Atopic dermatitis is a chronic inflammatory skin disease characterized by recurrent intense pruritus and a distinctive distribution of skin lesions. The topical calcineurin inhibitors tacrolimus and pimecrolimus were approved in the USA, as an ointment and a cream, respectively, for the treatment of atopic dermatitis in 2000 and 2001, respectively. In 2005, the Pediatric Advisory Committee of the US FDA implemented a 'black box' warning for tacrolimus ointment and pimecrolimus cream due to the lack of long-term safety data and the potential risk of the development of malignancies. This article focuses on the safety aspects of these agents by discussing the findings from preclinical and clinical studies and postmarketing reports with regard to malignancies occurring after the use of tacrolimus ointment and pimecrolimus cream.