DEBIO PHARM
developing innovative therapeutics

# *PRESS RELEASE*

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**FOR IMMEDIATE RELEASE**

## DEBIOPHARM S.A. ANNOUNCES A PATENT APPLICATION ON A HYDROSOLUBLE PRODRUG OF CYCLOSPORIN A

Lausanne, Switzerland, November 19, 2002 -- Debiopharm S.A. today announced the publication of an International patent application relating to a prodrug of cyclosporin A, a promising product for the local treatment of immune ocular disorders, especially those inducing keratoconjunctivitis sicca, also known as dry eye syndrome.

Cyclosporin A is effective in a number of ocular immune pathologies. However its systemic administration induces severe renal and cardiovascular complications that could be prevented by a local ocular application of the drug. The highly hydrophobic properties of the molecule require that, for topical administration, the formulation of native cyclosporin A be included in different vegetable oils, thus resulting in a poor local tolerance by the patient. Because of its beneficial properties, cyclosporin A has been widely studied in various ocular disorders such as dry eyes, but it remains to be successfully developed for topical application in ophthalmology.

Debiopharm S.A. has initiated an extensive screening program to select a hydrosoluble prodrug of cyclosporin A, capable of delivering the mother compound when in contact with the enzymes normally present in tears. The local release of cyclosporin A will eliminate the severe systemic side effects associated with its oral administration. This screening program has allowed Debiopharm to successfully select a lead compound. The latter, a highly hydrosoluble molecule, releases cyclosporin A minutes after its topical ocular administration in experimental models such as the rabbit. This results in local ocular therapeutic concentrations of cyclosporin A in the tears of the animal.

According to Dr. R.-Y. Mauvernay, founder and CEO of Debiopharm, **"**Currently, there is a serious unmet need for an effective therapy for dry eyes and the results we have so far point to a very promising product. Since cyclosporin A has been widely studied in this field, we believe that our chances of success are high. The advantage of our product is that it will help patients while providing them with improved comfort and higher observance of treatment. We intend to conduct additional proof-of-concept studies and bring the product to Phase I, then to license this product out to a pharma partner with expertise in the ophthalmology field.**"**

Topical cyclosporin A indications include among others, prevention of corneal graft rejection, ocular surface inflammatory diseases with an autoimmune component such as Sjögren disease, vernal conjunctivitis, and peripheral ocular rheumatoid ulceration. However the most important indication is represented by what is known as keratoconjuncitivits sicca (or "dry eye disease"), where a major autoimmune component appears during the course of the pathology.

Dry eye disease is a painful, burning and irritating condition affecting approximately 10 million people in the US, and a sizeable proportion of the population in other parts of the world. The disease has many causes, however it is often a result of the normal aging process. It is estimated that nearly 75% of people over the age of 65 will experience dry eye syndrome. Symptoms can be alleviated temporarily with artificial tears, however to this day there is no approved, pharmacologically active treatment for this common condition.

Another potential of a hydrosoluble prodrug of cyclosporin A is for intravenous administration, which is indicated for the prophylaxis of organ rejection after transplantations. Debiopharm S.A. has shown experimentally that there is an immediate release of cyclosporin A in the blood after an administration of a simple aqueous solution of the prodrug. Current intravenous formulations of cyclosporin A include cremophor, an excipient that complicates its use as well as adding toxicity problems. These can be avoided by the prodrug.

Debiopharm, Debio R.P. and Debioclinic are an established and proven group of three synergistic and complementary companies, that have a successful track record in developing, registering and bringing to the market new chemical entities both in Europe and in the United States. Products successfully registered and launched include oxaliplatin for advanced colorectal cancer and triptorelin pamoate for prostate cancer, both market leaders in their therapeutic areas. Specialized in oncology, hormonal and niche products for serious medical conditions, Debiopharm is a partner of research institutions, pharmaceutical and biotechnology companies who seek to develop and register their drugs. Debio R.P., Debiopharm's sister company, is a leading world player in the research, development and manufacturing of polymer-based controlled release injectable formulations for peptides and proteins, including proprietary technologies suitable for other therapeutic modalities such as soluble polymer cytotoxic-drug conjugates for parenteral administration. Debio R.P. also carries out scale-up under current good manufacturing practice (cGMP) and has an FDA-inspected plant. Debioclinic, the third Debio company, is a contract research organisation fully dedicated to clinical development.

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