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PORTFOLIO AND PHARMACY

PHARMACOCLINICAL PROTOCOL FOR THE USE OF DUPILUMAB IN SEVERE ATOPIC DERMATITIS IN ADULT PATIENTS IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

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The experts who have participated in preparing this protocol (ordered alphabetically by first surname)**:**

Adriana Alvarez Nonay. Representative for Aragon

Montserrat Bosch Ferrer. Representative for the Spanish Clinical Pharmacology Society (SEFC)

Tomás Caro-Patón Carmona. Representative for Castilla y León

Gemma Garrido Alejos. Representative for Cataluña

Sagrario Garrido López. Representative for Castilla y León

León Montserrat Gasol Boncompte. Representative for Cataluña

Pedro Herranz Pinto. Representative for the Spanish Academy of Dermatology and Venereology (AEDV)

Milagros Lázaro Sastre. Representative for the Spanish Allergy and Clinical Immunology Society (SEAIC)

Emilio Monte Boquet. Representative for the Spanish Hospital Pharmacy Society (SEFH)

María Bibiana Pérez García. Representative for the AEDV

María Olatz Ibarra Barrueta. Representative for the SEFH

Antonio Luis Valero Santiago. Representative for the SEAIC

Coordinated by Nuria Aguilar Garcia Subdirectorate General for Quality of Medicines and Health Products. Directorate-General for the Basic Portfolio of Services of the NHS and Pharmacy.

Participant in designing the protocol for its implementation in VALTERMED: Juan Luis Moreno González. Subdirectorate General for Quality of Medicines and Health Products. Directorate-General for the Basic Portfolio of Services of the NHS and Pharmacy.

All the experts have made a conflict of interest declaration

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1. INTRODUCTION

Atopic dermatitis (AD) is a non-contagious inflammatory skin disease characterised by the presence of eczematous lesions, xerosis and intense pruritus. It is a chronic disease that occurs in outbreaks of varying duration and intensity, followed by periods of remission although, in some cases, the symptoms may be continuous. The clinical manifestations of the disease produce significant sleep disturbances, psychological and social impacts and have a significant impact on the quality of life of patients, especially in moderate and severe forms of the disease.
It occurs frequently in families with a history of atopic diseases such as atopic dermatitis, bronchial asthma and/or allergic rhinoconjunctivitis.

The severity of the disease can be defined based on different scales, which measure: the extent of the affected areas, the severity of the lesions and the subjective symptoms of the patient. The most widely accepted are:

-**SCORAD** (*Scoring Atopic Dermatitis,* score 0-103 points) - designed and approved by the *European Task Force on Atopic Dermatitis*. It evaluates the intensity and extent of the lesions and the patient's subjective symptoms; and,
-**EASI** (Eczema Area and Severity Index, score 0-72 points), it evaluates the intensity and extent of the disease, but does not include subjective symptoms.

Based on these scales, severe AD can be defined as: SCORAD >50 or EASI 21-50 (very severe >50-72).

Other scales used are:
- IGA/PGA- (*Investigator´s-Physician´s-Global Assessment*), scale 0 to 4 (cleared dermatitis=0, minimal=1, mild=2, moderate=3, severe=4) which takes into account erythema, papule formation and exudate; and,
-**NRS** *(Pruritus Numerical Rating Scale*) a numerical scale that measures the intensity of pruritus, with 0 indicating the absence of pruritus and 10 the highest intensity.

The standard treatment focuses on using topical anti-inflammatory drugs (corticosteroids, calcineurin inhibitors) and skin hydration, although patients severely affected by the

disease may require phototherapy or systemic treatment with conventional immunosuppressants or with biological agents.

It is generally agreed that patients with severe forms of AD (SCORAD>50) are candidates for systemic immunosuppressive treatment. According to the recommendations from expert panels, the decision to initiate systemic treatment should include an assessment of the severity of the disease and the patient's quality of life and at the same time consideration of the patient's general health status on an individual basis. In addition, compliance with topical treatment should be ensured, patient education should be provided and alternative diagnoses should be ruled out. If the severity of AD does not improve despite this, phototherapy may be considered before or at the same time as systemic immunosuppressive treatment.
The most widely used drugs include systemic corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The only systemic immunosuppressive therapy authorised in the EU for the treatment of severe AD is cyclosporine, which is considered the treatment of choice.

The following factors should be taken into account when considering the treatment of AD:

- AD is a chronic recurrent disease, which affects both the pediatric and adult population, and in certain cases can be disabling and have a high social-work impact.
- In most cases it is benign and has a good response to topical treatment. Therefore, a step-by-step approach to AD management is considered well justified. Thus, the management of AD continues to be essentially topical therapy, restricting the use of systemic immunosuppressive treatment to more severe cases or cases that do not respond to topical treatment.
- Cyclosporine is the only systemic treatment with a licensed indication for AD, with strong short- to medium-term evidence of efficacy, limited long-term data, extensive experience of use and a known safety profile.
- To date there is no evidence that any treatment is superior to cyclosporine in the treatment of AD requiring systemic immunosuppressive therapy.
- Dupilumab would be a treatment option in adult patients with severe atopic dermatitis refractory to topical medication who also have previous experience of use with cyclosporine and unsatisfactory response, or in whom cyclosporine use is not considered appropriate due to contraindication or intolerance.

In order to guarantee the equitable, safe and efficient use of the drug in the National Health System (NHS), as well as to be able to carry out patient monitoring and a long-term evaluation of the results obtained from treatment in real practice, it is necessary to establish a pharmacoclinical protocol and a pharmacotherapeutic monitoring register.

Collecting information in the register and analysis of the results will allow to address any remaining uncertainties after clinical trials.

2. TREATMENT OBJECTIVE

The objectives for the treatment of severe atopic dermatitis with dupilumab in adult patients refractory to topical medication who also have previous experience of cyclosporine use and unsatisfactory response, or in whom the use of cyclosporine is not considered appropriate due to contraindication or intolerance are to reduce symptoms (pruritus and dermatitis), prevent exacerbations and minimise the risks of continued use of immunosuppressive therapy.

3. PATIENT SELECTION CRITERIA

Patients with severe atopic dermatitis who **meet all the following criteria** are considered **candidates** for commencing treatment with dupilumab:

1. Age ≥ 18 years.
2. Eczema Area and Severity Index (EASI) ≥21
3. Physician global assessment (PGA/IGA) ≥3
4. Minimum body surface area involvement (BSA) ≥ 10%
5. Candidates for systemic treatment
6. Refractory to topical medication
7. With previous experience in using cyclosporine:
   - with an unsatisfactory response or,
   - when contraindicated.

Initiation of therapy should be carefully considered in patients with[a]:

[a] Populations excluded from the clinical trials. No data are available.

1. History of immunosuppression including history of invasive opportunistic infections (e.g. tuberculosis, histoplasmosis, listeriosis, aspergillosis, pneumocystosis, coccidiomycosis).
2. Infection (chronic or acute) requiring systemic treatment with antibiotics, antivirals, antiparasitic, antiprotozoa or antifungals in the 2 weeks before starting treatment.
3. History of HIV infection or HIV-positive serology, active hepatitis B or hepatitis C virus infection.
4. History of cancer within 5 years prior to initiating treatment, except completely treated cervical carcinoma in situ or completely treated and resolved non-metastatic basal cell or squamous cell carcinoma of the skin.
5. Severe concomitant diseases: uncontrolled diabetes, severe renal impairment (dialysis patient), cardiac failure NYHA III-IV, hepato-biliary involvement, active major autoimmune disease.
6. Active parasite infection.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH DUPILUMAB

The recommendations included in the summary of product characteristics should be taken into account.

The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection.

Concomitant medication

Dupilumab can be used with or without topical corticosteroids.

Corticosteroid therapy should not be abruptly discontinued; dose reductions should be made gradually and supervised by a doctor.

Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Live vaccines should not be administered during treatment.

Method of administration.

Dupilumab is administered by subcutaneous injection into the thigh or abdomen, avoiding the area about 5 cm around the navel. If someone other than the patient gives the injection, the upper arm may also be used.

It is recommended that the injection site be rotated with each administration. Dupilumab should not be injected into sensitive, damaged, bruised or scarred skin.

Special populations

Very limited data are available in patients with severe renal impairment and no data are available in patients with hepatic impairment.

There are limited data from the use of dupilumab in pregnant women. Dupilumab should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

It is not known whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision on whether to discontinue breast-feeding or discontinue dupilumab treatment should be made taking into account the benefit of breast-feeding for the child and the benefit of treatment for the mother.

5. OUTCOME VARIABLES (BASED ON OBJECTIVES INCLUDED IN THE PAYMENT-BY-RESULTS AGREEMENT)

Responders will be considered those patients who at 16 weeks meet the following results (both) and where these are maintained in the measurements at 24 and 52 weeks:

- ✓ Patients reaching EASI-50 from baseline and
- ✓ Reduction by ≥ 2 PGA points from baseline.

Patients who do not meet the above variables will be considered non-responders and their treatment will be discontinued.

Measurements will be made in week 16, 24 and 52 with a justified deviation of ±2 weeks.

6. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS Code[b]
- CIP/CITE Code[b:]
- NIF/NIE[b]
- Health Card No.[b]
- Medical Record No.:
- Sex[c]:
- Date of birth[c]:

Characterisation of the diagnosis of severe atopic dermatitis

BASELINE DATA (MANDATORY)

- Date of diagnosis of severe atopic dermatitis:
- Scale measurement date:
  - EASI Score
  - PGA/IGA Score (0-4)
  - BSA (%)
- Patient referred through compassionate use: (yes/no)
- Patient from clinical trial and with compassionate use: (yes/no)
- **Previous treatment** received
  - Topical medication (yes/no):
    - Date of last administration
  - Systemic medication:
    - Previous experience with ciclosporine: (yes/no)

    If the answer is yes (unsatisfactory/intolerance) Indicate date of last administration

    If the answer is no, explain reason: (contraindication/other),

[b] It is mandatory to fill in at least one of these fields.

[c] Required fields.

Prior to starting treatment, it must be ensured that the patient meets the clinical conditions for administration in accordance with funding criteria and the payment by results agreement.

- Other treatments **(OPTIONAL):**

Dupilumab administration (REQUIRED)

- Start date of treatment (first administration).
- Definitive discontinuation of treatment[d]: (yes/no)
  Causes for discontinuation (Serious side effects/Intolerance/Non-responder)
  Date of last administration:
  Discontinuation stage (0-16/ 17-24/ 25-52):
  Number of injections administered to date:

Dupilumab administration (OPTIONAL)

- Interruptions to treatment**:** (yes/no)
  Interruption/restart date:
  Reason:
  - Patient's decision
  - Adverse effects (not including definitive discontinuation of treatment)
  - Other

Concomitant treatments (OPTIONAL)

- Concomitant topical treatment**:**
  - Corticosteroids: (yes/no)
    - Start/end date
  - Calcineurin inhibitors: (yes/no)
    - Start/end date

[d] Problems related to intolerance or serious adverse effects leading to definitive discontinuation of treatment must be reported. These problems should be exclusively and unequivocally correlated with the drug.

Response evaluation at 16±2 weeks after initiation of treatment

COMPULSORY.

- Scale measurement date:
  - EASI Score — EASI-50: (yes/no)
  - PGA/IGA Score (0-4) — Reduction: ≥2 points (yes/no)

If deviation by ±2 weeks, justification: (no appointments available / no-show / holidays or public holidays/other)

Response evaluation at 24 and 52 (±2) weeks after initiation of treatment

COMPULSORY.

Minimum mandatory criterion maintaining the response obtained at week 16 and 24 respectively

- Scale measurement date:
  - EASI Score
  - IGA Score (0-4)
  - Maintenance/improvement over previous tranche: (yes/no)

Response evaluation every 24 weeks from week 52 (OPTIONAL)

- Scale measurement date:
  - EASI Score
  - IGA Score (0-4)

Safety continuous safety monitoring will be performed and recorded whenever relevant in VALTERMED, specifically for serious adverse events leading to definitive discontinuation of treatment. In particular, the following must be recorded:

- Conjunctivitis, ocular pruritus or blepharitis
- Other ocular disorders
- Herpes simplex virus skin infections
- Eosinophilia (absolute eosinophil count≥500mcL)
- Headache

- Cancer
- Cardiac disorders
- Central nervous system disorders
- Haematological disorders
- Any other treatment-related adverse reactions such as respiratory tract, urinary tract, digestive tract infections

In addition, all suspected adverse reactions will be reported through the appropriate regional pharmacovigilance centre (www.notificaram.es).

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