Woulgan® biogel – an advanced wound healing product

I. Executive Summary

- Biotec Pharmacon (“the Company”) develops wound treatment products based on its unique and patented immunomodulating soluble beta-glucan (SBG) technology. The Company has 25 years experience in beta-glucan research and development and is the market leader within this segment.

- The Company has recently developed a novel wound healing hydrogel (Woulgan® biogel) demonstrated to be very effective in inducing healing of diabetic ulcers. The hydrogel contains Biotec Pharmacon’s soluble yeast beta-glucan (SBG), and is far more effective in wound healing than a number of well-established comparator hydrogel formulations tested.

- The first generation SBG product was in advanced drug development (phase III) whereas the novel hydrogel (Woulgan® biogel) is soon to be filed as a medical device class III, rule 13 in Europe. The product is foremost intended for treatment of chronic wounds including treatment of diabetic foot ulcer.

- SBG has been documented to have a very favourable safety profile both in numerous preclinical and clinical studies. No adverse events have been related to the compound, neither after oral, parenteral or topical administration.

- SBG is produced at the Company’s own manufacturing plant in Tromsø, Norway.

- Woulgan® biogel is protected by a large number of patents and trademarks.

- The market potential for Woulgan® biogel is large. The market for advanced wound healing is in continuous growth and in need of effective and novel products. To the best of our knowledge there is no similar effective, competing product on the market.

- The Company is presently seeking partners for filling and/or distribution of the Woulgan® biogel.

II. About Biotec Pharmacon ASA

The biopharmaceutical company Biotec Pharmacon has developed the bioactive substance SBG (soluble beta-glucan), which has shown efficacy in the treatment of diabetic ulcers and prevention and treatment of oral mucositis. The Company, through its wholly owned subsidiary Biotec BetaGlucans AS, currently focuses on developing a medical device for treatment of wounds, and especially for treatment of diabetic ulcers. The Company’s clinical development program also includes the treatment of oral mucositis, the immune therapy of cancer where combination treatments with beta-glucan and monoclonal antibodies are being studied in clinical phase I/II, as
well as the treatment Inflammatory Bowel Disease (IBD) where phase I safety studied have been performed. In addition, the Company is involved in several preclinical studies with SBG. The beta-glucan technology owned by Biotec Pharmacon is patent protected and the products are manufactured in the Company’s GMP-approved factory in Tromsø.

Biotec Pharmacon also produces and markets non-pharmaceutical health products and diagnostic products through the marine enzyme company ArcticZymes AS.

Biotec Pharmacon is listed at the Oslo Stock exchange (Ticker: biotec). Web page: www.biotec.no

III. The product:

1. Short summary of the product:

Biotec Pharmacon has developed a novel and very effective hydrogel containing the Company’s proprietary compound SBG (soluble beta-glucan) for use in wound treatment. The gel product, called Woulgan® biogel, offers the typical features of a medical device hydrogel formulation in addition to the biological wound healing enhancing ability of the soluble beta-glucan component, considered to be an ancillary medicinal product in the formulation. Woulgan® biogel is a sterile, non-preserved amorphous and thixotropic wound filling gel formulation based on water, glycerol and water soluble polymer chains (Carboxymethyl-Cellulose (CMC) and beta-glucan (SBG)).

Woulgan® biogel has been developed for dry to moderate exuding partial and full thickness wounds such as:

- diabetic ulcers
- pressure ulcers
- leg ulcers
- graft and donor sites
- post-operative surgical wounds
- trauma wounds
- 1st and 2nd degree burns
- Abrasions and lacerations

Woulgan® biogel is initially intended to be applied to the wound every third day until complete wound healing or for a maximum of 12 weeks unless improvements are seen at that stage.

The product is already available as prototype (see the present product features in the image below).
The product has now been tested in several studies in diabetic mouse wound models with excellent results showing superiority in healing efficacy compared to all the other hydrogel formulation tested, including commercial products having well renowned healing capabilities and strong market positions.

Figure 1 below shows a comparison of the product Woulgan® biogel with water (negative control; green line) and a growth factor (positive control; GF just approved for animal trials; black line). Woulgan® biogel was compared to a 1% CMC gel (purple line) and a commercially available hydrogel. This trial shows that Woulgan® biogel significantly outperformed the product Intrasite® in this diabetic mouse model.

![Graph showing wound healing comparison](image)

*Figure 1 demonstrates the superior effect of Woulgan® biogel in wound healing as compared to dressing alone or two hydrogel controls (CMC and Intrasite).*
2. Soluble Beta-Glucans ("SBG") – the biologically active component of Woulgan® biogel

SBG is derived from *Saccharomyces cerevisiae*. Beta-glucans are known to bind to specific receptors on white blood cells of the innate immune system, notably macrophages, dendritic cells, and granulocytes, and corresponding cells in tissue surfaces. The specific interaction between the immunomodulatory type of beta-glucans and such white blood cells results in a modulation of cellular responses. When administered topically to wounds and ulcers beta-glucans are known to assist in wound healing. In particular, highly immunomodulatory beta-glucans have been looked at as potential agents for normalizing macrophage functions in diabetic ulcers. Lately the more physical wound promoting abilities, like the excellent water holding capacity, of the Biotec Pharmacon’s soluble yeast beta-glucans have also been explored with positive results.

The Company’s Soluble Beta-Glucans are according to chemical nomenclature beta-1,3/1,6-glucans, polysaccharides with glucose as the only building block and where the glucose molecules are linked together in branched chains. The chain consists of beta-1,3-linked glucose, and the branching points are beta-1,6 linkages as illustrated below. The ability of this molecule to strengthen innate immune functions depends on primary structure as well as the so-called supramolecular higher-order organization. This structure binds to specific receptors found in macrophages, dendritic cells granulocytes, natural killer cells resulting in improved wound healing.

![Molecular structure of SBG](image)

*Figure 2: Molecular structure of SBG: Branched chains of glucose molecules linked by beta-1,3-glycosidic bonds and a beta-1,6-glycosidic bond at each branching point.*

SBG is completely water soluble and pure native yeast beta-1,3,1,6-glucan with high biological activity and a good safety profile. SBG is produced by the Company.

3. The Mode of Action and Characteristics of Woulgan® biogel in treating ulcers and wounds

Wounds in the skin will normally heal without complications if the damage is not too large. Macrophages and other connective tissue cells contribute to the different phases in the healing process including formulation of new tissue and prevention of infections. Inappropriate immune responses are important factors in the development of chronic wounds and ulcers, and do often lead to a poor regulation of the normal sequence of wound healing. Macrophages are main coordinators of the healing process, and are therefore suitable targets for correcting impaired wound healing.

Diabetes patients have reduced ability to repair wounds partly because macrophages in this group of patients are dysfunctional. This may explain the propensity of diabetics to develop serious
complications such as diabetic ulcers. Ulcers among diabetes patients are a severe and recurring medical problem lacking an effective treatment with tolerable side-effects.

Immunomodulatory beta-glucans are known to act on tissue macrophages restoring normal activity also of dysfunctional macrophages as found in patients with diabetes. This being the scientific rationale behind the explorative clinical trials carried out with pure SBG on diabetic patients with severe foot and leg ulcers. The results showed better efficacy compared to standard treatment of such patients.

Beta-glucans also have a number of favourable physical properties that would be important for the wound healing process, where the ability to maintain a moist wound bed allowing autolytic debridement is the single most important. The product would also, when formulated in an appropriate concentration, have the ability to absorb exudates from the wound, and to provide a physical barrier for bacterial infection and general protection of the wound bed. The above qualities are being established as critical for a well-functioning medical device and in the new stabilized gel formulation containing SBG such properties have been emphasized.

The SBG active itself has been developed during the last 20 years and has been documented with respect to safety and efficacy in a number of studies, including more than 10 clinical studies. The uniform picture is that SBG seems to be very well tolerated and safe both when administered orally and topically even in maximum achievable dosages. The Company has also performed several studies to examine potential adverse effects of applying Soluble Beta-Glucan onto skin and wounds. As for the other studies it was concluded that SBG formulations tested were safe and well tolerated.

4. The SBG and Woulgan® biogel development program for topical wound treatment - in a nutshell

The Company has performed a series of pre-clinical and clinical trials with Soluble Beta-Glucan in treatment of Diabetic Ulcer and planned to register the product as a drug after successful clinical studies including phase II. The former product formulation however failed in the pivotal phase III as it turned out that it lacked sufficient stability. The product has then been reformulated to a much more stabile form. It was decided to seek registration of the product as a medical device for the reformulated product, a route that regulatory authorities have indicated to be acceptable in the EU. The substantial clinical development program backing up the registration application is as outlined below:

- 2002-2011: Pre-clinical toxicology and pharmacology studies using SBG in animal models and in _in vitro_ models. All studies have confirmed a very good safety profile of the product, as would be expected from a poly-glucose molecule.

- 2003-2010: Six phase I/II safety studies in volunteers or in patients (cancer & and burns), all confirming the excellent safety profile.

• 2007-2010: Two double blinded placebo controlled phase III studies for prevention and treatment of diabetic ulcers. Overall not successful due to unstable product, but sub analysis showed good results in the part done with a stabile product
• 2010-2011: Three animal studies with a new medical device hydrogel composition
• 2010-2011: Several stability studies with a new medical device composition

5. Manufacturing of Soluble Beta-Glucan

The Company has invested in its own production plant, and developed know-how on how to produce bio-chemicals and products of pharmaceutical quality.

Biotec Pharmacon has a manufacturing license for medicinal products from the Norwegian Medicines Agency. The license covers production, packaging, labelling, quality control and release of SBG for use in clinical trials. It is also in process to have its quality system meeting the ISO 13485 standard for medical devices.

Presently the SBG ingredient is shipped to a European contract manufacturer where the final Woulgan biogel is formulated and filled into end user units.

IV. Governmental Regulations

The Governmental rules and regulations are constantly being adjusted and the following description is made to the best of the Company’s knowledge as of today. However, the Company recognize that such classification is for the sole discretion of each jurisdiction so this description should only be looked upon as guidance. It is also important to state that even though a product obtain a certain classification in a region it may be reclassified later. The manufacture and sale of medical devices and indeed pharmaceuticals in the Europe and most other markets are governed by a variety of laws and regulations.

At present the Company has decided to register the product in Europe as Class III, rule 13 product. The background for that decision is several folds. The EU market has a high concentration of Class IIa and Class IIb devices within the area of topical wound applications. With regard to such products, the breadth of associated label claims is very limited to the mechanical properties of the device. A potential advantage to the classification of SBG as a Class III device by mutual agreement with a notified body will allow greater exclusivity for SBG, as well as allowing additional information and claims to be made for SBG as a medical device. The claims to be pursued for the registration of this class III medical device product are as follows:

– Primary claims related to physical characteristics, like moist, autolytic debridement, protective, etc
– Secondary (ancillary) claims, related to the beta-glucan effect as a medicinal product improving specific wound healing mechanisms
V. The market and the competition

The present wound treatment formulation developed by Biotec Pharmacon as the product Woulgan® biogel focuses basically on treatment of diabetic ulcers. Diabetic ulcers occur on the feet and are a major complication of diabetes caused by two factors. Diabetic patients may suffer from peripheral nerve damage as a result of higher than usual blood sugar levels. This nerve damage means patients may not know if they injure their feet, and such injuries may develop into ulcers. In addition, diabetics have an increased risk of atherosclerotic disease, which can reduce blood flow to the arteries in the legs and blood supply to the feet. Skin with a poor blood supply does not heal as well, meaning diabetics may find their wounds take longer to heal, which may also lead to them becoming ulcerated. While most diabetic foot ulcers do respond to treatment, infection can occur and more serious problems can develop such as gangrene which, in extreme cases, may lead to amputation. There is also a high reoccurrence rate for diabetic ulcers.

According to a World Health Organization Report, the prevalence of diabetes for all age-groups worldwide is estimated to rise from 2.8% in 2000 to 4.4% in 2030, with the total number of people with diabetes projected to increase from 171 million in 2000 to 366 million in 2030. The International Diabetes Federation has even higher estimates, estimating there were 285 million people with diabetes globally in 2009 and that the total number will exceed 435 million in 2030 if current rates of growth continue unchecked. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people aged 65 years or over. In addition, rising levels of obesity are a major factor in the increase in the number of people with Type II diabetes.

With the numbers of patients with diabetes increasing, there is a corresponding rise in the number of diabetic ulcers requiring treatment, leading to strong demand for advanced wound care products in the future. Developed world studies have estimated that 15% of people with diabetes will ultimately have diabetic foot ulcers, with an annual incidence in at least 2.2% of people with diabetes, according to a Lancet article published in 2005.

According to the National Diabetes Factsheet 2007, produced by the Department of Health and Human Services at the US Center of Disease Control and Prevention, there were approximately 23.7 million people with diabetes in the US in 2007, which amounted to 7.8% of the total population. The total prevalence of diabetes increased by 13.5% from 2005 to 2007. In 2007, the total annual economic cost of diabetes in the US was US$174 billion. Medical expenditure totaled US$116 billion and comprised US$27 billion for diabetes care, US$58 billion for chronic diabetes-related complications and US$31 billion for excess general medical costs.
Based on estimates that 15% of people with diabetes will develop a diabetic foot ulcer in their lifetime, this represents 3.6 million ulcers in the US alone. Over 60% of non-traumatic lower-limb amputations occurred in people with diabetes and, in 2004, approximately 71,000 such amputations were performed in people with diabetes. There is therefore definitely a need to develop improved diabetic ulcer treatments that can reduce the amputation rate.

The wound care market comprises two main sectors: traditional dressings that operate in a dry environment, basically protecting the wound from some external contaminants and soaking up some fluids; and advanced wound care products, which are designed to provide a therapeutic effect that actively aids wound healing. Traditional products are used widely by healthcare professionals and consumers, while advanced wound care products are generally professional-use products. Traditional wound care dressings consist mainly of low technology gauze-based dressings such as woven and non-woven sponges, conforming bandages and non-adherent bandages. While traditional dry dressings are useful for uncomplicated and superficial wounds, they are not effective for more complicated cases such as chronic wounds and other hard-to-heal wounds such as diabetic ulcers. Advanced wound care products better address these types of wounds. The advanced wound care market is extremely diverse and includes an array of competing technologies such as moist wound dressings (hydrogels, hydrocolloids, alginates, foams and transparent films); biological products such as growth factors, skin substitutes and tissue-engineered products; and wound healing devices that deliver therapies such as negative pressure wound therapy (NPWT), oxygen therapy, electrical stimulation and ultrasound to promote wound healing.

The Professional Wound Care Market Forecast and its Growth for these different wound healing products can be summarized in Figure 4 below:

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<th>Professional Wound Care Market Forecast, 2010-2015 (US$ million)</th>
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<td>Traditional Dry</td>
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<td>Total Wound Care</td>
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*Source: Epicom Internal estimates.*

*Estimates are based on dry traditional product sales in the professional healthcare market only.*

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<th>Global Wound Care Market Growth by Product, 2008-2015E (%)</th>
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*Estimates are based on dry traditional product sales in the professional healthcare market only.*
**Competition:**

The overall field of wound treatment comprises a large number of different product and applications as defined above. Competition is very high. Nevertheless, in niche fields like treatment of diabetic ulcers, there are only a few products on the market. These products include the Rx/growth factor Regranex which is black-boxed (cancerogenic) as well as class-II medical devices like hydrogels, silver-containing products or the like. At present there are only a very few number of class-III medical device products available.

Woulgan® biogel differs from these products in the following way:

1. Safety: The product is completely safe. No SAEs were observed in any of the clinical study conducted
2. The product is highly documented in preclinical and clinical settings
3. The product is significantly more effective compared to the golden standards in the industry
4. Woulgan® biogel is a low cost (low COGs)/high margin product
5. Woulgan® biogel is covered by broad IP with prospective patent protection until 2031
6. The product is intended to be classified as a class 3, rule 13 medical device
7. Customer preference due to faster healing time and convenience of product application
8. Strong reimbursement arguments due to significantly reduced number of patient visits to physicians and reduced numbers of amputations

**VI. Intellectual Property**

Woulgan® biogel and the ingredient SBG are patent protected. This includes a patent family covering the use of Biotec beta glucans for wound treatment. Expiry of those patents is in 2020. Further 3 new patent families were filed in Q4 2010 covering the process of production and certain compositions of old and new SBG-variants. Expiry of those patents is in 2031. The trademark Woulgan® itself is also registered in Norway and further trademark applications are pending in several major countries amongst others in Europe (CTM), USA, The Russian Federation, Australia, China, Japan and South Korea. SBG is also a registered Community Trademark.

**VII. Present developments and future outlook**

- The Company has finalized the preparation of the final product (a prototype is available for evaluation).
- Intended filing of the technical dossier in Q2 2012.
- The first large scale batches have been produced.
- Discussions are ongoing with potential partners that can help the Company to a successful market launch and penetration.
- A clinical trial is planned for use as a marketing tool.
- Follow-up products are under development (second generation product and different modes of application).