

## Short Ardox-X® technology information

### General

Oxygen is the source of life. Until recently the only medically documented method for increasing oxygen was by enclosing patients in hyperbaric oxygen chambers. Hyperbaric oxygen therapy has been used all over the world. High concentrations of oxygen into the human tissue are pharmaceutically beneficial and have healing properties. The drawback is that the chambers are costly, technically not easy to handle and as such only available to few patients.



Besides molecular oxygen O<sub>2</sub>, its active form has enhanced pharmaceutical behaviour and can be formulated in patient friendly applications like all sorts of liquid and solid state preparations: balm, cream, gel, rinse, powder formulations etc.

### Common used oxygen donors

The most common used active oxygen donors are (carbamide) peroxides which liberate oxygen radicals/hydroxyl radicals (O· and ·OH). These oxygen radicals are damaging species. For this reason cosmetic manufacturers add Vitamin C and E to skin crèmes: to capture the free oxygen radicals penetrating the skin from the atmosphere. These radicals create skin damage and will lead to accelerated skin aging. As these oxygen radicals are highly effective, BUT severely damage the skin tissues, form toxic substances and damage the DNA, they cannot be applied in pharmaceutical and OTC products.

## **New Safe Ardox-X® technology**

Ardoz was successful in the stabilisation of active oxygen in liquid and solid state applications opening doors for massive use of cosmetic, medical device and pharmaceutically active safe oxygen applications. The Ardox-X® complex consists of a suitable oxygen donating compound (as described in patent WO 2006/038802) with specific carriers as mentioned in the patent like i.e. glycerol and cellulose. Together with specific stabilizers and modulators, these complexes have the benefit that they can act more specifically on target sides. Because of the nature of these complexes, there will be less tendency to form molecular oxygen when the complex decomposes, compared to the decomposition of hydrogen peroxide. This means that much lower concentrations of the oxygen donor can reach the same results as is the case with hydrogen peroxides in some important applications. Furthermore, one can, by choosing specific stabilisers and carriers in an application, increase the oxygen concentration and control the release time of the active oxygen (fast vs. slow release). When a product, in which the Ardox-X® complex is present, is applied on the skin or in the oral cavity, the complex will be disrupted (due to excessive saliva, enzymes, transepidermal waterloss (TEWL), pH) and active oxygen in a non-radical character hence, anionic types of oxygen species are released. The latter are safe and do not have the damaging behaviour of the free radical species generated by hydrogen peroxide. The benefit of these “soft” active oxygen species is that they can be used for many cosmetic, medical device and pharmaceutical indications without harming the tissue or cells in any way. Indications: tooth bleaching, daily antibacterial dental applications (toothpaste, mouthwash), oral mucositis, periodontitis, implantology, bonegrowth, diabetes ulcera, psoriasis, eczema, onychomycosis, tinea pedis.

The Ardox-X® complex is stable in an aqueous composition in the package (balm, cream, shampoo, gel etc) but also in powder formulations.

The mechanism of action of the Ardox-X® active complex is based on an active oxygen donating system, which increases the oxygen content in tissue leading i.e. to whitening, anti-bacterial, anti-fungal, promotion of woundhealing, anti-inflammatory and others actions.

## Some publications and reports:

Since several new patents, filed by the company, are still in the confidential phase, a defensive publication strategy at this time is followed. However, the following three publications have been performed at the IADR 2006 in Brisbane concerning some studies on the Ardox-X® complex by the Queens University, Belfast School of Clinical Dentistry:

1. Bleaching of Tooth Discolouration Compounds by Peroxoborate-Glycerol Ester Adducts (Dr. K. Julian, Prof. M. Grootveld, Dr. C. Silwood, Dr. J. Blackburn and Prof. E. Lynch)  
*Conclusion: Peroxoborate- esters are effective in bleaching melanoids, by oxidative transformation.*
2. <sup>1</sup>H NMR Investigations of the Oxidising Actions of Dentifrices containing Peroxoborate-Glycerol Esters (Prof. E. Lynch, Prof. M. Grootveld, Dr. C. Silwood and Dr. J. Blackburn)  
*Conclusion: <sup>1</sup>H NMR technique is a valuable tool to investigate the oxidising capacity of Peroxoborate-ester adducts to certain amino acids, the precursors of VSC's and human salivary biomolecules like pyruvate.*
3. Multicomponent B-11 NMR Analysis of Novel Peroxoborate-Containing Tooth Whitening Formulations (Dr. C. Silwood, Prof. M. Grootveld, Prof. E. Lynch). *Conclusion: Analysis of Peroxoborate-ester adduct shows the negligible formation of borate [B(O<sub>2</sub>H)<sub>3</sub>(OH)] and boric acid [B(OH)<sub>3</sub>], revealing the formation of Peroxoborate-glycerol/CMC esters as seen on TES-051005-01-1001 a non interfering mixture on the <sup>11</sup>B-NMR signal.*

Prof Yiming Li, long term adviser of the American Dental Association (adviser of the FDA), Loma Linda University, California, has published the following study concerning the Ardox-X® technology:

4. "Cytotoxicity and Mutagenicity of a non-peroxide based tooth whitening gel" (Prof. Y. Li in co-operation with Dr. W. Zhang and Dr. J. Jang) *Conclusion: The whitening gel based on Ardox-X is not mutagenic and does not impose risks associated with cytotoxicity.*
5. "Peroxide Content and Free Radical Generation by OT7051"( Prof. Y. Li in co-operation with Dr. W. Zhang, Y. XU, J. Davis and J. Klaunig) *Conclusion: The whitening gel does not contain or produce hydrogen peroxide and it generates negligible amounts of free radicals that is significantly lower than that detected in a 10% carbamide peroxide bleachinggel*

6. Effect of various reactive oxygen donors on DNA damage (Prof Y. Li (USA) & Prof F. Ramaekers (The Netherlands)) Report also issued to the European Union for evidence of damaging effect of peroxides and safety of Ardox-X®. *Conclusion: The Ardox-X® technology shows very limited DNA damage in cells treated with relatively high concentrations of the product. Hydrogen peroxide and carbamide peroxide showed a clear DNA-damaging effect, which resulted in cellular necrosis.*

A review article on clinical test with Ardox-X® technology based products performed at dental clinics and hospitals in the Netherlands on the indications periodontitis and peri-implantitis has been submitted:

7. Ardox-X® topical active oxygen application in periodontitis and peri-implantitis –a pilot study (Berendsen JLM, el Allati I, Sylva LH, Blijdorp PA, Meijer GJ; Different dental clinical centres, Department of Periodontology & Biomaterials and Oral & Maxillofacial Surgery, Radboud University Nijmegen). *Conclusion: From the case control periodontitis study results could be concluded that adjunctive Ardox-X® yielded better average total pocket depth reduction percentages(56%) than generally reported in the literature for other treatment strategies like current goldstandard chlorohexidine treatment (4,2%). From the Ardox-X® protocol peri-implantitis study results could be concluded that the clinical situation around implants improved markedly within 3 to 6 weeks in all cases. After 3 months, 75% of cases were clinically cured. Radiographically evidenced re-osseointegration of 2mm could be noted in 60 % and of 3 mm in 15 % of cases after 6 months. These figures are indicative for faster and better pocket and peri-implantitis healing than reported in the literature for the generally accepted– ‘gold standard’ – adjunctive treatment regimens.*

There are several Ardox-X® based products in the markets under Cosmetic (1223/2009/EG) and Medical Device (93/42/EC) directives.