from targeted therapies

2006 International Society of Oncology Pharmacy Practitioners Annual Meeting, Kuala Lumpur, MALAYSIA
Invited Lectures: Mucositis Guidelines
Pathobiology of mucositis

2006 Malaysian Regional Geriatrics meeting: South Australian Perspective. Kuala Lumpur
Invited Lecture: Cancer in the Elderly

2006 UICC World Cancer Congress Bi-annual meeting, Washington, USA
Symposium on supportive care
Producing guidelines for mucositis

2005 World Gastrointestinal Cancer Conference, Barcelona, SPAIN
Satellite Educational Symposium (Sponsor: Amgen)
The management of mucositis

2005 MASCC/ISOO Annual Scientific Meeting, Geneva, SWITZERLAND
Invited speaker and session chair
The 2005 Mucositis Guidelines Update

2005 American Society of Clinical Oncology (ASCO) Annual Scientific Meeting, Orlando, USA
Meet the Professor Session
Gastrointestinal toxicity following chemotherapy

2004 13th International Conference on Cancer Nursing, Sydney AUSTRALIA
Joint session with MASCC
Innovations in supportive care: mucositis

2004 MASCC/ISOO Annual Scientific Meeting, Miami Beach, USA
Keynote speaker
Gastrointestinal Toxicity of Cancer Treatment

2004 ISOO Continuing Education Course,
Chairman and invited speaker
Mucositis-inducing treatment: A Medical Oncologist's Perspective

2004 MASCC Plenary Session
Chairman and invited speaker
Putting the guidelines into practice

2004 American Society of Clinical Oncology, Annual Scientific Meeting, New Orleans, USA
Education Session: Treatment-induced gastrointestinal toxicity in patients with cancer

2003 9th International Conference on Oral Cancer, Melbourne
Invited lecture: What's new in the management of Mucositis?

2003 MASCC/ISOO Annual Scientific Meeting, Berlin, Germany
Invited lecture: Gastrointestinal Mucositis

2002 MASCC/ISOO Annual Scientific Meeting, Boston, USA
Invited lecture: Improving the management of Mucositis
Symposium: Cytokine support in cancer therapy
Evolving Strategies for improved patient care
Plenary Lecture: Guidelines for the management of Mucositis

2002 MASCC/ISOO Mucositis Study Group Consensus Conference, Houston, USA
Primary reviewer for gastrointestinal mucositis

VISITING PROFESSOR

2012 Visiting Professor, School of Nursing, University of Maryland, Baltimore, USA

2004 Sonis Visiting Professor
Division of Oral Medicine, Oral and Maxillofacial Surgery and Dentistry
Brigham and Womens' Hospital, Boston, USA
Lecture: Mucositis from top to bottom of the Alimentary Canal

2004 Visiting Expert
Department of Oral Medicine, Carolinas Medical Centre, Charlotte, USA
Lecture: Pathobiology and treatment of gastrointestinal Mucositis

Invited National Presentations

2013 Clinical Oncological Society of Australia
Annual Conference, Adelaide, South Australia
Opening Plenary Chair, Invited Speaker, Panelist and Debater

2012 MOGA Advanced Trainee Basic Science of Oncology Weekend
The Science of Toxicity

2011 Tasmanian Haematology Immunology And Neoplasia Group (THING)
Lecture: Regimen-related toxicity in the era of targeted anti-cancer therapy.

2011 Royal Australian College of Surgeons, Annual Scientific Meeting, Adelaide, SA
Mucosal Toxicity in Head and Neck Cancer

2010 Clinical Oncological Society of Australia, Annual Conference, Melbourne, Vic
COSA/MASCC workshop on Pelvic Radiation Disease: Convenor
Supportive Care Workshop speaker

2008 PRIME (SA GP Education Weekend)
The changing face of medical oncology

2007 PRISM (SA Physician Education Weekend)
The changing face of medical oncology

2006 South Australian Palliative Care Conference
The modern management of mucositis

2005 Tasmanian Haematology, Immunology and Oncology Group (THING)
Lectures: Pathobiology of mucositis
Management of mucositis

2005 Royal Hobart Hospital Grand Round
Modern Mucositis Management

2004 Clinical Oncological Society of Australia Annual Scientific Meeting
Plenary lecture: Developments in management of gastrointestinal mucositis in oncology

2004 HONE (Haematology/Oncology Nurse Education meeting)
Cancer in the Elderly

2004 Amgen Clinical Pharmacy Weekend
Mucositis

2004 BMT Network NSW, Annual Scientific Forum
Modern Mucositis Pathobiology and Management

2003 Thoracic Society of Australia & New Zealand Annual Scientific Meeting
Chemotherapy for Mesothelioma

2002 Medical Oncology Group of Australia Annual Scientific Meeting
Breakfast session: Guidelines for management of mucositis

2002 Clinical Oncological Society of Australia
Meet the Professor Breakfast Session: Management of mucosal toxicity

1999 Medical Oncology Group of Australia Annual Scientific Meeting
Mucositis: can we beat it?

1999 Clinical Oncological Society of Australia
Small intestinal and oral mucositis: an overview

1988 Brian Prout Memorial Lecture, Cornwall Postgraduate Centre
Tall Ships Medicine

CONTRIBUTIONS TO THE WIDER DISCIPLINE

2012- Joanna Briggs Institute
Chair, Cancer Node

2011- National Cancer Expert Review Group
Member

2009- Cancer Institute NSW
Chair Data Manager Grant Review Committee

2007 – 2010 Cancer Australia National Strategic Forum
Member

2006-10 Reviewer for Australian Medicine's Handbook
Chemotherapy and Supportive Care drugs

MEMBERSHIP OF COMMITTEES

2013- SAHMRI
Member, SA Comprehensive Cancer Consortium Steering Committee

2012- SAHMRI
Member, Beat Cancer Project Research Leadership Group

2012- SAHMRI
Member, Clinical Research and Drug and Device Development Pillar Committee

2010- SA Cancer Research Collaborative
Scientific Advisory Group member

2008 External grant reviewer, NHMRC

2003-2006 & 2009-11 Chair, The Cancer Council South Australia, Cancer Research Advisory Committee

2003-2006 National Grants Steering Committee, The Cancer Council Australia

1999-2001 Member, The Cancer Council South Australia, Cancer Research Advisory Committee

EDITORIAL BOARD/EDITOR

2008-2012 Associate Editor Journal of Supportive Care in Cancer

2007- 2010 Oral Oncology

2007-2009 Guest Editor for March 2008 edition of Cancer Forum on Geriatric Oncology

2007- Asia-Pacific Journal of Clinical Oncology

2007-2011 Current Opinions in Supportive and Palliative Care

2006-2011 Editor for the gastrointestinal section of the "Current Opinions in Palliative and Supportive Care".

2005-2010 Supportive Cancer Therapy

2005-2010 Journal of Cancer Pain and Symptom Palliation

AD HOC REFEREEING OF PAPERS SUBMITTED TO JOURNALS

Nature Cancer Reviews
Lancet Infectious Diseases
Lancet Oncology
Annals of Oncology
Cancer Biology and Therapy
International Journal of Radiation Biology
Supportive Care in Cancer

EXTERNAL MEMBERSHIP OF BOARDS, COMMITTEES

2010-2012 & 2013-2014 President of MASCC (The Multinational Association for Supportive Care in Cancer)

2009-2013 Member, South Australian Clinical Senate

2008-2010 President-Elect and Vice-President, MASCC (The Multinational Association of Supportive Care in Cancer)

2007-2010 Chair, Optimising Cancer Care Subcommittee, Cancer Clinical Network

2006-2008 National Breast Cancer Centre, Communication Steering Committee
2006-2008 Cancer Council Helpline Advisory Panel, Cancer Council South Australia
2006-2010 Chair, Governance Subcommittee, MASCC

2005-2006 Member Workforce Subcommittee, Statewide Cancer Control Plan, SA (An initiative of the Cancer Council SA and the State Government)

2004-2008 Member Board of Directors, MASCC

2004-2008 Chair, Mucositis Study Group, MASCC

2003-2011 Member Board of Directors, The Cancer Council South Australia

2003-2006 Member, Peter Nelson Leukemia Research Fellowship Committee

2002-2006 Member, Education Subcommittee, Medical Oncology Group of Australia

RESEARCH FUNDING

2014 Role of Inflammatory Signalling on Burden of Illness in Mucositis. Keefe D, Gibson R, Bowen J & Coller J. TRIAD $12,000

2014 Prevention of dacomitinib induced diarrhoea by targeting chloride secretion. Bowen J & Keefe D. Pfizer $80,000

2014 South Australian Health and Medical Research Institute – SAHMRI. Innovative Cancer Imaging and Therapeutics Facility. C Mulligan, T Hughes, A Zannettino, S Gronthos, D White, D Keefe, T Mondo, D Roder, W Tilley, T Price and P MacKenzie. ACRF $1.8M

2014 Cancer Data and Aboriginal Disparities – CANDAD. Development and testing of an integrated cancer monitoring and surveillance system for Aboriginal People in South Australia. A Brown, D, Rodda, M Cargo, D Keefe, M Eckert, G Farshid. NHMRC $1,034,270

2013 Studies on the effect of Enteragam on gastrointestinal mucositis. D Keefe & E Bateman. Entera Health $100,000

2013 Protecting tissues from chemotherapy. Callen D, Keefe D, Neilsen P, Smid S. NHMRC $565,847

2012 Study into effect of Elsiglutide on gastrointestinal mucositis. Keefe, Bowen, Stringer and Bateman. Helsinn Healthcare. $130,000

2012 Identification Of Biomarkers Of Response And Toxicity To Chemoradiotherapy For Oesophageal Tumours. D Watson, D Keefe, D Hussey and J Bowen. NHMRC $481,175

2012 A Nanostructured Drug Delivery Approach for Improved Colorectal Cancer Therapy. C Prestidge, B Boyd & D Keefe. NHMRC $541,010

2012 Cyclotherapy: a promising new approach to prevent the side effects of chemotherapy. P M Neilsen & D M K Keefe. RAH Research Committee $35,000

2010 Improving colorectal cancer therapy using a novel nanotechnology-based delivery system. C Prestidge, B Boyd, MP Brown, D Keefe, A Davey, Cancer Council SA, $110,000

2010 Oral Mucositis Risk and Multicyle Chemotherapy: do multiple cycles multiply risk. L Elting, S Sonis and D Keefe. NIDCR $150,000

2010 CCRE in Oral Health, University of Adelaide, M Bartold, J Spencer, G Townsend, K Roberts-Thompson & D keefe, NHMRC, $2.5m

2009 Studies of Nutritional Supplements as prevention/treatment for gastrointestinal toxicity of chemotherapy. Nestec. $250,000

2008 Investigation of probiotic VSL #3 in DA rat model of mucosal injury. VSL Pharma $100,000

2009 Faecal microflora and circulating pro-inflammatory cytokines: key elements to chemotherapy-induced diarrhoea. R Gibson, J Bowen, A Stringer, R Logan and D Keefe. Cancer Australia $75, 000

2008 Characterisation of Tyrosine Kinase inhibitor-induced gastrointestinal toxicity D Keefe & F Boyle. GSK $620, 000

2008 Distiller image analysis software and server. Tilley, Owens, Norman, Findlay, Keefe & al. NHMRC equipment grant. $52,000

2007 Automated image analysis system for the high throughput immuno-histochemical analysis of clinical and experimental samples. Tilley, Owens, Norman, Findlay, Keefe & al. NHMRC equipment grant. $100,695.83

2007 Triad Mucositis Burden of Illness Study: Chronic mucosal injury study, Elting, Keefe & Sonis. Amgen Inc. USD $900,000

2006 Triad Mucositis Burden of Illness Study: Acute mucosal injury cohort expansion, - Elting, Keefe & Sonis. Amgen Inc. USD $609,000

2006 Chemotherapy-induced diarrhoea: Characterisation of mechanism, D Keefe. The Cancer Council South Australia. $70,500

2006 Oral mucositis: clinical presentation, histological features and pro-inflammatory cytokine expression. R Logan, R Gibson, D Keefe & S Sonis. Australian Dental Research Foundation Inc. (ADRF) $3000

2005 Assessment of an oral supplement in adult cancer patients with mucositis. R Butler, P Bardy, T Price, J Davidson, D Keefe & J Webster Biotechnology Innovation Fund (BIF) Grant $490,000

2005 Triad Mucositis Burden of Illness Study. Elting, Keefe & Sonis. Amgen Inc. USD $3,600,000

2005 Triad Mucositis Burden of Illness Study: project scoping study. Elting, Keefe & Sonis. Amgen Inc. US$ 100,000

2005 Investigation of Probiotic effect on mucositis in the DA rat.D Keefe: Joint venture with Professor Claudio de Simone VSL $30,000

2004 Studies to investigate CG53135 for mucositis treatment in the DA rat mammary adenocarcinoma (DAMA) model D Keefe: Curagen. USD$300, 000

2004 Oral Mucositis in humans D Keefe RAH Research Fund - $15,000

2003 Studies of KGF/CPT-11 in the DAMA mucositis model D Keefe RAHCC Internal funding $60,000

2001 Keratinocyte growth factor research in mucositis D Keefe mgen Inc. $50,000

2001 Further studies in mucositis in rats and humans undergoing cytotoxic chemotherapy f or cancer. D Keefe. Anti-cancer Foundation $54,425

2000 Development of the DAMA model. D Keefe. RAHCC Internal Funding - $60,000

1999 Mucositis in the rat with breast cancer. D Keefe. The Queen Elizabeth Hospital (TQEH) Research Foundation $10,000

1999 Investigation and prevention of intestinal mucositis after chemotherapy in the rat with breast cancer. D Keefe. Anti Cancer Foundation $52,000

1997 Mucositis research. D Keefe& ACummins.B3 funding University of Adelaide $5,000

1997 Mucositis Research . D Keefe & A Cummins. TQEH Research Foundation $5,400

1995 The effect of cancer and chemotherapy on nutrition, and on inducing malabsorption by an immunological mediated enteropathy . D Keefe & A Cummins. Anti-Cancer Foundation $52,000

MEMBERSHIP OF SCIENTIFIC SOCIETIES

Multinational Association for Supportive Care in Cancer (MASCC)
International Society for Oral Oncology (ISOO)
Medical Oncology Group of Australia (MOGA)
Clinical Oncological Society of Australia (COSA)
American Society of Clinical Oncology (ASCO)
S.A. Breast Cancer Study Group
European Society for Medical Oncology (ESMO)

SCIENTIFIC MEETING ORGANISING COMMITTEES

International

2014 ASCO Inaugural Palliative Oncology Meeting, Boston, USA
2014 ESMO Annual Scientific Meeting, Madrid, Spain
2014 MASCC Annual Scientific Meeting, Miami, USA
2013 MASCC Annual Scientific Meeting, Berlin, Germany
2012 ESMO Annual Scientific Meeting, Vienna, Austria
2011 MASCC Annual Scientific Meeting, Athens, Greece
2010 ESMO Annual Scientific Meeting, Milan, Italy
2010 MASCC Annual Scientific Meeting, Vancouver, Canada
2009 MASCC Annual Scientific Meeting, Rome, Italy
2006 MASCC/ISOO Annual Scientific Meeting, Toronto, Canada
2005 MASCC/ISOO Annual Scientific Meeting, Geneva, Switzerland
2004 MASCC/ISOO Annual Scientific Meeting, Miami, Florida

National

1998 Medical Oncology Group of Australia, Adelaide, South Australia

PERSONAL AND PROFESSIONAL DEVELOPMENT

2012-14	Enrolled in MSc Medical Leadership, Birkbeck College, London, UK
2010-11	Hardy Group – Executive Learning Set
2006	University of Adelaide Advanced Leadership Program
2005	University of Adelaide Leadership Development Course
2004	Media Training
2003	Management Training: Oz Train
2002	Trained communication training facilitator, Pam MacLean Communication Centre, Sydney

PUBLICATIONS

Books/Monographs/Symposia/Book Chapters

1. Pathobiology of Cancer Regimen-related toxicity. Editors ST Sonis and DM Keefe. Springer (2013) : http://dx.doi.org/10.1007/978-1-4614-5438-0

Sole Author Works

2. The effect of cytotoxic chemotherapy on the mucosa of the small intestine. Keefe DMK (1999). Thesis for degree of Doctor of Medicine, University of Adelaide.
3. Practice of Medicine on a sailing ship from England to Australia. Keefe DMK., (1989). In: Travel Medicine. Steffen R., Lobel H.O., Haworth J. & Bradley D.J. (Eds.) Springer-Verlag, Berlin, Germany

Joint Author Works

4. Mucositis. Al-dasooqi N, Keefe DMK and Sonis ST, in Pathobiology of Cancer Regimen-related toxicity. Editors ST Sonis and DM Keefe. Springer (2012) in press
5. Biology of Treatment-induced mucositis. Keefe, DMK, Gibson RJ, Bowen JM and Bateman E. in Principles and Practice of Palliative Care and Supportive Oncology. 4th Edition. Berger AM, Shuster, JL, Von Roenn JH (Eds). 2012 (in press)
6. Mucositis (Oral and Gastrointestinal) Chapter 25 in The MASCC Textbook of Cancer Supportive Care and Survivorship Lalla, R.V. and Keefe DMK. I.N. Olver (ed) The MASCC Textbook of Cancer Supportive Care and Survivorship, DOI 10.1007/978-1-4419-1 25, Springer New York Dordrecht Heidelberg London
7. Gastrointestinal Complications of Hematopoietic Stem Cell Transplantation. Sonis ST, Treister NS, Lees J and Keefe DMK. (2009) In: Wingard JR, Gastineau D, Leather HL, Snyder EL, Szczepiorkowski ZM, eds. Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians. Bethesda, MD, USA: AABB
8. Oral complications of Cancer and its treatment. Keefe DMK & Logan RM. (2009) in: Palliative Medicine, D Walsh et al. (Eds) Elsevier.
9. The use of Project Teams in preclinical development, Chapter in: Preclinical Development Handbook. Keefe, DMK, Bowen JM & Gibson RJ. Ed: S. C. Gad. Wiley.
10. The use of animal models in preclinical development, Chapter in: Preclincal Development Handbook. Gibson RJ, Bowen JM & Keefe, DMK. Ed: S. C. Gad. Wiley.

Invited Editorial

11. Gastrointestinal Toxicity of Targeted Anti-cancer Therapy. Keefe DMK, Bateman E, invited editorial for Treatment Strategies – Oncology 224-227.
12. The potential successes and challenges of targeted anti-cancer therapies. Keefe DMK and Stringer AM. *Current Opinion in Supportive and Palliative Care*. 2010 Mar 4(1):16-8.

13. Tyrosine kinase inhibitors and gut toxicity: a new era in supportive care. Keefe DMK & Lowell A. Current Opinion in Supportive&Pallitive Care: Editorial Review Vol 2 (1) March 2008; 19-21.
14. Geriatric Oncology: A medical subspecialty whose time has come. Keefe DMK & Prowse RJ. Invited Editorial.Cancer Forum (2008). 32(1): 3-5.
15. Mucositis Guidelines: what have they achieved, and where to from here? Keefe DMK. Invited Editorial. Support Care Cancer 2006 Jun;14(6)489-491 (IF 1.59)

Refereed Journal Articles

Sole Author Articles

16. Intestinal Mucositis: mechanisms and management. Keefe DMK, Curr Opin Oncol. 2007 Jul;19(4):323-7
17. Supportive care silos: time to forge cross-links, using mucositis as an example. Keefe DMK. Current Opin Support Palliat Care. 2007 Apr;1(1):40-2. doi: 10.1097/SPC.0b013e32814e6bd3.
18. Mucositis Management in patients with cancer. Keefe DMK (2006). Supportive Cancer Therapy. 2006 Apr 1;3(3):154-7. doi 10.3816/SCT.2006.n.013.
19. Gastrointestinal mucositis: a new biological model. Keefe DMK. Support. Care Cancer. 2004 Jan;(12):6-9.
20. Supportive Care in Colon Cancer (Commentary). Keefe DMK. (2006) Supportive Cancer Therapy 3(3): 171-172.

Joint Author Articles

21. Risk and outcomes of chemotherapy induced diarrhea (CID) among patients with colorectal cancer receiving multi-cycle chemotherapy. Keefe DMK, Elting LS, Nguyen HT, Grunberg SM, Aprile G, Bonaventura A, Selva-Nayagam SS, Barsevick A, Koczwara B, Sonis ST. Cancer Chemotherapy and Phamacology. doi: 10.1007/s00280-014-2526-5.
22. Impact of CINV in earlier cycles on CINV and chemotherapy regimen modification in subsequent cycles in Asia Pacific clinical practice. Kim H-K, Hsieh RK, Chan A, Yu S, Han B, Gao Y, Banos A, Ying X, Burke TA, Keefe DMK. Supportive Care in Cancer. doi: 10.1007/s00520-014-2376-z.
23. Antiemetic therapy in Asia Pacific countries for patients receiving moderately and highly emetogenic chemotherapy – a descriptive analysis of practice patterns, antiemetic quality of care, and use of antiemetic guidelines. Yu S, Burke TA, Alexandre C, Kim H-K, Hsieh RK, Hu X, Liang, J-T, Banos A, Spiteri C, Keefe DMK. Supportive Care in Cancer. doi: 10.1007/s00520-014-2372-3.
24. Baseline patient characteristics, incidence of CINV, and physician perception of CINV incidence following moderately and highly emetogenic chemotherapy in Asia Pacific countries. Hsieh RK, Chan A, Kim H-K, Yu S, Kim JG, Lee M-A, Dalen J, Jung H, Liu YP, Burke TA, Keefe DMK. Supportive Care in Cancer. doi: 10.1007/s00520-014-2373-2.
25. Rationale and design of the Pan Australasian chemotherapy-induced emesis burden of illness study. Keefe DMK, Chan A, Kim H-K, Hsieh RK, Yu S, Wang Y, Nicholls RJ, Burke TA. Supportive Care in Cancer. doi: 10.1007/s00520-014-2374-1.
26. Incidence and predictors of anticipatory nausea and vomiting in Asia Pacific clinical practice – a longitudinal analysis. Chan A, Kim H-K, Hsieh RK, Yu S, Lopes Jr. GdeL, Su W-C, Banos A, Bhatia S, Burke TA, Keefe DMK. Supportive Care in Cancer. doi: 10.1007/s00520-014-2375-0.
27. Risk and outcomes of chemotherapy-induced diarrhea (CID) among patients with colorectal cancer receiving multi-cycle chemotherapy. Keefe DMK, Elting LS, Nguyen HT, Grunberg SM, Aprile G, Bonaventura A, Selva-Nayagam S, Barsevick A, Koczwara B, Sonis ST. Cancer Chemotherapy and Pharmacology. doi:10.1007/s00280-014-2526-5.
28. Involvement of matrix metalloproteinases (MMP-3 and -9) in the pathogenesis of irinotecan-induced oral mucositis. Al-Azri AR, Gibson RJ, Bowen JM, Stringer AM, Keefe DMK, Logan RM. (2014) Journal of Oral Pathology and Medicine. In press.

29. Gastrointestinal Complications of Hematopoietic Stem Cell Transplantation. Lees J, Keefe, DMK. (2014) Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians, 2nd edition. AABB. (In press)
30. The Changing Paradigm for Supportive Care in Cancer Patients. Chan A, Pharm D, Lees J, Keefe DMK. (2014) Journal of Supportive Care in Cancer: Volume 22, Issue 6, Page 1441-1445. DOI 10.1007/s00520-014-2229-9.
31. Influence of periodontitis on the experience of oral mucositis in cancer patients undergoing head and neck radiotherapy. A pilot study. Khaw A, Linerali S, Logan R, Keefe DMK, Bartold D. (2014) Journal of Supportive Care in Cancer. In press
32. MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy. Lalla RV, Bowen JM, Barasch A, Elting L, Epstein J, Keefe DMK, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber J, Sonis S. (2014) Cancer
33. Microbiota and their role in the pathogenesis of oral mucositis. Vanhoecke BW, Deryck T, Stringer A, Vandewiele T, Keefe DMK. (2014) Journal of Oral Diseases.
34. What sort of follow-up services would Australian breast cancer survivors prefer if we could no longer offer long-term specialist based care? - a Discrete Choice Experiment. Bessen T, Chen G, Street J, Eliott J, Karnon J, Keefe DMK, & Ratcliffe J. BJC (2013) British Journal of Cancer , (14 January 2014) doi:10.1038/bjc.2013.800
35. Biomarkers of chemotherapy-induced diarrhea: A clinical study of intestinal microbiome alterations; intestinal inflammation and circulating matrix metalloproteinases. Stringer AM, Al-Dasooqi N, Bowen JM, Tan TH, Radazum M, Logan RM, Mayo B, Keefe DMK and Gibson RJ (2013) Supportive Care in Cancer, 2013 Jul;21(7): 1843-1852. DOI: 10.1007/s00520-013-1741-7.
36. Investigation of Effect of Nutritional Drink on Chemotherapy-Induced Mucosal Injury and Tumor Growth in an Established Animal Model. Bateman E, Bowen J, Stringer A, Mayo B, Plews E, Wignall A, Greenberg N, Schiffrin E, Keefe DMK. Nutrients. 2013 Sep 30;5(10):3948-3963
37. Predictors of acute adverse events from rapid rituximab infusion. DSP Lang, Keefe DMK, T Schultz and A Pearson. Journal of supportive Care in Cancer, 2013 Aug;21(8):2315-20. DOI 10.1007/s00520-013-1788-5
38. Systematic review of agents for the management of gastrointestinal mucositis in cancer patient. Gibson R, Keefe DMK, Lalla R; Bateman E, Blijlevens N; Fijlstra M; King E; Stringer A, Van der Velden W; Yazbeck R; Elad S; Bowen J. Journal of Supportive Care in Cancer. 2013 Jan;21(1):313-26. DOI 10.1007/s00520-012-1644-z.
39. Implementation of a hospital oral care protocol and recording of oral mucositis in children receiving cancer treatment: a retrospective and a prospective study. Qutob AF, J Allen GJ, Gue S, Revesz T, Logan R, PhD; Keefe DMK. Journal of Supportive Care in Cancer (2012) In press.
40. Matrix metalloproteinases: do they play a role in mucosal pathology of the oral cavity? Al-Azri A, Gibson R, Keefe DMK and Logan R. Oral Oncology (2012) in press.
41. Development of a rat model of oral small molecule receptor tyrosine kinase inhibitor-induced diarrhoea. Bowen J, Bateman E, Plews E, Mayo B, Boyle F, Finnie J, Stringer A & Keefe DMK. Cancer Biology and Therapy. 2012 Nov;13(13):1269-75. DOI: 10.4161/cbt.21783.
42. Prevention of oral mucositis in children receiving cancer therapy: a systematic review and evidence-based analysis. Qutob A, Gue S, Revesz T, Logan R & Keefe DMK. Oral Oncology (2012) in press.
43. The prevention of oral mucositis in patients with blood cancers: current concepts and emerging landscapes.Niscola P, Tendas A, Cupelli L, Catalano G, Scaramucci L, Giovannini M, Trinchieri V, Sharma A, Efficace F, Cartoni C, Piccioni D, Perrotti A, Dentamaro T, de Fabritiis P, Keefe DMK. Cardiovasc Hematol Agents Med Chem . 2012 Dec; 10(4):362-75. Review.
44. New Frontiers in Mucositis. Peterson, D.E., Keefe DMK & Sonis, S.T. In: Govindan R, ed. 2012 ASCO Educational Book. Alexandria,VA: ASCO; 2012; 545-551.
45. Potential Successes and Challenges of Targeted Cancer Therapies. Keefe DMK., & Bateman, E.H. Journal of the National Cancer Institute, article in press, (2011).

46. Tumour control versus adverse events with targeted anticancer therapies. Keefe DMK. & Bateman E.H. Nature Reviews – Clinical Oncology. Dec 20(9):98-109. doi: 10.1038/nrclinonc.2011.192. Review.
47. Oral Mucositis due to Cancer therapy. Lalla, R., Brennan M., Gordon S., Sonis S., Keefe DMK. Journal of the National Cancer Institute, article in press (2011).
48. Supportive Care in Cancer: Developments in Treatment and Symptom Management. Keefe DMK. & Bateman E.H. Journal of JSCO Educational Book (2011).
49. Animal models of mucositis: implications for therapy. Bowen JM, Gibson RJ, & Keefe DMK. Journal of Supportive Oncology, 2011 Sep-Oct; 9(5):161-8. doi: 10.1016/j.suponc.2011.04.009.
50. Irinotecan-induced alterations in intestinal cell kinetics and extracellular matrix component expression in the Dark Agouti rat. Al-Dasooqui N, Bowen JM, Gibson R J, Logan R M, Stringer A M, Keefe DMK Chemotherapy. International Journal of Experimental Pathology. 2011 Oct;92(5):357-65. Doi: 10.1111/j. 1365-2613.2011.00771.x.
51. Patient-Reported outcomes in supportive oncology. Bateman E & Keefe DMK. Seminars in Oncology. 2011 38(3): 358-61.
52. Non Cardiac Vascular Toxicities of Vascular Endothelial Growth Factor Inhibitors in Advanced Cancer: A Review. Keefe DMK, Bowen JM, Gibson RJ, Tan TH, Okera M, Stringer AM, The Oncologist. 2011 16(4):432-44.
53. Selection of Housekeeping Genes for Gene Expression Studies in a Rat Model of Irinotecan-Induced Mucositis. Al-Dasooqi N, Bowen JM, Gibson R J, Logan R M< Stringer A M, Keefe DMK. Chemotherapy. 2011 Feb ;57(1)43-53. doi 10.1159/000321477.
54. Matrix Metalloproteinases are possible mediators for the development of alimentary tract mucositis in the dark agouti rat. Al-Dasooqui, N., Gibson, R.J., Bowen, J.M., Logan, R.M., Stringer, A.M., Keefe DMK. Experimental Biology and Medicine 2010 Oct; 235:1244-1256. Doi 10.1258/ebm.2010.010082.
55. Pro-inflammatory cytokines play a key role in the development of radiotherapy-induced gastrointestinal mucositis. Ong, ZY, Gibson RJ, Bowen JM, Stringer AM, Darby JM, Logan RM, Yeoh ASJ, Keefe DMK. *Radiation Oncology*. 2010 Mar 16;5:22. doi: 10.1186/1748-717X-5-22.
56. Kinetics and regional specificity of irinotecan-induced gene expression in the gastrointestinal tract. Bowen J, Tsykin A, Stringer A, Logan R, Gibson R, Keefe DMK. *Toxicology*. 2010 Feb 28;269(1):1-12. doi: 10.1016/j.tox.2009.12.020.
57. Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients. Al-Dasooqi N, Bowen JM, Gibson RJ, Sullivan T, Lees J, Keefe DMK. *Investigational New Drugs. 2009 Apr;* 27(2):173-8. doi 10.1007/s10637-008-9152-1.
58. HER2 targeted therapies for cancer and the gastrointestinal tract. Al-Dasooqi N, Gibson R, Bowen J, Keefe DMK. *Current Drug Targets* 10:537-542, 2009.
59. Matrix metalloproteinases: key regulators in the pathogenesis of chemotherapy-induced mucositis? Al-Dasooqi N, Gibson RJ, Bowen JM, Keefe DMK. *Cancer Chemotherapy and Pharmacology.2009 Jun;*64(1):1-9. doi 10.1007/s00280-009-0984-y.
60. Links between regimen-related toxicities in patients being treated for colorectal cancer. Aprile G, Ramoni M, Keefe DMK, Sonis S. *Current Opinion in Supportive and Palliative Care* 3:50-54, 2009.
61. Role of the cyclooxygenase pathway in chemotherapy-induced oral mucositis: a pilot study. Lalla RV, Pilbeam CC, Walsh SJ, Sonis ST, Keefe DMK, Peterson DE. *Supportive Care in Cancer*. 2010 Jan;18(1):95-103. doi 10.1007/s00520-009-0635-1.
62. . Is the pathobiology of chemotherapy-induced alimentary tract mucositis influenced by the type of mucotoxic drug administered? Logan RM, Stringer AM, Bowen JM, Gibson RJ, Sonis ST, Keefe DMK *Cancer Chemotherapy and Pharmacology. 2009 Jan;*63(2):239-51. doi 10.1007/s00280-008-0732-8.
63. Gastrointestinal microflora and mucins may play a critical role in the development of 5-Fluorouracil-induced gastrointestinal mucositis. Stringer A, Gibson RJ, Logan R, Bowen JM, Yeoh AS, Hamilton J, Keefe DMK. *Experimental Biology & Medicine (Maywood. 2009 Apr;* 234(4):430-441. doi 10.3181/0810-RM-301.

64. Chemotherapy-induced modifications to gastrointestinal microflora: Evidence and implications of change. Stringer AM, Gibson RJ, Bowen JM, Keefe DMK. *Current Drug Metabolism. 2009 Jan;*10(1):79-83.
65. Irinotecan-induced mucositis manifesting as diarrhoea corresponds with an amended intestinal flora and mucin profile. Stringer AM, Gibson RJ, Bowen JM, Logan RM, Ashton K, Yeoh AS, Al-Dasooqi N, Keefe DMK. *International Journal of Experimental Patholog. 2009 Oct;*90(5):489-499. doi: 10.1111/j.1365-2613.2009.00671.x.
66. Irinotecan-induced mucositis is associated with changes in intestinal mucins. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Laurence J, Keefe DMK. *Cancer Chemotherapy & Pharmacology. 2009 Jun;*64(1):123-32. doi: 10.1007/s00280-008-0855-y.
67. Faecal microflora and β-glucuronidase expression are altered in an irinotecan-induced diarrhoea model in rats, Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh ASJ, Keefe DMK (2008) *Cancer Biology and Therap. 2008 Dec;*7(12):1919-25. IF 2.873
68. New Pathways for alimentary mucositis. Bowen JM & Keefe DMK. Journal of Oncology.2008;2008:907892. doi: 10.1155/2008/907892.
69. Emerging drugs for chemotherapy-induced mucositis. Keefe DMK, Sonis ST & Bowen JM. Expert Opinion on Emerging Drugs. 2008 Sep; 13(3):511-22. doi 10.1517/14728214.13.3.511.
70. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: Demonstration of increased frequency, severity, resistance to palliation and impact on quality of life. Elting LS, Sonis ST, Keefe DMK et al. Cancer 2008. Nov 15;113(10):2704-13. doi 10.1002/cncr.23898
71. Technological advances in mucositis research: New insights and new issues. Gibson RJ, Bowen JM, Keefe DMK. Cancer Treat Rev. 2008 Aug; 34(5): 476-82. doi 10.1016/j.ctrv.2008.02.001. PMID: 18358615
72. Mucositis in the treatment of haematological malignancies. P Niscola, L Scaramucci, C Romani, L Cupelli, A tendas, T Dentamaro, M Ales, M. Giovannini[1], D. Piccioni[1], B. Tolu[1], M. Giovannini[1], A. Perrotti[1], Keefe DMK[3] & P. de Fabritiis. *Annals of Oncology 19 (supplement 7): vii 141-vii 145 (2008).*
73. Serum levels of NF Kappa B and pro-inflammatory cytokines following administration of mucotoxic drugs. Logan RL, Stringer AM, Bowen JM, Gibson RJ, Sonis ST & Keefe DMK *Cancer Biology and Therapy. 2008 Jul;7(7):1139-45.*
74. Application of distance matrices to define associations between acute toxicities in colorectal patients receiving chemotherapy. Aprile, G., Ramoni, M., Keefe, DMK, Sonis, S., (2007). *Cancer*. 2008 Jan 15; 112(2): 284-92. (IF. 4.8)
75. Severe mucositis: how can nutrition help? Keefe DMK, Rassias G & O'Neil L. Curr Opin Clin Nutr Metab Care. 2007 Sep;10(5):627-31. PMID: 17693748
76. A Phase I study to assess the safety and activity of topical Lovastatin (FP252S) for the prevention of chemotherapy-induced alopecia. Joshi R, Olver I, Keefe DMK, Marafioti T & Smith K . Support Care Cancer. 2007 Sep; 15(9):1109-12. Epub 2007 May 22. (IF 1.59)
77. Developing a process of continuous quality improvement in medical school assessment: lessons from one school. Jones A, Wilson I & Keefe, DMK. Focus on Health Professional Education. 2007.
78. VSL#3 probiotic treatment reduces chemotherapy-induced diarrhoea and weight loss. Bowen JM, Stringer AM, Gibson RJ, Yeoh ASJ, Hannam S & Keefe DMK. Cancer Biol Ther. 2007 Sep;6(9): 1449-54. Epub 2007 Jun 23. PMID: 17881902 (IF. 2.98)
79. Characterisation of mucosal changes in the alimentary tract following administration of irinotecan: implications for the pathobiology of mucositis. Logan, R.M., Gibson, R.J., Bowen, J.M., Stringer, A.M., Sonis, S.T. & Keefe DMK. Cancer Chemother Pharmacol. 2008 Jun;62(1):33-41. Epub 2007 Aug 17.
    PMID: 17703303. (IF 2.24)
80. A novel animal model to investigate fractionated radiotherapy-induced gastrointestinal mucositis: The role of apoptosis, p52, NF-kappa B, Cox-1 and Cox-2. Yeoh ASJ, Gibson RJ, Yeoh EEK, Bowen JM,

Stringer AM, Giam KA & Keefe DMK. Mol Cancer Ther. 2007 Aug;6(8):2319-27. PMID: 17699727 (IF 5.14)

81. The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: Pathobiology, animal models and cytotoxic drugs. Logan RM, Stringer AM, Bowen JM, Yeoh ASJ, Gibson RJ, Sonis ST & Keefe DMK. Cancer Treat Rev. 2007 Aug;33(5):448-60. Epub 2007 May15. PMID: 17507164 (IF. 4.37)
82. Gene expression analysis of multiple gastrointestinal regions following cytotoxic chemotherapy by oligonucleotide microarrays. Bowen JM, Gibson RJ, Tsykin A, Stringer AM, Logan RM & Keefe DMK. Int. J Cancer. 2007 Oct 15;121(8):1847-56. PMID: 17594691. (IF 4.7)
83. A survey of paid term-time employment in undergraduate medical students at the University of Adelaide. Duggan P and Keefe DMK. Focus on Health Professional Education. 2007
84. Velafermin improves gastrointestinal mucositis following Irinotecan treatment in tumour-bearing DA rats Gibson RJ, Bowen JM, Logan RM, Stringer AM & Keefe DMK, Cancer Biol Ther. 2007 Apr;6(4):541-7. PMID: 17457046. (IF 2.98)
85. Chemotherapy-induced diarrhoea is associated with changes in the luminal environment in the DA rat. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh ASJ, Burns J, Finnie JW, Keefe DMK. (2007) Exp Biol Med. 232(1): 96-106 (IF 2.85)
86. The role of p53 in irinotecan-induced intestinal cell death and mucosal damage. Bowen JM, Gibson RJ and Keefe DMK. Anti-Cancer Drug. 2007 Feb;18(2): 197-210 (IF 1.9)
87. Irinotecan changes gene expression in the small intestine in the rat with breast cancer. Bowen JM, Gibson RJ, Cummins AG, Tsykin A, & Keefe, DMK.(2007) Cancer Chemoth Pharm. 2007 Feb;59(3): 337-348 (IF 2.24)
88. Updated Clinical Practice Guidelines for the Prevention and Treatment of Mucositis. Keefe, DMK, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati C McGuire DB, Hutchins RD & Peterson DE. (2007) Cancer Mar 1;109(5):820-31. PMID: 17236223. (IF 4.8)
89. Establishment of a single dose Irinotecan model of gastrointestinal mucositis. Gibson RJ, Bowen JM, Alvarez E, Finnie JW, Keefe DMK (2007). Chemotherapy. 2007;53(5):360-9. Epub 2007 Aug 21. PMID: 17713326 (IF 1.41).
90. Nuclear Factor κB (NfκB) And Cyclooxygenase-2 (Cox-2) Expression In The Oral Mucosa Following Cancer Chemotherapy. Logan RM, Gibson RJ, Sonis ST & Keefe DMK. (2007) Oral Oncol. 2007 Apr;43(4):395-401. Epub 2006 Sep 18. (IF 2.27)
91. The combination of oral and small intestinal mucositis, paediatrics and biomarkers: a particularly tricky problem! Keefe DMK & Gibson RJ. (2006) Cancer Biol Ther. 2006 Oct;5(10):1282-4 (IF2.98)
92. Gemcitabine and carboplatin in carcinoma of unknown primary site: a phase 2 Adelaide Trials and Education Collaborative (ACTEC) Trial. Pittman K, Olver I, Koczwara B, Karapetis C, Keefe DMK, Parnis F, Price T, Patterson W, & Yeend S. (2006) Brit J.Cancer.95:1309-13. (IF 4.1)
93. Mucosal Injury from Targeted Anticancer Therapy. Keefe DMK & Gibson RJ. Support Care Cancer. 2007 May;15(5):483-90. Epub 2006 Nov 14. (IF 1.59).
94. Sucrose Breath Testing and Intestinal Mucositis. Keefe DMK and Gibson RJ. (2006) Cancer Biol Ther. 2006 Sep;5(9):1196-8. Epub 2006 Sep 7 (IF 2.98)
95. Chemotherapy-induced mucositis: the role of gastrointestinal microflora and mucins in the luminal environment Stringer, A.M., Gibson, R.J., Logan, R.M., Bowen, J.M., Yeoh, A.S.J., and Keefe, DMK., Journal of Supportive Oncology. 2007 Jun;5(6):259-67.
96. Radiation therapy-induced mucositis: Relationships between fractionated radiation, NF-kB, Cox-1 and Cox-2,Yeoh, A.S.J., Gibson, R.J., Bowen, J.M., Stringer, A.M., Logan, R.M., Yeoh E, and Keefe, DMK. (2006) Cancer Treat Rev 32,645-651 (IF 4.55)
97. Developing Evidence-based guidelines for the management of Alimentary Mucositis: Processes and Pitfalls. Keefe DMK, Peterson D & Schubert M. Support Care Cancer, 2006 Jun;14(6)492-498 (IF 1.59).
98. Alimentary Tract Mucositis in Cancer Patients: Impact of Terminology and Assessment on Research and Clinical Practice. Peterson D, Keefe DMK, Hutchins R & Schubert M (2006) Support Care Cancer. 2006 Jun;14(6)499-504(IF 1.59).

99. Growth Factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. von Bultzingslowen I, Brennan M, Spijkervet F, Logan R, Stringer A, Raber J & Keefe DMK (2006) Support Care Cancer, 14(6)519-527(IF 1.59).
100. Anti-inflammatory Agents in the Management of Alimentary Mucositis. Lalla R, Schubert M, Bensadoun R-J & Keefe DMK (2006) Support Care Cancer, 14(6)558-565(IF 1.59).
101. Amifostine in the management of Radiation-induced and Chemotherapy-induced Alimentary mucositis. Bensadoun R-J, Schubert M, Lalla R & Keefe DMK (2006) Support Care Cancer,14(6)566-572(IF 1.59).
102. Palifermin for oral mucositis in the high dose chemotherapy and stem cell transplant setting: the Royal Adelaide Hospital Experience. Keefe DMK, Lees J and Horvath N. (2006) Support Care Cancer, 14(6)580-582(IF 1.59).
103. Alimentary Mucositis: putting the guidelines into practice. Brennan M, von Bultzingslowen I, Schubert M & Keefe DMK. (2006) Support Care Cancer, 14(6)573-579(IF 1.59).
104. Cancer Chemotherapy-Induced Diarrhoea and Constipation: Mechanisms of Damage, Possible Prevention Strategies and Treatment of the Clinical Problem. Gibson R & Keefe DMK. Support Care Cancer. 2006 Sep;14(9):890-900(IF 1.59).
105. Apoptosis occurs early in the basal layer of the oral mucosa following cancer chemotherapy, Gibson R.J., Cummins A.G., Bowen J.M., Logan R.M., Healey T., & Keefe, DMK. (2006), Asia Pacific Journal of Clinical Oncology 2:39-49.
106. Intestinal mucositis: the role of the Bcl-2 family, p53 and caspases in chemotherapy-induced damage, Bowen, J.M., Gibson, R.J., Cummins, A.G., and Keefe, DMK., Support Care Cancer. 2006 Jul;14(7)713-31(IF 1.59).
107. Nuclear Factor <kappa>B (NF<kappa>B) and Cyclooxygenase-2 (Cox-2) Expression in the Irradiated Colorectum is Associated with Subsequent Histopathological Changes. Yeoh A, Gibson R, Bowen J & Keefe DMK. Int J Radiat Oncol Biol Phys. 2005 Dec 1;63(5):1295-303 (IF 4.56).
108. Cytotoxic chemotherapy increases pro-apoptotic Bax and Bak expression in crypts of the rat and human small intestine. Bowen, J.M., Gibson, R.J., Keefe, DMK., & Cummins, A.G. Pathology; 2005 Feb;37(1):56-62 (IF 1.47).
109. A Phase I study of prolonged ambulatory infusion of Ifosfamide with oral mesna. Olver I, Keefe DMK, Myers M & Caruso D (2005). Chemotherapy; 51:142-146 (IF1.41).
110. A Phase II study of prolonged infusion carboplatin and oral etoposide for patients progressing through hormonal therapy for prostate cancer. Olver I, Keefe DMK & Myers M. (2005) Intern. Med. J, 35:405-408 (IF 1.58).
111. Relationship between dose of methotrexate, apoptosis, p53/p21 expression and intestinal crypt proliferation in the rat. Gibson, R.J., Bowen, J.M., Cummins, A.G., & Keefe, DMK. (2005) Clin Exp Med. 4:188-195 (IF1.23).
112. Palifermin reduces diarrhea and increases survival following Irinotecan treatment in tumour-bearing DA rats. Gibson RJ, Bowen JM, & Keefe DMK Int J Cancer. 2005 Sep 1;116(3):464-70 (IF 4.7).
113. Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy-Induced Oral and Gastrointestinal Mucositis. Rubenstein EB, Peterson DE., Schubert M, Keefe DMK, McGuire D, Epstein J, Elting LS., Fox PC., Loprinzi CL., Sonis ST. Cancer (2004) Supplement (100) 9:2026-2046 (IF 4.8).
114. Perspectives on Cancer Therapy – Induced Mucosal Injury: Pathogenesis, Measurement, Epidemiology and Consequences for Patients. Sonis ST., Elting L S., Keefe DMK, Peterson DE, Schubert M, Hauer-Jensen, M, Bekele BN, Raber-Durlacher J, Donnelly J P, Rubenstein E. (2004) Cancer Supplement (100) 9: 1995-2025 (IF 4.8).
115. Gastrointestinal Mucositis. Keefe DMK., Gibson RJ., Hauer-Jensen M. Seminars in Oncology Nursing. 2004 Feb;20(1): 38-47.
116. Novel Therapies. Peterson DE., Beck SL., Keefe DMK. Seminars in Oncology Nursing, 2004 Feb;20(1):53-8.

117. Irinotecan causes severe small intestinal damage, as well as colonic damage, in the rat with implanted breast cancer. Gibson, R.J., Bowen, J.M., Inglis, M.R.B., Cummins, A.G., and Keefe, DMK. J Gastroen Hepatol, 2003 Sep;18:1095-100 (IF 1.72).
118. The Effect of Keratinocyte Growth Factor on Tumour Growth and Small Intestinal Mucositis after Chemotherapy in the Rat with Breast Cancer. Gibson, R.J., Keefe, DMK., Clarke, J.M., Regester, G.O., Thompson, F.M., Goland, G.J., Edwards, B.G., Cummins, A.G. Cancer Chemoth Pharm. 2002 Jul;50: 53-8 (IF 2.24).
119. Endocrine Responsiveness and tailoring adjuvant therapy for postmenopausal lymph node-negative breast cancer: a randomized trial. Goldhirsch A. for the IBCSG (including Keefe DMK).(2002) J Natl Cancer Inst. 94 (14):1054-1065 (IF 15.17).
120. Phase I study of the GM-CSF Antagonist E21R. Olver, I.N., Hercus, T., Lopez, A., Vadas, M., Samogyi, A.A., Doyle, I., Foster, D.J.R., Keefe, DMK., Taylor, A., Brown, M.P., To, B., Cole, J., Rawling, T., Cambareri, B., Myers, M., Olszewski, N., Bastiras, S., Senn, C., Hey, A., Verma, M., Wigley, P. A (2002) Cancer Chemoth Pharm 50: 177-178 (IF 2.24).
121. The effect of interleukin- 11 on ameliorating intestinal damage after methotrexate treatment of breast cancer in rats. Gibson, R.J., Keefe, DMK., Thompson, F.M., Goland G.J., Cummins, A.G. Digest Dis Sci. 2002 Dec;47(12):2751-7 (IF 1.388).
122. Treatment-induced gastrointestinal toxicity in patients with cancer. Elting LS, Keefe DMK & Sonis ST, (2004). ASCO Educational Booklet: 536-541.
123. Chemotherapy for Cancer Causes Crypt Apoptosis that Precedes Hypoplasia in the Small Intestine of Humans. Keefe DMK., Brealey J.K, Goland G.J, Cummins A.G. (2000) Gut 47: 632-637 (IF 7.7).
124. Phase II Study of Epirubicin, Cisplatin and Continuous Infusion 5-Fluorouracil (ECF) for Carcinoma of Unknown Primary Site. Parnis, FX., Olver, IN., Kotasek, D, Norman J Taylor, A, Russell, J., Patterson, K., Keefe, DMK., Marafioti, T. (2000) Ann Onc 11: 883-884 (IF 4.32).
125. Malignant Severe Adverse Reaction to High Dose Epirubicin and Cyclophosphamide for Poor Prognosis Breast Cancer. A report of three cases. Turtle, C J., Keefe, DMK., Bell, D, Wheeler, H, David, D.F. (1999)ANZ J Med (IF 1.52).
126. Multicycle High-Dose Chemotherapy and Filgrastim-Mobilized Peripheral-Blood Progenitor Cells in Women With High-Risk Stage II or III Breast Cancer: Five-Year Follow-Up. Basser, R L., To, BL., Collins, J P., Begley, G C., Keefe, DMK., Cebon, J., Basford, J., Durrant, S., Szer, J., Kotasek, D., Juttner, C A., Russell, I., Maher, D W., Olver, I., Sheridan, W P., Fox, R M., Green, M D. (1999) J Clin Oncol 17(1): 82-89 (IF 11.8).
127. The effect of high-dose chemotherapy on intestinal permeability in humans Keefe, DMK., Cummins, A.G., Dale, B.M., Kotasek, D., Robb, T.A. & Sage, R.E. (1997) Clin. Sci 92, 385-389 (IF 2.64).
128. Haemorrhagic gastritis in two patients treated with all-trans-retinoic acid in acute promyelocytic leukaemia. Patterson, W.K., Sage, R.E. & Keefe, DMK., (1994). ANZJM, 24:314-5 (IF 1.52).

.