European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 19 March 2009
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
MODIGRAF

International Nonproprietary Name (INN): ***tacrolimus***

On 19 March 2009 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Modigraf, 0.2 mg and 1 mg granules for oral suspension intended for: "Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients."
The applicant for this medicinal product is Astellas Pharma Europe B.V.

The active substance of Modigraf is Tacrolimus, a macrolide immunosuppressant medicinal product *(ATC Code:* L04AA05*)* that inhibits the activation of serine threonine phosphatase, calcineurin, in T-lymphocytes and thus, suppresses T-cell activation, and the subsequent generation of cytotoxic lymphocytes, thereby down-regulating processes leading to acute graft rejection. T-helper cell dependent B-cell proliferation is also affected.

The benefit with Modigraf is mainly that it offers an oral formulation of tacrolimus suitable for children and for seriously ill adults with difficulties to swallow capsules.
The most common side effects observed from the paediatric clinical trials are fever, infections and abnormal liver function tests. Other adverse reactions seen with the use of tacrolimus are renal impairment, glucose metabolism disorders and hypertension, although the adverse reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications. However, many of the adverse reactions are reversible and/or respond to dose reduction.
A pharmacovigilance plan for Modigraf, as for all medicinal products, will be implemented as part of the marketing authorisation.

The approved indication is: Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients."
It is proposed that Modigraf is prescribed by physicians experienced in immunosuppressive therapy and the management of transplant patients.

Detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SPC) which will be published in the European Public Assessment Report (EPAR) and will be available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that there is a favourable benefit to risk balance for Modigraf and therefore recommends the granting of the marketing authorisation.

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* Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion.

** Applicants may request a re-examination of any CHMP opinion, provided they notify the EMEA in writing of their intention to request a re-examination within 15 days of receipt of the opinion.

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