HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
15 DECEMBER 2021

The legally binding text is the original French opinion version

upadacitinib

RINVOQ 15 mg prolonged-release tablets
New indication

RINVOQ 30 mg prolonged-release tablets
Inclusion on list

Key points

In adults

Favourable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy **in the event of failure, intolerance or contraindication to ciclosporin.**

Unfavourable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adults in whom topical therapies have failed and who are **ciclosporin-naïve, in the absence of comparative data.**

In adolescents 12 years and older

Favourable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy.

What therapeutic improvement?

In adults

Therapeutic improvement compared to DUPIXENT (dupilumab) in the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy, in the event of failure, intolerance or contraindication to ciclosporin.

In adolescents 12 years and older

No clinical added value in the treatment of moderate to severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy, which includes DUPIXENT (dupilumab).

Role in the care pathway?

The overall objective of atopic dermatitis (AD) treatment is to improve patients' quality of life by treating their skin lesions and preventing the risk of secondary infections in the event of flare-ups, early relapses and xeroderma. Outside inflammatory flare-ups, all patients should be treated using adjuvant measures (hygiene, emollients) and relapses should be treated at an early stage.

Management in adults

The treatment of acute flare-ups is initially based on the use of topical treatments: topical corticosteroids or, in the event of failure/contraindication, a calcineurin inhibitor (tacrolimus). The wet wrapping technique may be used in the event of an inadequate response.

Phototherapy is mainly recommended in the management of the chronic phase but can be used as second-line treatment in acute flare-ups in the event of failure of topical treatments, although its use is limited by its accessibility.

Systemic treatments are reserved for severe chronic atopic dermatitis resistant to topical corticosteroids or phototherapy. The choice of systemic treatment depends on various factors, in particular comorbidities, age, clinical experience or potential pregnancy plans.

Non-biologic systemic treatments are currently available, including ciclosporin used as first-line treatment and immunosuppressive therapies used off-label (methotrexate, mycophenolate mofetil and azathioprine). Their use should be time-limited due to the unfavourable long-term safety profile.

Other treatment options have also become available recently: biologic interleukin inhibitors, an anti-IL4 and anti-IL13, dupilumab (2017) and an anti-IL-13, tralokinumab (June 2021) administered subcutaneously, and a janus kinase inhibitor (anti-JAK 1 and 2) administered orally, baricitinib (2020). These treatments are recommended by the Transparency Committee in the event of failure, intolerance or contraindication to ciclosporin.

Alitretinoin, a systemic retinoid, has an MA exclusively for the treatment of severe chronic eczema of the hands, following the failure of potent topical corticosteroids.

Management in adolescents aged 12 years and older

According to French and international guidelines, the treatment of acute flare-ups of atopic dermatitis (AD) in children and adolescents is initially based on the use of topical corticosteroids, as in adults, potentially with use of the wet wrapping technique if necessary. Topical tacrolimus has an MA in the treatment of severe atopic dermatitis in children and adolescents in the event of failure or contraindication to topical corticosteroids. However, the Transparency Committee considered that its clinical benefit in this age group was insufficient and it is only reimbursed in adults in France.

The use of phototherapy in the paediatric population is very marginal given the little data available in these patients, the administration conditions requiring several visits per week to a dermatologist with the required equipment, and the serious cumulative toxicity (mutagenic/carcinogenic risk, in particular).

In the event of an inadequate response to these treatments, ciclosporin is proposed in adolescents; however, its MA indicates that its use is not recommended in patients under the age of 16 years. In refractory atopic dermatitis in adolescents, other systemic immunosuppressants, such as methotrexate, azathioprine and mycophenolate mofetil, are proposed off-label. Their use should be time-limited due to an unfavourable long-term safety profile.

Since 2019, dupilumab has been an option in adolescents with moderate to severe atopic dermatitis who are candidates for systemic therapy (MA of 01/08/2019) and is reimbursable in this indication (Transparency Committee opinion of 11/03/2020).

Role of the medicinal product in the care pathway

In adults

As knowledge currently stands, in the absence of a direct comparison of upadacitinib (JAK1 and JAK1/3 inhibitor) with oral ciclosporin following the failure of topical treatments, its role compared to ciclosporin cannot be determined in first-line systemic therapy (following the failure of topical corticosteroids).

Consequently, RINVOQ 15 mg and 30 mg (upadacitinib) is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis, who are candidates for systemic therapy, in the event of failure, intolerance or contraindication to ciclosporin.

The Transparency Committee specifies that the choice of second-line systemic therapy should be made on a case-by-case basis depending on the severity of the disease, patients' characteristics, their treatment history, the risks of intolerance and contraindications to the various treatments available.

As regards upadacitinib, it is necessary to take into account its less favourable safety profile than that of dupilumab (see the respective SPCs of these medicinal products), the need to monitor various laboratory parameters (haematological, lipid and hepatic), its contraindication in the event of pregnancy, as with other JAK inhibitors, as well as uncertainties, in particular relative to the cardiovascular, venous thromboembolic and carcinogenic risks indicated in the RMP for upadacitinib and shared by other JAK inhibitors.

The superiority of upadacitinib compared to dupilumab was only demonstrated at the 30 mg dose, which the SPC indicates is reserved for patients with high disease burden or with an inadequate response to the 15 mg dose.

In adolescents 12 years and older

Given the toxicity of ciclosporin, contraindicated in patients under the age of 16 years, the Committee considers that RINVOQ 15 mg (upadacitinib) is a first-line systemic treatment to be reserved for moderate to severe forms of atopic dermatitis in adolescents in whom topical treatment has failed.

As in adults, the choice of first-line systemic therapy should take into account the severity of the disease, patients' characteristics, their treatment history, the risks of intolerance and contraindications to the various treatments available.

As regards upadacitinib, it is necessary to take into account its less favourable safety profile than that of dupilumab (see the respective SPCs of these medicinal products), the need to monitor various laboratory parameters (haematological, lipid and hepatic), its contraindication in the event of pregnancy, as with other JAK inhibitors, as well as uncertainties, in particular relative to the cardiovascular, venous thromboembolic and carcinogenic risks indicated in the RMP for upadacitinib and shared by other JAK inhibitors.

Special recommendation

The Committee wishes to highlight the fact that upadacitinib is contraindicated during pregnancy, due to the teratogenic effects demonstrated in animals, and that for women of childbearing potential effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib (see the SPC for more details).

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

In adults (15 mg and 30 mg strengths)

◗ Atopic dermatitis is not usually a serious disease but in its moderate to severe forms, it has a significant impact on the quality of life of patients and marked social repercussions.

◗ RINVOQ (upadacitinib) 15 mg and 30 mg prolonged-release tablets have a suspensive effect on symptoms.

◗ In the absence of direct comparison with ciclosporin, the efficacy/adverse effects ratio of upadacitinib has not been established in adults with moderate to severe atopic dermatitis in whom topical treatments have failed and who are ciclosporin-naive.
In patients in whom ciclosporin has failed, its efficacy/adverse effects ratio is high.

◗ There are medicinal alternatives.

◗ This medicinal product is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis, in the event of failure, intolerance or contraindication to ciclosporin (see section 08 Role in the care pathway).

Public health impact

Considering:

- the seriousness of the disease in its severe forms requiring systemic treatment and its significant impact on patients' quality of life,
- the high prevalence of the disease (between 2 and 5% of the population),
- the medical need that is partially met in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy,
- the partial response to the identified need, due to:
    - a demonstrated impact on morbidity (particularly in terms of IGA 0 or 1, EASI-75, EASI-90, EASI-100 responses and pruritus) according to placebo-controlled studies, as monotherapy or in combination with topical corticosteroids in adults and adolescents (around 15% of the study population), or studies versus dupilumab as monotherapy in adults),
    - a clinically relevant impact demonstrated versus placebo, as monotherapy, in terms of quality of life in patients who are candidates for systemic therapy,
    - a comparable safety to that observed in the other indications, but including important identified risks (such as the risk of serious infections), uncertainties relative to the cardiovascular, venous thromboembolic and carcinogenic risks, in particular, indicated in the RMP, and a contraindication during pregnancy,
    - the expected impact for this medicinal product administered orally on the organisation of care and the patient's life pathway (reduction in need for nursing care, hospitalisations required to administer biologic therapies and use of medical transport), but considering:
        - the need to monitor haematological, hepatic and lipid parameters during treatment,
        - the need for women of childbearing potential to use effective contraception,

RINVOQ (upadacitinib) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of RINVOQ (upadacitinib) 15 mg and 30 mg prolonged-release tablets is:

- **substantial in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy, in the event of failure, intolerance or contraindication to ciclosporin;**
- **insufficient to justify public funding cover in view of the available alternatives in the treatment of moderate to severe atopic dermatitis in adults in whom topical therapies have failed and who are ciclosporin-naïve, in the absence of comparative data.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance or contraindication to ciclosporin and at the MA dosages.

◗ **Recommended reimbursement rate: 65%**

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of moderate to severe atopic dermatitis in adults in whom topical therapies have failed and who are ciclosporin-naïve, in the absence of comparative data.

In adolescents (15 mg strength)

◗ Atopic dermatitis is not usually a serious disease but in its moderate to severe forms, it has a significant impact on the quality of life of patients and marked social repercussions.

◗ RINVOQ (upadacitinib) 15 mg prolonged-release tablets have a suspensive effect on symptoms.

◗ Its efficacy/adverse effects ratio is high in adolescents with moderate to severe atopic dermatitis who are candidates for systemic therapy.

◗ There are few suitable medicinal alternatives in adolescents insofar as ciclosporin (recommended only from 16 years of age) and the other systemic immunosuppressants used off-label have a low level of evidence of their efficacy and an unfavourable long-term safety profile. Apart from ciclosporin, only dupilumab has an MA in atopic dermatitis for adolescents.

◗ This medicinal product is a first-line systemic treatment to be reserved for moderate to severe forms of atopic dermatitis in adolescents in whom topical treatment has failed (see section 08 Role in the care pathway).

Public health impact

Considering:

- the seriousness of the disease in its severe forms requiring systemic treatment and its significant impact on patients' quality of life,
- the high prevalence of the disease (14.3% in adolescents),
- the medical need that is partially met in adolescents with moderate to severe atopic dermatitis who are candidates for systemic therapy,
- the partial response to the identified need, due to:
  - demonstration in studies having included adults and adolescents (around 15% of the study population) of the superiority of upadacitinib at the 15 mg dose (the only dose recommended in adolescents) versus placebo as monotherapy or in combination with topical corticosteroids, on clinically relevant endpoints, such as EASI-75 and EASI 90, EASI-100, IGA 0 or 1 responses (with an improvement of at least 2 points) and pruritus, and the results of subgroup analyses in adolescents that are consistent with those of the total population of these studies,
  - a comparable safety to that observed in the other indications, but including important risks (such as serious infections), and uncertainties relative to the cardiovascular, venous

thromboembolic and carcinogenic risks, in particular, and a contraindication during pregnancy,
- a clinically relevant impact demonstrated versus placebo, as monotherapy, in terms of quality of life (total population analyses of studies having included adults and adolescents, and exploratory analyses in the adolescents subgroup),
- the expected impact for this medicinal product administered orally on the organisation of care and the patient's life pathway (reduction in need for nursing care, hospitalisations required to administer biologic therapies and use of medical transport), but considering:
  - the need to monitor haematological, hepatic and lipid parameters during treatment,
  - the need for women of childbearing potential to use effective contraception,

RINVOQ (upadacitinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RINVOQ (upadacitinib) 15 mg prolonged-release tablets is substantial in adolescents 12 years and older who are candidates for systemic therapy.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

In adults

◗ Within the reimbursement scope retained by the Committee

Considering:

- demonstration in studies having included patients with moderate to severe atopic dermatitis requiring systemic treatment:
  - of the superiority of upadacitinib 15 mg and 30 mg compared to placebo, with a substantial effect size, in terms of IGA 0 or 1, EASI-75, EASI-90 responses, and pruritus after 16 weeks of treatment (ranked endpoints), as monotherapy (MEASURE-Up 1 and 2 studies) or in combination with topical corticosteroids (AD-Up study) in adult or adolescent patients (approximately 15% of the study population),
  - of the superiority of upadacitinib 30 mg compared to dupilumab, a medicinal product that currently has a high level of evidence, in terms of EASI-75 response (71% versus 61.1%, p = 0.006), EASI-90 response (60.6% versus 38.8%, p < 0.001) and change in worst pruritus score (WP-NRS: -66.88 versus -49.04, p < 0.001) after 16 weeks of treatment, in the HEADS-Up study having included adults;
- demonstration of clinically significant and clinically relevant differences versus placebo in terms of quality of life (different ranked endpoints including DLQI) in monotherapy studies in adults and adolescents;

despite:

- uncertainties with respect to maintenance of efficacy beyond 52 weeks of treatment,
- a comparable safety to that observed in the other indications, but including important risks (such as serious infections), the need to monitor various laboratory parameters (haematological, lipid and hepatic), uncertainties relative to the cardiovascular, venous thromboembolic and carcinogenic risks, in particular, and a contraindication during pregnancy,

The Committee considers that RINVOQ (upadacitinib) 15 mg and 30 mg prolonged-release tablets provide a minor clinical added value (CAV IV) compared to DUPIXENT (dupilumab) in adults with atopic dermatitis who are candidates for systemic therapy in the event of failure, intolerance or contraindication to ciclosporin.

◗ Within the scope not retained for reimbursement

Not applicable.

In adolescents

Considering:

- demonstration of the superiority of upadacitinib 15 mg compared to placebo, with a substantial effect size, in terms of IGA 0 or 1, EASI-75, EASI-90 responses, and pruritus after 16 weeks of treatment (ranked endpoints), as monotherapy (MEASURE-Up 1 and 2 studies) or in combination with topical corticosteroids (AD-Up study) in populations including adults and adolescents (approximately 15% of the study population) with moderate to severe atopic dermatitis who are candidates for systemic therapy;
- the results of subgroup analyses in adolescents having demonstrated results that are consistent with those of the total population of these studies,
- demonstration of clinically significant and clinically relevant differences versus placebo in terms of quality of life (different ranked endpoints including DLQI) in monotherapy studies in adults and adolescents;

But:

- uncertainties with respect to maintenance of efficacy beyond 52 weeks of treatment,
- the absence of a direct comparison between upadacitinib 15 mg and dupilumab in either adolescents or adults,

- a comparable safety to that observed in the other indications, but including important identified risks (such as serious infections), the need to monitor various laboratory parameters (haematological, lipid and hepatic), and uncertainties relative to, in particular, the cardiovascular, venous thromboembolic and carcinogenic risks indicated in the RMP, and a contraindication during pregnancy,

the Committee considers that RINVOQ (upadacitinib) 15 mg prolonged-release tablets provide no clinical added value (CAV V) in the treatment of atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy, which includes DUPIXENT (dupilumab).