

INDENA INTRODUCES POLINACEA A NEW HIGHLY EFFECTIVE INGREDIENT FROM ECHINACEA

SupplySide West in Las Vegas saw the launch of Polinacea™: a most innovative immunobooster

18th December 2002 - Indena, the leading botanical extract manufacturer, has launched its totally new natural immunobooster, an innovative standardised extract derived from the roots of *Echinacea angustifolia*. The new immune-boosting herbal ingredient, branded Polinacea™, was presented to an invited audience of partners and professionals during the SupplySide West trade fair in Las Vegas, on December 6th.

Dr. Edward M. Croom, Scientific and Regulatory Affairs Manager of Indena USA East, was keen to stress that not all Echinacea extracts were alike however. "Conceived as the most innovative immune booster from Echinacea, Polinacea™ alone is characterised by a unique triple standardisation that makes it different from all other Echinacea extracts. Furthermore, Polinacea™ is obtained through original extraction procedures that make use of only food solvents starting from selected and cultivated biomass". Polinacea™ is chemically defined by at least a 4% echinacoside content and 5% IDN5405, a newly discovered polysaccharide which contributes to immune stimulating effects. It has been identified in the roots of the plant for the first time. Moreover, Polinacea™ does not contain isobutylamides as they do not add any biological activity but it does contain inulin, in order to enrich the extract with a prebiotic profile. During the meeting, Dr. Croom illustrated the research on this new ingredient, drawing on evidence from a series of *in vitro* and *in vivo* trials. On the basis of the results obtained, Polinacea™ may well be considered an excellent immune response improver. In immunocompetent mice challenged with the parasitic infection *Leishmania major*¹, the extract reduced the experimentally induced *leishmaniasis* by 25%. In addition, Polinacea™ reduced by 30% and 40%, respectively, the *Candida Albicans* induced mortality in immunocompetent and in cyclosporin A² treated mice. In the same model, the best selling Echinacea product, used as a benchmark and compared to a placebo, failed to produce such results. The mechanism of action, which confirms these results, consists in a direct action on T cells.

"At Indena it's imperative to promote and guarantee the safety, quality, and efficacy and safety of all our products, allowing consumers to demand and recognise the best in the natural dietary supplements they purchase", added Ed Croom. "In toxicological studies, Polinacea™ did not exhibit any adverse effect at doses ranging from 1g/die up to 1Kg/die. This specific characteristic of Polinacea™ entitles it to be considered a high-profile candidate as a functional ingredient in the enhanced food category in several countries." The recommended and suggested dose in health food application is 100-200 mg Polinacea/die for two weeks consumption.

Indena is based in Milan, Italy with US branches in Seattle, WA and Parsippany, NJ. Indena was founded in 1921 and is a private, family-owned business. The company employs a staff of 700 and is specialised in the extraction of plant-based active principles and derivatives for the pharmaceutical, dietary supplement and cosmetic industries.

¹ *Leishmania major* is one of the most representative experimental *in vivo* models utilized to check the immunobooster capability of drugs.

² Cyclosporin A is the standard drug utilized to suppress the immune-system.

A NEW MOLECULE OBTAINED FROM PLANTS CAN MAKE CHEMOTHERAPY MORE TOLERABLE AND EFFECTIVE

Three Italian studies presented in Frankfurt by Indena

Milan, 9th December 2002 - A great deal of recent research work in the oncological field was presented by the Italian company Indena at the Symposium on "Molecular Targets and Cancer Therapeutics", held in Frankfurt, 19th - 22nd November, 2002, under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR).

With three preclinical studies, the attention of Indena researchers has focused on the new experimental molecule IDN 5390 which belongs to the class of taxanes, already noteworthy for having enabled the development of important chemotherapy drugs such as paclitaxel. In previous studies the new molecule had already demonstrated a promising profile of low toxicity, a selective activity in the inhibition of angiogenesis and it may be administered orally. These characteristics make it less invasive than the chemotherapy drugs commonly in use today.

The latest *in vitro* and *in vivo* tests conducted have in fact evaluated the combination of IDN 5390 with paclitaxel. The results presented at Frankfurt have shown this combination to increase the efficacy of the treatment, with no increase in toxicity. In particular IDN 5390 allows metronomic chemotherapy treatment, which put simply means lower, less toxic doses over a longer treatment time.

"The possibility of combining an oral taxane, targeting both cancer cells and tumour vessels, with chemotherapy drugs currently in use, opens the way to an additional therapeutic strategy, in accordance with current guidelines discussed during this important international symposium", states Dr Antonella Riva, senior researcher at Indena.

This work is fruit of collaboration between Italian and American institutes such as *Rome's Catholic University of the Sacred Heart*, the *Istituto Nazionale dei Tumori* in Milan, the *Roswell Park Cancer Institute* in Buffalo and New York's *Stony Brook University*.

The results of these studies are yet further proof of the successes obtained by Indena research into cancer therapies derived from the Yew Tree. The Italian company has made possible the manufacture of paclitaxel on an industrial scale and is today recognised by the American FDA as one of the major producers. Their recently discovered anti-cancer molecule IDN 5109 has led to a new licensing agreement with Bayer.

"For us in Indena these studies confirm a commitment which we intend to maintain," comments Chief Executive Dario Bonacorsi. "Emphasis is firmly placed on research into new active principles for the cancer therapies which can then be licensed to large drug companies. And it is thanks to the great work of our researchers that we can take up this challenge".

REDUCTION OF MENOPAUSAL SYMPTOMS WITHOUT USE OF OESTROGENS: THE EFFICIENCY OF A PARTICULAR SOY EXTRACT IS SCIENTIFICALLY DEMONSTRATED

Milan, August 1st 2002 - The Italian company, Indena, which researches and produces active plant principles and extracts, has undertaken pharmaco toxicological and clinical studies to explore the effectiveness of its soy extract, Soyselect.

Soyselect is a special patented extract characterised by a double standardisation of isoflavones (13-17%) and saponins (25%). Two clinical trials on Soyselect, carried out at the Policlinico Gemelli in Rome, and at the Columbia Hospital in New York, have been published in the scientific journal *Menopause*. The two studies mentioned represent today the only clinical studies on a standardised Soy extract performed according to the double blind, randomised, placebo-controlled method. These evaluations have proved the excellent clinical effect of Soyselect, which, after a six-week treatment, reduces all menopausal symptoms by 45%. These results are in line with epidemiological data, which highlight in certain oriental populations, including the Japanese, a lower incidence of symptoms related to menopause and post-menopause. Responsible for these differences is the soy enriching the oriental diet. Indena therefore, set out to test the efficacy of these active principles with pharmaco toxicological and clinical methods, thereby corroborating the epidemiological data.

In the clinical study conducted by Indena in conjunction with Policlinico Gemelli, a progressive diminution of the number of hot flushes per week was recorded. During the 6 weeks in clinic, 39 women in menopause, divided randomly in two groups, were administered 50 mg/day of soy isoflavones and placebo. The diminution of hot flushes was significantly greater in the group treated with Soyselect compared with those receiving placebo while no aspecific or correlated side-effect was found with regard to oestrogens. It was concluded that treatment with Soyselect is well-tolerated and effective against climacteric symptoms and may be recommended for women who cannot undergo hormone therapy.

The efficacy of Soyselect is guaranteed due to the presence of two different specific molecular classes: the isoflavones and the saponins. Isoflavones are able to imitate some of the biological effects of oestrogens on menopausal and post-menopausal complaints without any simultaneous increase in neoplastic risk. Thanks to their ability to lower cholesterol, saponins are an effective instrument in preventing cardiovascular damage and, administered orally, are an excellent vehicle for the isoflavonic component.

Soyselect may be a safe and efficacious therapy for relief of menopausal symptoms in women who refuse or have indications for not using HRT. In consideration of its high degree of innovation, the Indena product has applied for the Italian patent and an international extension in the USA, Japan, Canada and Australia.

¹ Published in *Food and Chemical Toxicology* 37 (1999) 493-502 and *Breast Cancer Research and Treatment* 69 (2001) 153-164

² Published in *Menopause: The Journal of the North American Menopause Society* Vol 7, No. 2 (2000) 105-111; Vol 7, No. 4 (2000) 236-242

Understanding the Implications of the EU Traditional Herbal Medicine Directive: Indena shows the way in London

Indena sets out the importance for Higher Quality of Botanical Raw Materials

Milan, April 19th 2002 - The Royal College of Physicians in London's Regent's Park was the prestigious setting for a one-day seminar, 'Meeting the Challenge of the Traditional Herbal Medicine Directive', organised under the auspices of The Council for Responsible Nutrition (CRN) and co-sponsored by Indena, a leading company in the identification, development and production of botanical derivatives. The meeting, which took place on April 16th, was attended by over 100 people including representatives of the Medicine Control Agency (MCA) and members of major UK herbal product manufacturers.

Opening the proceedings, CRN Vice-Chairman Anthony Bush said the objective was "to raise awareness of the implications of the directive amongst UK Herbal Product manufacturers and marketers, and to have them register their unlicensed products under the new regulations". Two Indena delegates, Scientific Director Paolo Morazzoni, together with Valerio Bombardelli, Head of Regulatory Affairs, illustrated the company position, pointing out the importance of a clear directive for the regulation and Quality Control of Raw Materials and illustrating the fundamental aspects required to comply with current EU legislation as well as with Pharmaceutical GMPs.

Indena underlined the importance of a clear set of rules for the regulation of Raw Materials, which form the basis of Traditional Herbal Medicine. In fact, as GMPs must be granted for the manufacturing of finished products (tablets, packaging), they must be applied, upstream in the production of botanical raw materials. By not implementing, in fact, quality controls and standardization of Botanical Raw materials, the resulting final product is debatable from a quality point of view, since the compounds it contains are not certain. For this reason it is extremely important to apply the same GMPs to Botanical Ingredients. Paolo Morazzoni showed how standardisation measures in the Manufacturing and Quality Control Processes of Raw Materials could guarantee a reproducible quality of botanical extracts. Standardisation was a hard task, he affirmed, but only highly standardised extracts, in terms of reproducibility, could compete with pure pharmaceutical compounds. Comprehensive checks during the production process are required to reach high quality standards. These include: establishing validated standard operating procedures to cover plant taxonomic identification, seeding and plant cultivation in accordance with Good Agricultural Practices (GAPs), and processing in line with Good Manufacturing Practices (GMPs), in-process controls.

The final botanical extract is then extensively tested. Every step of the procedure, from the initial GAP-compliant bio-mass, its chemical isolation and the characterisation of the active reference compounds, to the setting-up of validated analytical methods, and finally to the GMP approved production, leads to a product that is reproducible in terms of active ingredients and/or chemical markers.

Valerio Bombardelli highlighted different aspects of the European approach to the registration of herbals as pharmaceutical products, based on a proposal for a "traditional use directive".

Under this proposal, the quality data will be submitted, as for any other medicinal product, while the safety and efficacy data are waived on the basis of 30 years of "safe usage". "The EU pharmaceutical legislation is designed to register pure chemical compounds as medicines", says Dr Bombardelli, "for this reason it is very difficult to obtain marketing authorisation for an herbal extract and so far only six herbal medicinal products have been successfully licensed under the mutual recognition procedure." The Traditional Herbal Medicine Directive should avoid any confusion with the Well Established Use Directive".

Indena's strength in this field is based on skills acquired through their 80 years of experience in botanical derivatives. Indena already offers advice and consultancy on the quality and safety of botanical extracts in the US and Japan and it would be pleased to do so also in EU.

INDENA U.S.A. FREE OF PATENT INFRINGEMENT SUIT

United States Appeals Court dismisses

International Nutrition Company's patent infringement suit against Indena U.S.A.

Seattle, February 15th 2002 - The United States Court of Appeals for the Federal Circuit has affirmed a decision by the United States District Court for the District of Connecticut dismissing the patent infringement suit brought by International Nutrition Company against Indena U.S.A..

INC had alleged in that lawsuit that Indena U.S.A. was infringing United States Patent No. 4,698,360 concerning methods of preventing and fighting the harmful biological effects of free radicals in humans by administering a plant extract containing proanthocyanidins.

The Federal Circuit held that INC had no right to sue Indena U.S.A. for infringement because INC had no ownership interest in the patent. The Federal Circuit's decision was partially based on a French Court decision invalidating an alleged assignment of a co-ownership interest in the patent to INC from Société Civile d'Investigations Pharmacologiques d'Acquitaine (SCIPA), an alleged co-owner of the patent. Moreover, the Federal Circuit stated that even if INC were a co-owner, the lawsuit would not be proper because Horphag Research LTD, another co-owner of the patent, had refused to join the lawsuit as required by United States patent law.

INDENA'S SABALSELECT® CHOSEN FOR NIH SPONSORED CLINICAL TRIALS

The high quality of Indena's herbal products supported by their employment in American clinical trials

Milan, January 30th 2002 - Indena has been chosen as the supplier of saw palmetto extract - Sabalselect® - for the first large clinical trial of this herbal product to take place in the United States. Investigators at the University of California, San Francisco, supported by the National Institutes of Health, will examine the effect of saw palmetto on urinary symptoms in men with moderate to severe Benign Prostatic Hyperplasia (BPH). The employment of Indena's extract in clinical trials suggests the high-quality standards pursued and developed by the company for all herbal products and proceeding from its accurate extraction and manufacturing operations.

According to Project Director Stephen Bent, Assistant Professor of Medicine at UCSF *"Evidence from smaller trials conducted in Europe suggests that there may be a substantial benefit, similar to that found with prescription drugs without some of the troubling side effects."* Dr. Bent also notes that there is *"a clear need to clarify the treatment efficacy and safety of commonly used herbal remedies in order to allow patients to make informed decisions about using them."* He believes that *"the specific products that are tested in clinical trials are the ones consumers should choose, rather than untested brands with uncertain composition and efficacy."*

After over a year of careful planning and preparation, the clinical trial is now open for enrollment and will be underway at the San Francisco VA Medical Centre. Over a hundred patients have been screened for eligibility and interest, and the first set of patients randomly assigned to saw palmetto or placebo capsules. During the next year, the investigators hope to enroll 224 patients for observation over the ensuing 12 months, whilst the study should be completed by the end of 2003.

Saw Palmetto (*Serenoa repens*) is a small palm tree with large leaves and deep red berries, grown in the United States. The fruits of *Serenoa repens*, have been used for a long time in the preparation of alcoholic, hydroalcoholic and oily extracts, that are used in the treatment of pathological conditions connected with benign prostatic hyperplasia. In recent years, mostly in Europe, Saw Palmetto extracts have been extensively researched in the treatment of BPH. In countries such as Italy, Germany, France and Spain, where ethical specialities containing *Serenoa repens* are registered, phytotherapy now represents the first-line therapeutical option and one of the most widely used active principles to treat BPH. Currently, in the United States phytotherapeutical agents are available as non-prescription dietary supplements.