SUMMARY

Reassessment of JAK inhibitors in atopic dermatitis

CIBINQO (abrocitinib) 50 mg, 100 mg and 200 mg, tablets

OLUMIANT (baricitinib) 2 mg and 4 mg, tablets

RINVOQ (upadacitinib) 15 mg and 30 mg, tablets

Reassessment at Transparency Committee's request

Original French opinion adopted by the Transparency Committee on 25 October 2023

The legally binding text is the original French opinion version

Transparency Committee's Conclusions

Clinical Benefit

CIBINQO (abrocitinib)

- Atopic dermatitis is not generally a serious condition, but in its moderate to severe forms, it has a substantial impact on patients' quality of life and significant psychosocial repercussions.
- CIBINQO 50 mg, 100 mg and 200 mg (abrocitinib), film-coated tablet, is a suspensive symptomatic medicinal product.
- Given the lack of direct comparison to ciclosporin, the efficacy/adverse effects ratio of abrocitinib is not defined in adults with moderate to severe atopic dermatitis who have failed to respond to topical treatments and are ciclosporin treatment-naive. On the basis of the latest data available, its efficacy/adverse effects ratio remains high only for patients who have failed to respond to ciclosporin.
- This proprietary medicinal product is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis in cases of failure to respond, intolerance or contraindication to ciclosporin. It must be prescribed in strict compliance with the SPC and the Committee's recommendations.

➔ Public health benefit

In view of:

- the seriousness of the condition in its severe forms requiring systemic treatment, and its substantial impact on patients' quality of life;
- the prevalence of the condition (between 2 and 5% of the population);
- the partially met medical need for adults with moderate to severe atopic dermatitis requiring systemic treatment;
- the partial response to the identified need on account of:
  - evidence of an impact in terms of morbidity (particularly on IGA 0 or 1, EASI-75, EASI-90 responses and pruritus) according to the studies versus placebo or versus dupilumab, as monotherapy or in a topical basic treatment combination in adults,
  - a safety including high risks in certain at-risk populations and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study,
  - the lack of evidence of an impact, for this orally administered medicinal product, on the delivery of care and the patient's life pathway (particularly in terms of reducing the need for nursing care, hospital admissions required to administer biological medicines and the need for medical transport) and considering the need:
    - to monitor haematological and lipid parameters during treatment;
    - to set up effective contraception for women of reproductive age;

CIBINQO (abrocitinib) is unlikely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the clinical benefit of CIBINQO 50 mg, 100 mg and 200 mg (abrocitinib), film-coated tablet:

- **remains substantial only for the treatment of moderate to severe atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin,**
- **remains insufficient to justify public funding in view of the alternatives available in the other contexts covered by the MA.**

The Committee:

- **approves the continued inclusion of CIBINQO 50 mg, 100 mg and 200 mg (abrocitinib), film-coated tablet, in the list of covered drugs for outpatients and in the list of covered drugs for inpatients only for the treatment of moderate to severe atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin and at the MA dosages.**
- **disapproves inclusion in the list of covered drugs for outpatients and in the list of covered drugs for inpatients for the treatment of moderate to severe atopic dermatitis in adults, who have failed to respond to topical treatments and are ciclosporin treatment-naive, failing comparative data.**

➔ Recommended reimbursement rate for inclusion in the list of covered drugs for outpatients: 65%

OLUMIANT (baricitinib)

- Atopic dermatitis is not generally a serious condition, but in its moderate to severe forms, it has a substantial impact on patients' quality of life and significant psychosocial repercussions.
- OLUMIANT 2 mg and 4 mg (baricitinib), film-coated tablet, is a suspensive symptomatic medicinal product.
- Given the lack of direct comparison to ciclosporin, the efficacy/adverse effects ratio of baricitinib is not defined in adults with moderate to severe atopic dermatitis who have failed to respond to topical treatments and are ciclosporin treatment-naive. On the basis of the latest data available, its efficacy/adverse effects ratio remains low for patients who have failed to respond to ciclosporin.
- This proprietary medicinal product is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis in cases of failure to respond, intolerance or contraindication to ciclosporin. It must be prescribed in strict compliance with the SPC and the Committee's recommendations.

Public health benefit

In view of:

- the seriousness of the condition in its severe forms requiring systemic treatment, and its substantial impact on patients' quality of life;
- the prevalence of the condition (between 2 and 5% of the population);
- the partially met medical need for adults with moderate to severe atopic dermatitis requiring systemic treatment;
- the partial response to the identified need on account of:
  - evidence of a low impact in terms of morbidity versus placebo,
  - a safety including high risks in certain at-risk populations and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study,
  - the lack of evidence of an impact, for this orally administered medicinal product, on the delivery of care and the patient's life pathway (particularly in terms of reducing the need for nursing care, hospital admissions required to administer biological medicines and the need for medical transport) and considering the need:
    - to monitor haematological and lipid parameters during treatment;
    - to set up effective contraception for women of reproductive age;

OLUMIANT (baricitinib) is unlikely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the clinical benefit of OLUMIANT 2 mg and 4 mg (baricitinib), film-coated tablet, remains low for the treatment of atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin.

The Committee approves the continued inclusion of OLUMIANT 2 mg and 4 mg (baricitinib), film-coated tablet, in the list of covered drugs for outpatients and in the list of covered drugs for inpatients for the treatment of moderate to severe atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin and at the MA dosages.

➔ **Recommended reimbursement rate for inclusion in the list of covered drugs for outpatients: 65%**

The Committee disapproves inclusion in the list of covered drugs for outpatients and in the list of covered drugs for inpatients for the treatment of moderate to severe atopic dermatitis in adults, who have failed to respond to topical treatments and are ciclosporin treatment-naive, failing comparative data.

RINVOQ (upadacitinib)

- **For adults (15 mg and 30 mg dosage)**

➔ Atopic dermatitis is not generally a serious condition, but in its moderate to severe forms, it has a substantial impact on patients' quality of life and significant social repercussions.

➔ RINVOQ 15 mg and 30 mg (upadacitinib), prolonged-release tablet, is a suspensive symptomatic medicinal product.

➔ Given the lack of direct comparison to ciclosporin, the efficacy/adverse effects ratio of upadacitinib is not defined in adults with moderate to severe atopic dermatitis who have failed to respond to topical treatments and are ciclosporin treatment-naïve. On the basis of the latest data available, its efficacy/adverse effects ratio remains high only for patients who have failed to respond to ciclosporin.

➔ This proprietary medicinal product is a second-line systemic treatment to be reserved for adults with moderate to severe atopic dermatitis in cases of failure to respond, intolerance or contraindication to ciclosporin. It must be prescribed in strict compliance with the SPC and the Committee's recommendations.

➔ Public health benefit

In view of:

- the seriousness of the condition in its severe forms requiring systemic treatment, and its substantial impact on patients' quality of life;
- the prevalence of the condition (between 2 and 5% of the population);
- the partially met medical need for adults with moderate to severe atopic dermatitis requiring systemic treatment;
- the partial response to the identified need on account of:
  - evidence of an impact in terms of morbidity (particularly on IGA 0 or 1, EASI-75, EASI-90, EASI-100 responses and pruritus) according to the studies versus placebo, as monotherapy or in association with dermocorticosteroids in adults and adolescents (approximately 15% of the sample size), or versus dupilumab as monotherapy in adults),
  - evidence of a clinically relevant impact versus placebo, as monotherapy, in terms of quality of life among patients eligible for systemic treatment,
  - a safety including high risks in certain at-risk populations and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study,
  - the lack of evidence of an impact, for this orally administered medicinal product, on the delivery of care and the patient's life pathway (reducing the need for nursing care, hospital admissions required to administer biological medicines and the need for medical transport) and considering the need:
    - to monitor haematological, liver and lipid parameters during treatment;

- to set up effective contraception for women of reproductive age;

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

Considering all of these elements, the Committee deems that the clinical benefit of RINVOQ 15 mg and 30 mg (upadacitinib), film-coated tablet, remains substantial for the treatment of atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin.

The Committee approves the continued inclusion of RINVOQ 15 mg and 30 mg (upadacitinib), prolonged-release tablet, in the list of covered drugs for outpatients and in the list of covered drugs for inpatients for the treatment of moderate to severe atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin and at the MA dosages.

➔ **Recommended reimbursement rate for inclusion in the list of covered drugs for outpatients: 65%**

The Committee disapproves inclusion in the list of covered drugs for outpatients and in the list of covered drugs for inpatients for the treatment of moderate to severe atopic dermatitis in adults, who have failed to respond to topical treatments and are ciclosporin treatment-naive, failing comparative data.

- **For adolescents aged from 12 years (15 mg dosage)**

➔ Atopic dermatitis is not generally a serious condition, but in its moderate to severe forms, it has a substantial impact on patients' quality of life and significant psychosocial repercussions.

➔ RINVOQ 15 mg (upadacitinib), prolonged-release tablet, is a suspensive symptomatic medicinal product.

➔ The efficacy/adverse effects ratio is high.

➔ This is a first-line systemic treatment to be reserved for moderate to severe forms of atopic dermatitis in adolescents (aged from 12 years) who have failed to respond to topical treatments. It must be prescribed in strict compliance with the SPC and the Transparency Committee's recommendations.

➔ **Public health benefit**

In view of:

- the seriousness of the condition in its severe forms requiring systemic treatment, and its substantial impact on patients' quality of life;
- the high prevalence of the condition in adolescents (14.3%);
- the partially met medical need for adolescents with moderate to severe atopic dermatitis requiring systemic treatment;
- the partial response to the identified need on account of:
  - evidence of an impact in terms of morbidity in study including adults and adolescents (approximately 15% of the sample size), at the 15 mg dose of upadacitinib (only dose recommended for adolescents) versus placebo, as monotherapy or in association with dermocorticosteroids, on clinically relevant outcome measures, such as EASI-75 et EASI-

90, EASI-100, IGA 0 or 1 responses (with improvement by at least 2 points) and pruritus, and the findings of the subgroup analyses in adolescents, which are consistent with those of the total population of these studies,

- a comparable safety to that observed in the other indications, but including high risks, and persisting uncertainties for cardiovascular, venous thromboembolic and carcinogenic risks relating to the populations not studied in the ORAL Surveillance safety study.
- evidence of a clinically relevant impact versus placebo, as monotherapy, in terms of quality of life (total population analysis of the studies including adults and adolescents, and exploratory analyses in the adolescent subgroup),
- the lack of evidence of an impact, for this orally administered medicinal product, on the delivery of care and the patient's life pathway (reducing the need for nursing care, hospital admissions required to administer biological treatments and the need for medical transport) and considering the need:
  - to monitor haematological, liver and lipid parameters during treatment;
  - to set up effective contraception for women of reproductive age;

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

Considering all of these elements, the Committee deems that the clinical benefit of RINVOQ (upadacitinib) 15 mg, prolonged-release tablet, for adolescents remains substantial in the MA indication.

The Committee approves continued inclusion of RINVOQ (upadacitinib) 15 mg, prolonged-release tablet, in the list of drugs covered for outpatients and in the list of drugs covered for inpatients for adolescents in the indication and at the MA dosages.

➔ **Recommended reimbursement rate for inclusion in the list of covered drugs for outpatients: 65%**

Clinical Added Value

CIBINQO (abrocitinib)

➔ **Within the reimbursement scope selected by the Committee**

In view of:

- the evidence in phase III studies of good methodological quality including moderate to severe atopic dermatitis patients requiring systemic treatment:
  - the superiority of abrocitinib 100 mg and 200 mg versus placebo, with a substantial effect size, in terms of IGA 0 or 1, EASI-75 responses, and pruritus after 12 weeks of treatment (ranked outcome measures), as monotherapy (JADE MONO-1 and 2 studies) or in association with a topical basic treatment (JADE COMPARE study) in adult or adolescent patients;
  - the superiority of abrocitinib 200 mg in relation to dupilumab, in terms of EASI-90 response at week 4 (28.5% versus 14.6%, $p < 0.0001$) which was also maintained at week 16 (54.3% versus 41.9%, $p < 0.0008$) and the PP-NRS4 response percentage at week 2 (48.2% versus 25.5%, $p < 0.0001$) in the JADE DARE study (ranked outcome measures);
  - the probability of a lack of flare-up during the maintenance period in patients responding to the induction treatment, which was lower in the placebo group (19.1%) compared to the abrocitinib 200 mg group (81.1%, $p < 0.0001$) and to the abrocitinib 100 mg group (57.4%, $p < 0.0001$) in the JADE REGIMEN study;
- a safety profile in the studies among patients aged approximately 35 years on average primarily marked by acne, nausea, headaches, vomiting, creatine phosphokinase (CPK) elevation, upper abdominal pain, *herpes simplex* and vertigo;

but also considering:

- the lack of evidence of a benefit on patients' quality of life in a condition that particularly affects patients' quality of life with substantial psychosocial repercussions;
- the uncertainties around continued efficacy beyond 26 weeks of treatment for the outcome measures assessing seriousness of the condition and pruritus intensity, and beyond 52 weeks for the probability of a lack of flare-up during the maintenance phase in patients responding to the induction treatment;
- the lack of comparison to ciclosporin, the conventional first-line systemic treatment in atopic dermatitis;
- the risks of major cardiovascular events, malignant tumours, serious infections and all-cause mortality linked with JAK inhibitor class medicinal products requiring restrictions of their use in some patients and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study, in particular patients aged under 65 years (average age of approximately 35 years in studies on atopic dermatitis);

the Committee deems that CIBINQO 50 mg, 100 mg and 200 mg (abrocitinib), film-coated tablet, provides minor clinical added value (CAV IV) in relation to DUPIXENT (dupilumab) in adults with atopic dermatitis requiring systemic treatment in cases of failure to respond, intolerance or contraindication to ciclosporin.

OLUMIANT (baricitinib)

➔ **Within the reimbursement scope selected by the Committee**

In view of:

- the very modest effects observed with baricitinib versus placebo, in all of the phase III studies (as monotherapy or in association with dermocorticosteroids, in particular in patients failing to respond to ciclosporin) and on all of the outcome measures;
- the lack of evidence of a benefit on quality of life in a condition that particularly affects quality of life with substantial psychosocial repercussions;
- the lack of comparison to ciclosporin, the conventional first-line systemic treatment in atopic dermatitis;
- the lack of comparison to dupilumab after failure to respond to ciclosporin, even though it was feasible;
- a safety profile of baricitinib in the studies on atopic dermatitis primarily marked by infections (rhinopharyngitis or upper respiratory tract infections predominantly, *herpes simplex*) and headaches;
- the risks of major cardiovascular events, malignant tumours, serious infections and all-cause mortality linked with JAK inhibitor class medicinal products requiring restrictions of their use in some patients and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study, in particular patients aged under 65 years (average age of approximately 35 years in studies on atopic dermatitis);

the Committee deems that OLUMIANT 2 mg and 4 mg (baricitinib), film-coated tablet, provides no clinical added value (CAV V) in the therapeutic strategy of moderate to severe atopic dermatitis in adults requiring systemic treatment, in cases of failure to respond, intolerance or contraindication to ciclosporin.

RINVOQ (upadacitinib)

- **For adults**

➔ **Within the reimbursement scope selected by the Committee**

In view of:

- the evidence in phase III studies of good methodological quality including moderate to severe atopic dermatitis patients who require systemic treatment:
  - the superiority of upadacitinib 15 mg and 30 mg versus 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 outcome measures), as monotherapy (MEASURE-UP 1 and 2 studies) or in association with dermocorticosteroids (AD-Up study) in adult or adolescent (approximately 15% of the sample size) patients;
  - the superiority of upadacitinib 30 mg in relation to dupilumab, the medicinal product which currently has the strongest 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 pruritus score variation (WP-NRS: -66.88 versus -49.04, $p < 0.001$) after 16 weeks of treatment, in the HEADS-Up study including adults;
- the evidence of clinically significant and clinically relevant differences versus placebo in terms of quality of life (various ranked outcome measures including DLQI) in the studies as monotherapy in adults and adolescents;
- a safety profile of upadacitinib in the studies on atopic dermatitis primarily marked by upper respiratory tract infections, acne, herpes and headaches;

but:

- the uncertainties around continued efficacy beyond 76 weeks of treatment;

- the risks of major cardiovascular events, malignant tumours, serious infections and all-cause mortality linked with JAK inhibitor class medicinal products requiring restrictions of their use in some patients and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study, in particular patients aged under 65 years (average age of approximately 35 years in studies on atopic dermatitis);

the Committee deems that RINVOQ (upadacitinib) 15 mg and 30 mg, prolonged-release tablet, provides minor clinical added value (CAV IV) in relation to DUPIXENT (dupilumab) in adults with atopic dermatitis requiring systemic treatment in cases of failure to respond, intolerance or contraindication to ciclosporin.

- **For adolescents**

In view of:

- the evidence of superiority of upadacitinib 15 mg versus placebo, with a substantial effect size, in terms of IGA 0 or 1, EASI-75, EASI-90 responses, pruritus after 16 weeks of treatment (ranked outcome measures), as monotherapy (MEASURE-UP 1 and 2 studies) or in association with dermocorticosteroids (AD-Up study) in populations including adults or adolescents (approximately 15% of the sample size) with moderate to severe atopic dermatitis requiring systemic treatment;
- the findings of the subgroup analyses on adolescents showing consistent findings with those of the total population of these studies;
- the evidence of clinically significant and clinically relevant differences versus placebo in terms of quality of life (various ranked outcome measures including DLQI) in the studies as monotherapy in adults and adolescents;

but:

- uncertainties around continued efficacy beyond 76 weeks of treatment;
- the lack of direct comparison of upadacitinib 15 mg in relation to dupilumab in a specific study on adolescents;
- the risks of major cardiovascular events, malignant tumours, serious infections and all-cause mortality linked with JAK inhibitor class medicinal products requiring restrictions of their use in some patients and persisting uncertainties relating to the populations not studied in the ORAL Surveillance safety study, in particular patients aged under 65 years;

the Committee deems that RINVOQ (upadacitinib) 15 mg, prolonged-release tablet, provides no clinical added value (CAV V) for the treatment of atopic dermatitis in adolescents aged 12 years and over who require systemic treatment, this treatment including DUPIXENT (dupilumab) and ADTRALZA (tralokinumab).

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