Oscotec Inc.

PROJECT NAME (Ingredient Trade Name): OPB **Active Ingredient Scientific Name : *Rehmannia glutinosa Libosch* and *Eleutherococcus senticosus (Rupr. & Maxim.) Maxim*** **Submission Date : Mar/09/2011**
Description of Product: OPB is a functional food ingredient for prevention of osteoporosis independently developed by bone-specialized bioengineering company, oscotec Inc.

1. Supporting Evidence (Efficacy/Functionality):

Provide all supporting literature and research studies, publications, protocols, and analytical assessment.
Please separate data into:

- Mechanism of Action/s (MOA)
  - Bone is made up of not only calcium, but also bone proteins such as collagen, alkaline phosphatase, and osteopontin. Calcium particles attach to bone proteins secreted by bone-forming cells (osteoblasts), hardening it to form new bone tissue. Through these bone remodeling processes, overall bone mineral density (BMD) is maintained. Menopausal women, however, are at a higher risk of osteoporosis since various factors such as sudden hormonal changes can cause activation of bone destroying cell (osteoclast). Therefore, relatively increased bone resorption lead to bone mineral density decrease, and osteoporosis
    OPB activates osteoblasts and inhibits osteoclasts, thus increases BMD, and eventually prevents osteoporosis.

- Chemistry/Characterization data
  - OPB is a powder extracted from Rehmanniae Radix Preparata and Eleutherococcus senticosus (4:1)

- *In vitro* bioassay data
  - Activation of osteoblast, Alkaline Phosphatase(ALP) which promotes bone mineralization, expression of bone protein(collagen, ALP, osteopontin), activation of Runx2, essential transcription factor for bone formation, and osteoprotogerin(OPG) which inhibits differentiation of osteoclast were increased on a dose dependent manner.

- *In vivo* testing (Laboratory, Animal, and Human Clinical Studies)
  - Twenty Sprague Dawley rats of 13 week-old were divided into two groups: control group (ovariectomized, OVX)) and experimental group (OVX + OPB). The preventing effects of OPB on bone loss, OPB were fed with 100 mg OPB/kg body weight from 3 days after ovariectomization. The duration of the treatment period was 8 weeks. All bone mineral density, bone mineral content indices and bone strength indices measured by peripheral quantitative computerized tomography (pQCT) and serum bone marker assessment were carried out at end of experiment. pQCT scanning showed that OVX induced a significant decrease in cancellous bone mineral density in the proximal tibia (-29.8 ± 3.0%). These decreases were significantly prevented by the administration of OPB 100 mg/kg (-21.4±2.3%. $p<0.05$). Bone strength indices showed significant difference between OVX and OPB treated rats (anti-fracture, anti-twisting, $p<0.05$). These data suggested that administration of OPB inhibited the loss of bone in OVX rats. CTx level were lower than in the OPB-treated animals compared with OVX. However there was no significant difference between OVX and OPB treated OVX rat. Our results suggest that OPB is effective in preventing the development of bone loss induced by ovariectomy in rats.

- 1st Clinical Study Tested
  - Provide studies done by Company on the ingredient. - attached
  - Total number of clinical studies completed? – 1
  - Study design? (number of subjects, duration of the study/ies, double-blinded, placebo-controlled, case controlled, etc.)

- 36 patients, 1 year, double-blinded and placebo-controlled
- Dose and delivery form used in the study/ies
  - 500mg/day, capsules

- Published or not published, and in which journal/s?
  - Published. Korean J Physiol Pharmacol Vol 11: 121 - 127, June, 2007
- Recommended Delivery form/s? – Capsules or tablets
- Recommended dose/s? (mg per day) – 800mg/day
- Collaborating Organizations, professors or University Affiliations
  - Dankook university, Medical center
- Conclusions from the studies
  - In this study, we investigated the therapeutic effects of a novel formulation of low-dose calcium and vitamin D3, blended with Rehmannia glutinosa Libosch and Eleutherococcus senticosus Max (RE+), in postmenopausal women. The controls were given either a placebo or high dose calcium and vitamin D3 (Ca+ D). Bone mineral density (BMD) in the L2-3 lumber spines and femur regions was assessed, and serum osteocalcin, bone-specific alkaline phosphatase (BALP), and cross-linked N-telopeptide of type I collagen (NTx) were used as markers of osteoblast and osteoclast activity. Furthermore, all variables were measured before and after 6 and 12 months of treatment. The osteocalcin level was higher in the RE+ group, and BALP was almost the same in all groups. Serum NTx was significantly decreased in the RE+ group after 12 months ($p < 0.05$). The NTx in the Ca+ D and placebo groups showed no significant change. The decrease o f femur BMD was further demo nstrated in the placebo group, but significantly increased in the RE+ group after 6 and 12 months of treatment ($p < 0.05$). There were significant differences in the percent changes of femur BMD between the placebo and RE+ groups ($p < 0.01$) and Ca+ D and RE+ groups ($p < 0.05$). The decrease of spine BMD in the placebo group was inhibited both in the Ca+ D and RE+ groups, however, there was significant difference only between the placebo and RE+ groups ($p < 0.05$). These findings suggest that continuous oral therapy of the RE+ formulation reduces rapidly decreasing bone mineral density in postmenopausal women more effectively than high doses of calcium and vitamin D3 alone by inhibiting osteoclastic activity. Therefore, it seems that the RE+ has its own antiosteoporotic effects. We suggest larger clinical studies to determine the most efficacious dosage and benefits of this novel treatment.

- **<u>2nd Clinical Study on Processing (Updated)</u>**
  - Provide studies done by Company on the ingredient. - attached
  - Total number of clinical studies on processing? – 1
  - Study design? (number of subjects, duration of the study/ies, double-blinded, placebo-controlled, case controlled, etc.)
    - "A Phase II, Double Blind, Randomized, Placebo-Controlled Study of OPB® in Post-Menopausal Female Subjects with Osteopenia (low BMD) to Investigate the Safety and Efficacy with respect to Bone Mineral Density(BMD)"
    - To evaluate comparative safety and efficacy of OPB® in terms of its effects on bone mineral density in female subjects (90 patients) with osteopenia after 9 month oral administration
  - Dose and delivery form used in the study/ies
    - OPB® (800mg/day) or placebo will be taken orally twice a day as two hard capsules per administration with tap water 30 minutes for total period of 9 months. All subjects will be administered daily with oral supplement of calcium citrate 750mg and $VitD_3$ 400 I.U as a commercially available hard capsule.
    - Details of Subject
      1. Healthy post-menopausal female subjects, older than 45 and younger than 75 years, with a Body Mass index between 19.0 and 32.0 kg/m^2
      2. Subject who has agreed and signed the Informed Consent Form(ICF)
      3. Subject who can enrolled for whole study period and who has agreed to comply with all restrictions during study period
      4. Subject with appropriate functions in bone marrow, kidney and liver
      5. Female with BMD (-2.5 < T-score < -1.0) and sustained menopausal for more than one year

- Published or not published, and in which journal/s? N/A

- Recommended Delivery form/s? – Capsules or tablets
- Recommended dose/s? (mg per day) – 800mg/day
- Collaborating Organizations, professors or University Affiliations
  - SamSung Medical Center, Clinical Trial Center
- Criteria for Evaluation
  1. Bone mineral density(BMD) assessment (percent changes in lumbar spine and femur)
  2. Changes in bone turnover markers: bone resorption markers:serum C-telopeptide(CTX), crosslinked N-telopeptides of type I collagen (NTx) and bone formation markers: serum osteocalcin, bone specific alkaline phosphatese.
- Conclusions from the studies

  - It is ready in Early November 2011.

2. Intellectual Property / Exclusivity

Provide an IP Portfolio summary to include:

- Provide patent information
  - Provisional/non-provisional/PCT/
    - Korea : A herbal mixture extract of *Rehmanniae Radix* Preparata and *Acantho panacis Cortex* and composition comprising the same for prevention and treat ment of osteoporosis
      Application number 10-2005-0015049 (2005.02.23) / Publication number 10-20 06-0093918 (2006.08.28)
    - Filed a PCT application covering US, EU, Japan and China
  - Number of patents? - 1
  - Patent Type? (Process, Application, Combination, Composition, or other)
    - Korea : patent granted
    - PCT : applied
  - Patent Number/s, title, abstract, claims and application/issue dates
    - 1, A herbal mixture extract of *Rehmanniae Radix* Preparata and *Acanthopanacis Cortex* and composition comprising the same for prevention and treatment of osteoporosis
- Describe exclusivity options (MLM, all markets, global, etc.)

  - Out-licensing of intellectual property is available.