





## UPDATE ON MANAGEMENT OF ATOPIC ECZEMA

-  Atopic eczema (AE) is a common chronic inflammatory skin condition which can have a significant negative impact on quality of life
-  Topical therapies, which include emollients, topical corticosteroids and topical calcineurin inhibitors are the mainstay of mild to moderate AE therapy
-  Emollients improve epidermal skin barrier dysfunction and should be used even when the AE appears to be quiescent
-  Secondary infection should be considered in patients who do not respond to topical therapy

### INTRODUCTION

Atopic eczema (AE), also known as atopic dermatitis, is a chronic inflammatory skin condition that is characterised by intense itching, dry skin and recurrent erythematous lesions.<sup>1-3</sup> AE has a prevalence of up to 20% in children and up to 3% in adults.<sup>1,3-5</sup> **Although it can present at any age, up to 85% of patients are symptomatic before 5 years of age.**<sup>1,4,6,7</sup> AE generally presents as an episodic disease with repeated flare-ups, however it may also be continuous.<sup>1,6</sup> Although AE greatly improves or resolves by late childhood in the majority of patients,<sup>1,6</sup> **recent evidence suggests that the prevalence of persistent or adult-onset disease is higher than was previously considered.**<sup>1,6,7</sup> Early onset of AE is associated with persistent and more severe disease.<sup>4</sup>

Patients with AE have an increased risk of other atopic diseases such as asthma or allergic rhinitis;<sup>1,4,6</sup> however this increased risk is lower than previously assumed as recent evidence suggests that only 1 in 3 individuals with AE develop asthma.<sup>1</sup> Patients with severe AE are also at increased risk of other disorders such as attention-deficit hyperactivity disorder, depression and anxiety.<sup>1,8</sup> Even though AE is mild in up to 80% of patients, **it can have a significant negative impact on quality of life** for children and their parents and carers, due to itch, sleep deprivation and social embarrassment.<sup>1,3,6</sup> The effect of AE on health-related quality of life is thought to be similar to that of other major childhood disorders such as asthma and diabetes.<sup>1</sup>

This bulletin (which updates a previous bulletin) outlines the current approach to the management of AE.

### PATHOPHYSIOLOGY

The pathophysiology of AE is incompletely understood and includes a combination of genetic susceptibility and environmental factors.<sup>4,9,10</sup> **Key components are epidermal barrier dysfunction and cutaneous inflammation due to heightened immune response.**<sup>1,4,10</sup> The epidermal barrier is made up of structural proteins (including filaggrin [FLG]), whose role is to prevent water loss and penetration of environmental antigens, irritants and microbes.<sup>10</sup> **Gene mutations** for FLG, and other epidermal proteins, have been identified which predispose patients to epidermal barrier dysfunction, potentially allowing increased exposure to antigens.<sup>1,4,9</sup> However not all patients with AE have a FLG mutation and 60% of patients carrying the FLG mutation do not have an atopic disease.<sup>1</sup> The strongest risk factor for AE is a **positive family history** for atopic disease.<sup>1</sup> **Environmental risk factors** include western diets, small family size, high education level and living in urban settings.<sup>1</sup> It has been postulated that genetically susceptible individuals with environmental risk factors develop epidermal dysfunction on exposure to antigens such as soaps, detergents and exogenous proteases (e.g. from mite allergens).<sup>1,4,10</sup>

The immune response, which leads to cutaneous inflammation, is predominantly T-helper-2 (Th2) cell mediated, resulting in over-expression of interleukins (IL), which leads to an increased production of IgE and peripheral eosinophilia.<sup>4</sup>

### CLINICAL FEATURES AND DIAGNOSIS

Patients with AE present with pruritic (itchy), dry skin with varying degrees of erythema resulting in inflammatory patches and papules.<sup>1,9</sup> As the disease becomes chronic, lichenified (thickened) plaques occur due to persistent inflammation and scratching.<sup>9</sup> The distribution of lesions often follows a pattern based on age as shown in table 1.<sup>9,10</sup> Eczematous lesions do not generally present before the second month of life.<sup>1</sup> **Various triggers** may provoke disease flares including food, contact allergens, detergents, wool, fabrics, extremes of temperature and humidity, food, teething, infections, cutaneous microbial colonisation and psychological stress.<sup>1</sup>

**Table 1: Typical clinical appearance of atopic eczema at different ages**<sup>1,9,11</sup>

<b>Infants up to 2 years</b>
<ul style="list-style-type: none"> <li>• Dry skin, pruritic erythematous papules and vesicles on cheeks, forehead or scalp (may be exacerbated by teething)</li> <li>• Rash may extend to trunk and extensor surfaces of the limbs; napkin area is typically spared</li> <li>• Significant oedema of affected areas leading to oozing and crusting not related to secondary infection</li> </ul>
<b>Children aged 2 years up to puberty</b>
<ul style="list-style-type: none"> <li>• Dry skin, less likely to have exudative lesions seen in infancy; lichenified papules and plaques</li> <li>• Typically involvement of hands, feet, wrists, ankles, and flexures</li> </ul>
<b>Adolescents and adults</b>
<ul style="list-style-type: none"> <li>• Dry skin, often present with lichenified and excoriated plaques at flexures, wrists, ankles and eyelids</li> <li>• Head and neck involvement may also affect the upper trunk, shoulders and scalp</li> <li>• Weeping, crusting and exudation may occur but usually as a result of secondary infection</li> </ul>

**The diagnosis of AE is clinical based on the patient's history, characteristic clinical findings and exclusion of other dermatological conditions.**<sup>4,12,13</sup> The history should include questions on 1) the time of onset, pattern and severity of the AE, 2) potential trigger factors such as irritants (e.g. soaps and detergents), skin infections, contact allergens, food allergens and inhalant allergens, 3) the response to previous and current treatments, 4) the impact

of AE on the patient and 5) personal/family history of atopic diseases.<sup>6,14</sup> There are a number of diagnostic criteria for AE; the **UK Working Party diagnostic criteria** are the most widely used – see table 2.<sup>1,4,6</sup> In the majority of patients, the diagnosis is made exclusively on clinical features and investigations are unnecessary; elevated IgE levels may be seen in up to 80% of patients with AE, but it is not a specific test for AE and is not routinely indicated.<sup>4</sup>

**Table 2: UK Working Party diagnostic criteria for atopic eczema<sup>4,6</sup>**

<b>Patients must have a history of itchy skin plus at least 3 of the following:</b>	
•	Visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees (or visible dermatitis on the cheeks and/or extensor areas in children ≤ 18 months)
•	Personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children ≤ 18 months)
•	Personal history of dry skin in the last 12 months
•	Personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative if the patient is <4 years)
•	Onset of signs and symptoms <2 years (this criterion should not be used in children <4 years)

**Differential diagnoses:** AE should be differentiated from other common dermatological conditions, shown in table 3. **Patch testing (to exclude allergic contact dermatitis) may be useful in patients with difficult to control AE**, however it is not routinely indicated.<sup>4</sup> **Atypical presentations of AE require further evaluation**; for example, adult onset eczematous lesions, which are poorly responsive to topical treatment (to exclude cutaneous T cell lymphoma), and infants with severe extensive eczematous lesions associated with recurrent infections (to exclude Hyper IgE syndrome [pustular and eczematous rashes within first weeks of life, recurrent pneumonia, eosinophilia and high IgE levels], and Wiskott-Aldrich syndrome [X linked recessive disorder, occurs predominantly in boys with a clinical triad of microthrombocytopenia, eczema and recurrent infections]).<sup>1,10,13</sup>

**Table 3: Common differential diagnoses to consider in patients<sup>1,4,9</sup>**

Condition	Main age group	Characteristics and clinical features
Seborrhoeic eczema	Infants	Characteristic non-pruritic greasy scales; often on the scalp and napkin area; usually presents in first 6 weeks of life and clears within weeks
Seborrhoeic eczema	Adults	Erythematous patches with yellow, white or greyish scales in seborrhoeic areas, especially the scalp, central face and anterior chest
Nummular (Discoid) eczema	Children and adults	Coin-shaped scaly patches, mainly on the legs and buttocks; may or may not be associated with itch
Irritant contact dermatitis	Children and adults	Acute to chronic eczematous lesions, mostly confined to the site of exposure (common in napkin area); typically less pruritic than AE; might coexist with AE
Allergic contact dermatitis	Children and adults	Well-circumscribed erythematous rash with maximum expression at sites of direct exposure; lesions usually more pruritic than AE; might coexist with AE
Asteatotic eczema	Adults	Scaly, fissured patches of dermatitis overlying dry skin, most often on lower legs
Psoriasis	Adults and children	Well defined red and scaly plaques, typically affecting extensors in adults, may also affect nails, scalp, umbilicus and genital area, may be joint involvement
Dermatophyte infection	Children and adults	One or more demarcated scaly plaques with central clearing and slightly reddened edge; variable itch
Impetigo	Children	Demarcated erythematous patches with blisters or honey-yellow crusting
Scabies	Children	Itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia; might produce secondary eczematous changes

AE can be classified according to clinical severity (see table 4).

**Table 4: Severity of atopic eczema<sup>6</sup>**

Severity of skin presentation	
Clear	Normal looking skin and no itch, no evidence of active atopic eczema
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)

**Complications: Due to an impaired skin barrier, patients with AE are at risk of secondary infection** with bacteria, viruses and fungi.<sup>10</sup> *Staphylococcus aureus* colonises up to 90% of AE patients compared with 5% of healthy individuals;<sup>1,10</sup> this colonisation leads to infection and impetiginisation of lesions. **Signs and symptoms of secondary bacterial infection** include weeping and crusting of lesions, pustules, AE failing to respond to therapy, rapidly worsening AE, and rarely fever and malaise.<sup>6</sup> **Eczema herpeticum** is a severe skin infection with herpes simplex virus that occurs in up to 3% of AE patients, particularly in severely affected patients.<sup>1</sup> Patients present with symptoms and signs including 1) areas of rapidly worsening and painful AE, 2) clustered blisters consistent with early-stage cold sores, 3) punched out erosions usually 1 to 3 mm in diameter that are uniform in appearance (these may coalesce to form larger areas of erosion with crusting) and 4) possible fever, lethargy or distress.<sup>6</sup> Children and adults with AE also have an increased susceptibility to **molluscum contagiosum infection**.<sup>1</sup>

## MANAGEMENT OF ATOPIC ECZEMA

**The management of AE should be individualised to each patient, and the patient/carer should be involved in the decision making process.**<sup>1,6,13,14</sup> The main principles of treatment are: 1) continuous epidermal barrier repair with emollients, 2) avoidance of trigger factors and 3) anti-inflammatory therapy with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI). Severe cases of AE may require systemic therapy, however optimisation of topical therapy is required before considering systemic therapies.<sup>1,15</sup> **Education is important:** patients (and/or parents/carers) should be provided with information (in verbal and written format), which includes: 1) the quantity of treatment to use, 2) how often to apply the treatment, 3) when and how to step treatment up or down, 4) how to recognise and manage flares 5) how to recognise infected AE (in particular eczema herpeticum) and 6) advice on how to access treatment for infection.<sup>1,3,6,14,16</sup>

## Non-pharmacological Management

Good communication between healthcare professionals (HCPs) and the patient (and/or parents/carer) is essential as treatment failure due to poor adherence is common.<sup>1,6,14</sup> Bathing with water hydrates the skin however application

of emollients soon after bathing is required to maintain hydration.<sup>17,18</sup> There is an absence of good quality evidence to date to show the optimum frequency of bathing.<sup>3,6</sup> The effectiveness and safety of therapies such as homeopathy, massage, evening primrose oil and food supplements for the management of AE have not been adequately assessed in clinical studies.<sup>1,16,19-21</sup>

## Pharmacological Management

The majority of patients with AE respond to topical therapy, however for patients with severe AE who are not responding to topical therapy, phototherapy or systemic immunosuppressants may be required.<sup>1</sup>

### TOPICAL THERAPY

Topical therapies are the mainstay of treatment of mild to moderate AE and include emollients, TCS and TCI.

**Emollients** are the **cornerstone of management of AE and should be used even when the AE seems to be quiescent.**<sup>1,6,12,22</sup> The precise mechanisms through which emollients exert their beneficial effects are insufficiently understood; they help to restore the epidermal barrier function by forming an occlusive layer, reduce transepidermal water loss and reduce the exposure to bacterial and sensitising antigens.<sup>1,6,12,18,20,22</sup> Emollients improve the symptoms of itch and pain; **they also prolong the time to flare, reduce the number of flares and reduce the amounts of TCS needed to control AE.**<sup>4,22,23</sup> Unperfumed emollients should be used every day for moisturising;<sup>24</sup> they should be applied 2 to 3 times daily and also after bathing to prevent skin drying.<sup>12,17,22</sup> Emollients are available in formulations including ointments, creams and lotions. There is no evidence to show that one emollient is better than another;<sup>4,23</sup> **the choice of the emollient should address the patient's individual needs and preference.**<sup>1,6</sup> **Ointments** are richer in lipids than creams, they provide more lubrication and occlusion, and are useful for the treatment of dry and lichenified areas, while **creams** with intermediate lipid content are best applied on large and subacute areas.<sup>1</sup> **Lotions** have higher water content and can be used to cool or dry strongly inflamed or oozing lesions.<sup>1</sup> Of note, aqueous cream (which contains sodium lauryl sulphate) is no longer recommended as an emollient, as it may cause skin irritation including burning, stinging, itching and redness.<sup>24,25</sup> Emollients should be used in large quantities, up to 250-500g per week.<sup>6</sup>

**Topical corticosteroids** (TCS) are effective in treating the inflammation and pruritus associated with acute AE and are recommended as first-line topical therapy of acute flares.<sup>1,10,17</sup> Overall, the risks associated with TCS use do appear to be low with appropriate application and choice of potency, combined with periods of non-use.<sup>1,10,17</sup> TCS may be classified in terms of strength from mild to very potent, examples of which are shown in table 6.<sup>26</sup>

**Table 6: Potency of Topical Corticosteroids<sup>26\*</sup>**

Mild	Moderate	Potent	Very potent
Hydrocortisone 1%	Clobetasone butyrate 0.05%	Betamethasone valerate 0.1% Betamethasone dipropionate 0.05% Hydrocortisone <b>butyrate</b> 0.1% Mometasone furoate 0.1%	Clobetasol propionate 0.05%

\*the potency of a TCS preparation is as a result of the formulation as well as the corticosteroid, e.g. the inclusion of urea or salicylic acid increases the penetration of a TCS through the skin<sup>26</sup>

**The least potent TCS which is effective should be applied once or twice daily to the site of active AE;** the potency should be individualised to the patient and tailored to the severity of AE which may vary according to the body site involved.<sup>6</sup> There is evidence to suggest that once daily application of some potent TCS may be as effective as twice daily.<sup>1,16,18</sup> **In general, low potency TCS are preferred on the face, areas of thinner skin and in children;**<sup>1</sup> however during acute severe flares, the use of short-term higher potency TCS may be appropriate to control symptoms.<sup>17</sup> For example, children may require short term (3 to 5 days) use of moderate potency TCS for severe flares of the face and neck.<sup>6</sup> **Potent and very potent TCS should not be used in infants <12 months, and very potent TCS should not be used in children without specialist dermatological advice.**<sup>6</sup> TCS creams are suitable for moist or weeping lesions while ointments are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required.<sup>26</sup> The **finger-tip unit (FTU)** is recommended to patients for applying TCS in safe quantities.<sup>27,28</sup> One FTU is a squeeze of cream or ointment along the index finger from the tip to the first finger joint. It weighs approximately 0.5 grams and covers a surface area equal to the size of two adult hands including the fingers.<sup>27,28</sup> The recommended FTU of TCS will depend on the part of the body being treated.<sup>27-29</sup> The Irish Skin Foundation has a useful patient information leaflet which describes the number of FTUs required for different parts of the body in adults and children (available on <https://irishskin.ie/>).<sup>29</sup>

**Adverse effects** include purpura, telangiectasia, skin atrophy, hypertrichosis, folliculitis and acne.<sup>16</sup> Many of the adverse effects will resolve after discontinuing TCS use, but may take months; sites of treatment should be assessed regularly for these adverse effects.<sup>17</sup> The risk of hypothalamic-pituitary-adrenal axis suppression is low but increases with prolonged continuous use, especially in patients receiving corticosteroids in other forms.<sup>17</sup>

**Topical calcineurin inhibitors** (TCI) are anti-inflammatory agents that inhibit calcineurin-dependent T-cell activation, and have been shown to be safe and effective for adults and children with moderate to severe AE.<sup>30</sup> **TCI are used second-line for short-term and intermittent treatment;**<sup>1,12,17</sup> patients usually respond within 1 week.<sup>31,32</sup> Tacrolimus 0.03% and 0.1%, are authorised for adults and adolescents >16 years and tacrolimus 0.03% for children ≥2 years; it is applied as a thin layer to the affected area.<sup>31,32</sup> The potency of tacrolimus 0.1% is approximately equivalent to that of a moderately potent TCS.<sup>1</sup> TCI do not cause skin atrophy and are useful especially in delicate skin areas such as the face and the groin area.<sup>1,18</sup> **Adverse effects** include localised site reactions, e.g. stinging and pruritus.<sup>12,31,32</sup> The use of TCI should be avoided in patients with congenital or acquired immunodeficiencies and in those treated with immunosuppressants or phototherapy.<sup>31,32</sup> Caution is advised in relation to sun exposure while using topical tacrolimus; patients should minimise time in the sun, use a sunscreen product and cover the skin with protective clothing.<sup>18,31,32</sup> Rare cases of malignancy (e.g. skin cancer and lymphoma) have been reported with TCI, however a causal relationship has not been established.<sup>17,31,32</sup>

**Wet wrap therapy (WWT)** involves the application of a TCS and/or emollients, under two layers of cotton bandages or garments: a wet inner layer and a dry outer layer.<sup>17,33,34</sup> The wraps are left for 8 to 24 hours per day and used for



short-term (7 to 14 days) control of refractory flares.<sup>17,33,34</sup> WWT using TCS increase the risk of systemic adverse effects and **should only be initiated by a physician trained in its use.**<sup>6</sup>

## SYSTEMIC PHARMACOLOGICAL THERAPY

The majority of patients with AE respond to topical therapy, however systemic pharmacological treatment or phototherapy may be required for patients with severe AE when topical therapy has failed.<sup>1,6</sup> **Systemic therapy should only be undertaken by physicians with expertise in this area.**<sup>6,35</sup> The most widely used systemic pharmacological agents are ciclosporin, azathioprine, methotrexate and mycophenolate mofetil,<sup>1,3,15,18,36</sup> of which **only ciclosporin is authorised for use in AE.** Several targeted therapies (including tralokinumab) are under investigation for the treatment of moderate to severe AE;<sup>13</sup> dupilumab (a targeted therapy) has recently been authorised (currently not reimbursed in Ireland) for the treatment of moderate to severe AE.<sup>37</sup>

**Ciclosporin** suppresses T-cells and IL-2 production, and is effective for severe AE.<sup>36</sup> It is used first-line for severe AE when systemic pharmacological therapy is required.<sup>13,16,18,35</sup> **Adverse effects** include infection, renal toxicity, hepatotoxicity, hypertension, hyperlipidaemia, hyperkalaemia, risk of lymphomas and malignancies (especially skin), hypomagnesaemia, bone marrow suppression and potential drug interactions.<sup>35</sup> **Monitoring of the patient's blood pressure, lipids, renal and liver function is recommended.**<sup>13,35</sup>

**Dupilumab** is a monoclonal antibody administered subcutaneously, that targets IL-4 and IL-13; it has shown efficacy in clinical trials up to 1 year for the treatment of moderate to severe AE.<sup>13,37,38</sup> **Adverse effects** include conjunctivitis, herpes simplex, eosinophilia, headache and injection site reactions;<sup>37</sup> the long-term safety is unknown.<sup>13</sup>

**Systemic corticosteroids: Guidelines discourage the use of systemic corticosteroids for AE** due to an unfavourable risk-benefit profile.<sup>1,12,13,36,39,40</sup> Systemic corticosteroids do however provide rapid relief from intractable itch in AE and are used in exceptional circumstances such as for short-term use (< 3 weeks) to interrupt flares and when initiating other systemic therapy; rebound flares are commonly observed after discontinuation.<sup>1,18,36,40</sup>

## Other Pharmacological Therapies

**Oral antihistamines** are frequently used in AE but there is little evidence to show that they are effective.<sup>1,18</sup> They should not be used routinely in the management of AE;<sup>6</sup> short-term use of sedating antihistamines may be useful for patients with pruritus causing disturbed sleep.<sup>6,12</sup>

**Antibiotics:** Flucloxacillin is recommended as first-line treatment for staphylococcal and streptococcal infections; clarithromycin should be used for those who are allergic to flucloxacillin.<sup>6,41</sup> There is a lack of evidence to support the use of topical antimicrobials in AE.<sup>5,17,42</sup> The use of topical antibiotics including those combined with TCS should be reserved for localised infection only and for no longer than 2 weeks.<sup>6</sup>

**Antivirals: Systemic aciclovir should be commenced if eczema herpeticum is suspected and the patient should be referred for same day specialist advice.**<sup>1,6</sup> Treatment with oral aciclovir should be started in patients with a localised lesion suspected to be herpes simplex.<sup>6</sup>

## OTHER THERAPIES

**Phototherapy,** in particular narrow band ultraviolet B (NB-UVB), is recommended as second-line or adjuvant therapy in selected patients for moderate to severe AE, especially in adults and older children.<sup>1,13,15,36</sup> Phototherapy requires specialist dermatologist supervision and facilities and should not be used in combination with TCI or systemic ciclosporin due to a potentially cumulative increased risk of skin cancer.<sup>1</sup>

## PRACTICAL ASPECTS OF MANAGEMENT

The management of AE takes place predominantly in primary care. There is a lack of good quality controlled trials to guide the order of application of emollients and TCS.<sup>1,6</sup> In general it is recommended that a short interval is left between application of emollients and TCS or that they could be applied at different times of the day, to avoid dilution.<sup>1,6</sup> However **in relation to TCI, emollients should be applied at least 2 hours after tacrolimus.**<sup>31,32</sup> Of note, after stabilisation of an acute flare, remission should be maintained with continuous use of emollients.<sup>1,8,43</sup> **Application of TCS or TCI as maintenance therapy** to previously active sites of AE for 2 consecutive days per week ("weekend therapy") has been shown to reduce flares; this may be useful in patients with frequent outbreaks (e.g. ≥ 4 times per year) on the same body sites.<sup>1,6,12,31,32,43,44</sup> **In patients who continue to have flares despite good compliance, secondary bacterial or viral infection should be excluded.**<sup>4,6</sup>

**Referral for specialist dermatological advice** is recommended if: 1) the diagnosis is or has become uncertain, 2) standard management has not controlled the AE satisfactorily, 3) AE on the face has not responded to appropriate treatment, 4) contact allergic dermatitis is suspected, 5) AE is giving rise to significant social or psychological problems or 6) AE is associated with severe and recurrent infections.<sup>6</sup>

## USEFUL RESOURCES

- Patient information leaflets from the Irish Skin Foundation available online on <https://irishskin.ie/>
- National Eczema Society website contains useful information for healthcare professionals and patients <http://www.eczema.org/>
- The University of Bristol has an example of an Eczema Written Action Plan available on <http://www.bristol.ac.uk/primaryhealthcare/researchthemes/apache/ewap/> [http://www.bristol.ac.uk/media-library/sites/primaryhealthcare/documents/eWAP%20v1\\_0.pdf](http://www.bristol.ac.uk/media-library/sites/primaryhealthcare/documents/eWAP%20v1_0.pdf)
- The British Association of Dermatologists has useful patient information leaflets (on conditions including atopic eczema, contact dermatitis, discoid eczema, eczema herpeticum, seborrheic dermatitis, topical corticosteroids, patch testing) available on [www.bad.org.uk/leaflets](http://www.bad.org.uk/leaflets)
- The **Global Resource for Eczema Trials (GREAT)** database has a collection of systematic reviews and randomised controlled trials of eczema treatments <http://www.greatdatabase.org.uk/GD4/Browse/index.php>

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*List of references available on request. Date of preparation: January 2018*

*Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.*

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