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

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Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of denileukin diftitox for the treatment of cutaneous T-cell lymphoma

On 11 December 2001, orphan designation (EU/3/01/075) was granted by the European Commission to Ligand Pharmaceuticals UK Ltd, United Kingdom, for denileukin diftitox for the treatment of cutaneous T-cell lymphoma.
The sponsorship was transferred to Esai Ltd, United Kingdom, in March 2007.

What is cutaneous T-cell lymphoma?
Cutaneous T cell lymphoma is a type of cancer of the lymphatic system localized in the skin. It belongs to a group of lymphomas called non-Hodgkin's lymphoma (there are more than 20 different types of non-Hodgkin's lymphomas). The lymphatic system is part of the body's immune system and helps fighting infections. It is a complex system made up of organs such as the bone marrow, the thymus (a gland behind the breast bone), the spleen (an organ in the abdomen near the stomach), and the lymph nodes (or lymph glands, located throughout the body), which are connected by a network of tiny lymphatic vessels. There are two main types of cells, which make up the lymphatic tissue. These cells are called lymphocytes and belong to the group of white blood cells. The two types are called B lymphocytes (B cells) and T lymphocytes (T cells). Most lymphocytes start growing in the bone marrow. The B cells continue maturing in the bone marrow, whereas the T cells go from the bone marrow to the thymus and mature there. Cutaneous T-cell lymphoma is a cancer of the T-lymphocytes and most often occurs in people aged between 40 and 60.
Unlike other forms of non-Hodgkin's lymphoma, cutaneous T-cell lymphoma mainly affects the skin. It is caused by the uncontrolled growth of the T-cells. Cutaneous T-cell lymphoma is a serious and life-threatening condition.

What is the estimated number of patients affected by the condition?
At the time of designation, cutaneous T-cell lymphoma affected approximately 0.74 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 28,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?
Treatments for cutaneous T-cell lymphoma include local treatment and systemic treatment. Local treatments include medicines applied to the skin, therapies using light of a particular wavelength (ultraviolet light) and x-rays. Systemic treatments include medicines such as glucocorticosteroids (a group of medicines derived from cortisone and that are also used as agents against itching), cytotoxic agents (medicines that kill cells), immunotherapy (using drugs that stimulate the body's own immune

[*]Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 377,000,000 (Eurostat 2001) and may differ from the true number of patients affected by the condition.

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system to kill the cancer cells) and photopheresis (white blood cells are modified by exposure to ultraviolet light). Several products were authorised for the treatment of cutaneous T-cell lymphoma within the Community at the time of submission of the application for orphan drug designation. Denileukin diftitox might be of potential significant benefit for the treatment of cutaneous T-cell lymphoma because it may act in a different way to other drugs. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?
Denileukin diftitox is a medicinal product, which combines parts of a human natural protein (interleukin 2) and a toxin (from the bacteri corynebacterium diphteriae). Interleukin 2 belongs to a group of small proteins, which bind on a specific receptor (proteins with a specific shape, able to recognise and bind specific molecules) on the cell surface. Following interleukin 2 binding to the receptor, certain biologic reactions are activated. In cutaneous T-cell lymphoma, the T lymphocytes carry this specific receptor for interleukin 2. Denileukin diftitox might therefore bind to the cancer cells through its interkeukin 2 part, and once linked to the cell surface, it could then release the toxin into the cancer cell. The toxin in the cell could result in the destruction of the cancer cell.

What is the stage of development of this medicine?
The effects of denileukin diftitox were evaluated in experimental models. At the time of submission of the application for orphan designation, clinical trials in patients with cutaneous T-cell lymphoma were ongoing.

Denileukin diftitox had a marketing authorisation in the United States for the "treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor" at the time of submission. Orphan designation of denileukin diftitox was granted in the United States for the same indication.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 26 October 2001 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal product designations are based on the following three criteria:
- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the Community) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

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Translations of the active ingredient and indication in all EU languages

Language	Active Ingredient	Indication
English	Denileukin diftitox	Treatment of cutaneous T-cell lymphoma
Danish	Denileukin diftitox	Behandling af kutant T-celle-lymfom
Dutch	Denileukin diftitox	Behandeling van cutaan T-cel-lymfoom
Finnish	Denileukiini diftitoksi	Ihon T-solulymfooman hoito
French	Denileukin diftitox	Traitement des lymphomes cutanés à cellules T
German	Denileukin diftitox	Behandlung von Patienten mit kutanem T-Zellen-Lyphom
Greek	Denileukin diftitox	Θεραπεία ασθενών που πάσχουν από δερματικό λέμφωμα εκ κυττάρων Τ
Italian	Denileuchina diftitotossina	Trattamento di pazienti affetti da linfoma cutaneo a cellule T
Portuguese	Denileukina diftitox	Tratamento do linfoma cutâneo das células T
Spanish	Denileukin diftitox	Tratamiento de linfoma cutáneo de células T
Swedish	Denileukin diftitox	Behandling av kutant T-cellslymfom