Medicines Management Programme

Managed Access Protocol for high tech medicines for the treatment of moderate-to-severe atopic dermatitis:

abrocitinib (Cibinqo®)▼

dupilumab (Dupixent®)

tralokinumab (Adtralza®)▼

upadacitinib (RINVOQ®)▼

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
Date approved:	19/04/2023
Version:	5.0

▼ This medicinal product is subject to additional monitoring. This will allow timely identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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List of abbreviations

AAD	American Academy of Dermatology
BSC	Best supportive care
CDLQI	Children's Dermatology Life Quality Index
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
HSE	Health Service Executive
HTH	High Tech Hub
IFN-γ	Interferon gamma
IgG4	Immunoglobulin G4
IL	Interleukin
JAK	Janus Kinase
MACE	Major adverse cardiovascular events
MAP	Managed Access Protocol
MMP	Medicines Management Programme
PCRS	Primary Care Reimbursement Service
PFP	Pre-filled pen
PFS	Pre-filled syringe
SC	Subcutaneous
SmPC	Summary of product characteristics
STAT	Signal transducers and activators of transcription
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TSLP	Thymic stromal lymphopoietin
TYK2	Tyrosine kinase 2
VTE	Venous thromboembolism

1. High tech medicines for the treatment of atopic dermatitis: abrocitinib (Cibinqo®), dupilumab (Dupixent®), tralokinumab (Adtralza®) and upadacitinib (RINVOQ®)

There are currently four medicines referenced in this Managed Access Protocol (MAP) that are available under the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis; abrocitinib (Cibinqo®), dupilumab (Dupixent®), tralokinumab (Adtralza®) and upadacitinib (RINVOQ®).

Cibinqo® contains abrocitinib. Abrocitinib is a Janus kinase (JAK) 1 inhibitor. In biochemical assays, abrocitinib has selectivity for JAK1 over the other three JAK isoforms; JAK2, JAK3 and tyrosine kinase 2 (TYK2). In cellular settings, it preferentially inhibits cytokine-induced signal transducers and activators of transcription (STAT) phosphorylation by signalling pairs involving JAK1, and spares signalling by JAK2/JAK2, or JAK2/TYK2 pairs. Atopic dermatitis is driven by pro-inflammatory cytokines, including interleukin (IL)-4, IL-13, IL-22, thymic stromal lymphopoietin (TSLP), IL-31 and interferon gamma (IFN-γ), that transduce signals via the JAK1 pathway.

On 1 July 2022, three presentations of Cibinqo® were added to the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis:

- Cibinqo® 50 mg film-coated tablets ▼[i]
- Cibinqo® 100 mg film-coated tablets ▼[i]
- Cibinqo® 200 mg film-coated tablets ▼[i]

Dupixent® contains dupilumab. Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that inhibits IL-4 and IL-13 signalling. It is produced in Chinese hamster ovary cells by recombinant DNA technology.

On 1 April 2021, two presentations of Dupixent® were added to the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis:

- Dupixent® 200 mg solution for injection in pre-filled pen (Dupixent® 200 mg pre-filled pen [PFP])
- Dupixent® 300 mg solution for injection in pre-filled pen (Dupixent® 300 mg pre-filled pen [PFP])

[i] ▼ This medicinal product is subject to additional monitoring.

On 1 May 2021, a further two presentations of Dupixent® were added to the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis:

- Dupixent® 200 mg solution for injection in pre-filled syringe (Dupixent® 200 mg pre-filled syringe [PFS])
- Dupixent® 300 mg solution for injection in pre-filled syringe (Dupixent® 300 mg pre-filled syringe [PFS])

Adtralza® contains tralokinumab. Tralokinumab is fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine IL-13 and inhibits its interaction with the IL-13 receptors. It is produced in mouse myeloma cells by recombinant DNA technology.

On 1 March 2022, one presentation of Adtralza® was added to the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis:

- Adtralza® 150 mg solution for injection in PFS ▼[i]

RINVOQ® contains upadacitinib. Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

On 1 February 2022, two presentations of RINVOQ® were added to the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis:

- RINVOQ 15 mg prolonged-release tablets ▼[i]
- RINVOQ 30 mg prolonged-release tablets ▼[i]

1.1 Licensed indications

This MAP relates to the use of:

- Cibinqo®, Dupixent®, Adtralza® and RINVOQ® in the treatment of adult patients (aged 18 years or older) with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.
- Dupixent® and RINVOQ® in the treatment of adolescent patients (aged 12 – 17) with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

[i] ▼This medicinal product is subject to additional monitoring.

Dupixent® and RINVOQ® are also indicated in the treatment of a number of other inflammatory conditions[ii] which are outside of the scope of this MAP.

1.2 Reimbursement

Conditional reimbursement of Cibinqo®, Dupixent®, Adtralza® and RINVOQ® on the High Tech Arrangement under this MAP is confined to the treatment of moderate-to-severe refractory atopic dermatitis in adults (Cibinqo®, Dupixent®, Adtralza® and RINVOQ®) and adolescents 12 years and older (Dupixent® and RINVOQ®) for whom immunosuppressant treatment has failed, or is not tolerated or is contraindicated.

Prescribers are required to apply for reimbursement approval on an individual patient basis through the online application system.

If a patient is recommended for reimbursement by the MMP, the High Tech prescription for Cibinqo®, Dupixent®, Adtralza® or RINVOQ® should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated will not be eligible for reimbursement by the Health Service Executive (HSE)-Primary Care Reimbursement Service (PCRS). Treatment with Cibinqo®, Dupixent®, Adtralza® or RINVOQ® for moderate-to-severe atopic dermatitis should be initiated and supervised by physicians experienced in the diagnosis and treatment of the condition.

1.2.1 Cibinqo® dosing[ii]

The recommended starting dose of abrocitinib is 200 mg administered orally once daily. A starting dose of 100 mg once daily is recommended for patients ≥ 65 years of age. For other patients who may benefit from a starting dose of 100 mg, see the Summary of Product Characteristics (SmPC) for Cibinqo®.

During treatment, the dose of abrocitinib may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose of abrocitinib is 200 mg.

[ii] Please refer to each individual product's Summary of Product Characteristics (SmPC) for full prescribing information.

If a patient is recommended for reimbursement of Cibinqo®, reimbursement will be supported for the licensed dosage regimen as per the SmPC.

1.2.2 Dupixent® dosing[ii]

Table 1 outlines the licensed dosage regimens of dupilumab (Dupixent®) for the treatment of moderate-to-severe atopic dermatitis, relevant to this MAP.

Table 1: Licensed dosage regimens of Dupixent® for moderate-to-severe atopic dermatitis

Patient population	Route	Initial dose	Subsequent doses (every other week)
Adults	SC	600 mg (two 300 mg injections)	300 mg (one 300 mg injection)
Adolescents (age 12-17)			
< 60 kg	SC	400 mg (two 200 mg injections)	200 mg (one 200 mg injection)
≥ 60 kg	SC	600 mg (two 300 mg injections)	300 mg (one 300 mg injection)

Kg: kilogrammes; mg: milligram; SC: subcutaneous

Dupixent® is available as a PFP or PFS, with one pack containing two PFP or two PFS. If a patient is recommended for reimbursement of Dupixent®, reimbursement will be supported for a total of two packs of Dupixent® (each containing two PFP or two PFS) to cover the first four weeks of treatment, followed by one pack of Dupixent® (each containing two PFP or two PFS) every four weeks thereafter, i.e. in line with the licensed dose for the treatment of moderate-to-severe atopic dermatitis as per the SmPC.

1.2.3 Adtralza® dosing[ii]

Table 2 outlines the licensed dosage of tralokinumab (Adtralza®) for the treatment of moderate-to-severe atopic dermatitis.

Table 2: Licensed dosage of Adtralza® for moderate-to-severe atopic dermatitis

Patient population	Route	Initial dose	Subsequent doses (every other week*)
Adults	SC	600 mg (four 150 mg injections)	300 mg (two 150 mg injections)

mg: milligram; SC: subcutaneous

*At the prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. The probability of maintaining clear or almost clear skin may be lower with every fourth week dosing.

[ii] Please refer to each individual product's Summary of Product Characteristics (SmPC) for full prescribing information.

Adtralza® is available as a multipack containing two packs, each pack contains two PFS. If a patient is recommended for reimbursement of Adtralza®, reimbursement will be supported for a total of two multipacks of Adtralza® (each containing four PFS) to cover the first four weeks of treatment, followed by one pack of Adtralza (containing four PFS) every four weeks thereafter i.e., in line with the licensed dose as per the SmPC.

1.2.4 RINVOQ® dosing[ii]

Adults

The recommended dose of upadacitinib is 15 mg or 30 mg administered orally once daily based on individual patient presentation.

- A dose of 15 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy.
- A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or patients with an inadequate response to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients ≥ 65 years of age, the recommended dose is 15 mg once daily.

Adolescents (from 12 to 17 years of age)

The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

If a patient is recommended for reimbursement of RINVOQ®, reimbursement will be supported for the licensed dosage regimen for the treatment of moderate-to-severe atopic dermatitis as per the SmPC.

1.3 Reimbursement price

A commercial-in-confidence arrangement is in place with the marketing authorisation holders to reduce the net acquisition cost of Cibinqo®, Dupixent®, Adtralza® and RINVOQ® to the HSE.

1.3.1 Cibinqo® reimbursement price

The reimbursement price of Cibinqo® presentations available on the High Tech Arrangement as of 1 April 2023 are outlined in table 3.

[ii] Please refer to each individual product's Summary of Product Characteristics (SmPC) for full prescribing information.

Table 3: Reimbursement price of presentations of Cibinqo® available on the High Tech Arrangement as of 1 April 2023

Strength (pack size)	Reimbursement	
	Code	Price
Cibinqo® 50 mg film-coated tablets (28 pack)	89195	€1,085.40
Cibinqo® 100 mg film-coated tablets (28 pack)	89196	€1,085.40
Cibinqo® 200 mg film-coated tablets (28 pack)	89198	€1,085.40

mg: milligram

1.3.2 Dupixent® reimbursement price

The reimbursement price of Dupixent® presentations available on the High Tech Arrangement as of 1 April 2023 are outlined in table 4.

Table 4: Reimbursement price of presentations of Dupixent® available on the High Tech Arrangement as of 1 April 2023

Strength (pack size)	Reimbursement	
	Code	Price
Dupixent® 200 mg PFP (2 x 1.14 ml)	89072	€1,232.34
Dupixent® 300 mg PFP (2 x 2 ml)	89073	€1,238.19
Dupixent® 200 mg PFS (2 x 1.14 ml)	89074	€1,246.16
Dupixent® 300 mg PFS (2 x 2 ml)	89075	€1,246.16

mg: milligram; ml: millilitre; PFP: Pre-filled pen; PFS: Pre-filled syringe

1.3.3 Adtralza® reimbursement price

The reimbursement price of the Adtralza® presentation available on the High Tech Arrangement as of 1 April 2023 is outlined in table 5.

Table 5: Reimbursement price of presentation of Adtralza® available on the High Tech Arrangement as of 1 April 2023

Strength (pack size)	Reimbursement	
	Code	Price
Adtralza® 150 mg PFS (2 packs of 2 x 1 ml)	89167	€1,202.53

mg: milligram; ml: millilitre; PFS: Pre-filled syringe

1.3.4 RINVOQ® reimbursement price

The reimbursement price of RINVOQ® presentations available on the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis as of 1 April 2023 are outlined in table 6.

Table 6: Reimbursement price of presentations of RINVOQ® available on the High Tech Arrangement for the treatment of moderate-to-severe atopic dermatitis as of 1 April 2023

Strength (pack size)	Reimbursement	
	Code	Price
RINVOQ® 15 mg prolonged-release tablets (28 pack)	89057	€873.06
RINVOQ® 30 mg prolonged-release tablets (28 pack)	89155	€1,246.16

mg: milligram

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of Cibinqo®, Dupixent®, Adtralza® or RINVOQ® for the treatment of moderate-to-severe atopic dermatitis under the High Tech Arrangement.

2.1 Prescribers

The prescribing of Cibinqo®, Dupixent®, Adtralza and RINVOQ® for the treatment of moderate-to-severe atopic dermatitis under the High Tech Arrangement is confined to consultant dermatologists who have agreed to the terms of this MAP and have been approved by the HSE. Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient age

Applications for reimbursement approval of Dupixent® and RINVOQ® will only be considered for adults and adolescents 12 years and older at the time of application.

Applications for reimbursement approval of Cibinqo® and Adtralza® will only be considered for adults 18 years and older at the time of application.

2.3 Diagnosis

Clinicians will be required to confirm a diagnosis of atopic dermatitis at the time of application. This diagnosis should be made in line with the American Academy of Dermatology (AAD) criteria, as outlined in Appendix 1.

Reimbursement under the High Tech Arrangement will only be supported for patients who are classified as having chronic atopic dermatitis for:

- At least one year prior to the application date in adolescent patients aged 12-17 years (Dupixent® and RINVOQ®) or
- At least three years prior to the application date in patients aged 18 years and older (Cibinqo®, Dupixent®, Adtralza® and RINVOQ®).

2.3.1 Eczema Area and Severity Index (EASI) score

Clinicians will be required to confirm the patient's eczema area and severity index (EASI) score at the time of application. Reimbursement will only be supported for patients with an EASI score ≥ 16.

2.3.2 Children's Dermatology Life Quality Index (CDLQI)/Dermatology Life Quality Index (DLQI) score

Clinicians will be required to confirm either the children's dermatology life quality index (CDLQI) score or the dermatology life quality index (DLQI) score for the patient at the time of application.

2.4 Patient's medical treatment for atopic dermatitis

Reimbursement will only be supported in refractory atopic dermatitis, when:

- The patient has had an inadequate response[iii] to an immunosuppressant medicine, or where such treatment is not tolerated or is contraindicated, and
- The patient is using best supportive care (BSC) for atopic dermatitis.

The patient may or may not have trialled other treatments (such as phototherapy).

2.4.1 Immunosuppressant medicine response inadequate

Reimbursement will be supported for patients who have had an inadequate response to a trial of at least one immunosuppressant medicine. For the purpose of reimbursement approval, an adequate trial of a medicine is defined as a period of at least three consecutive months. The trial of an immunosuppressant medicine must have taken place within three years prior to the application date.

Clinicians will be required to demonstrate that at least one of the medicines from the current standard of care for moderate-to-severe atopic dermatitis has been trialled prior to the application. Such medicines include[iv]:

- Ciclosporin
- Methotrexate
- Azathioprine
- Mycophenolate mofetil

[iii] Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state.
[iv] Not all medicines are licensed for the treatment of moderate-to-severe atopic dermatitis. Please refer to each individual product's Summary of Product Characteristics (SmPC) for further details.

When reviewing applications, the MMP may request evidence to demonstrate that the patient has been adherent to the specified medicine for a period of at least three months.

2.4.2 Immunosuppressant medicine is not tolerated

In cases where a patient did not tolerate a medicine and experienced a clinically significant adverse reaction which led to discontinuation of treatment prior to completion of an adequate trial, information in relation to the duration of treatment and the adverse reaction experienced should be provided.

2.4.3 Immunosuppressant medicine is contraindicated

For patients in whom treatment with an immunosuppressant medicine is contraindicated, details of the contraindication, including supporting evidence, must be provided at time of application for reimbursement approval.

2.4.4 Best supportive care for atopic dermatitis

Reimbursement will only be supported for patients who are in receipt of BSC for atopic dermatitis. For the purpose of reimbursement approval, BSC consists of emollients, low-to-medium potency topical corticosteroids (TCS), topical calcineurin inhibitors (TCI) and as-needed short-term use of rescue treatments to manage disease exacerbations (including high-potency TCS, TCIs or systemic corticosteroids). Evidence to demonstrate the utilisation of BSC must be provided at the time of application for reimbursement approval.

3. Reimbursement criteria – Continuation

Clinical evidence indicates that:

- The majority of patients who respond to abrocitinib show clinical benefit within 24 weeks
- The majority of patients who respond to dupilumab or tralokinumab show clinical benefit within 16 weeks
- The majority of patients who respond to upadacitinib show clinical benefit within 12 weeks.

In patients with atopic dermatitis, the following is considered a clinically meaningful response to treatment:

- an improvement in EASI score of ≥ 50%, and
- an improvement in DLQI score of ≥ 4 points.

As this is a condition of reimbursement, patients not showing these improvements in the appropriate timeframe would be considered non-responders and consideration should be given to discontinuing treatment in such patients.

Therefore, following approval of a patient for reimbursement of a medicine for the treatment of moderate-to-severe atopic dermatitis under the High Tech Arrangement, the prescribing clinician may be required to submit follow-up information to the MMP as requested. Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

4. Prescribing of high tech medicines for the treatment of moderate-to-severe atopic dermatitis

Please refer to each individual product's SmPC for full prescribing information including monitoring and patient counselling requirements.

Prescriptions must be generated through the HTH (details outlined separately) and only approved prescribers will have access to prescribe High Tech medicines for the treatment of moderate-to-severe atopic dermatitis.

The following confirmations are required when prescribing High Tech medicines for the treatment of moderate-to-severe atopic dermatitis on the HTH:

- Confirmation that the High Tech medicine for the treatment of moderate-to-severe atopic dermatitis is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE
- Confirmation that prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP
- Confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed

** Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.*

Appendix 1: American Academy of Dermatology criteria for the diagnosis of atopic dermatitis[1]:

ESSENTIAL FEATURES - Must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

*Patterns include:

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

IMPORTANT FEATURES - Seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
    - Personal and/or family history
    - Immunoglobulin E reactivity
- Xerosis

ASSOCIATED FEATURES - These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (e.g. facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (e.g. perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS - It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

[1]Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014; 71: 116-32.