HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
07 OCTOBER 2020
The legally binding text is the original French opinion version

Cyproterone acetate
ANDROCUR 50 mg scored tablets

Reevaluation

Key points

Favourable opinion for reimbursement in:

- hirsutism only in **premenopausal women** in the indication of severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life **and** when satisfactory results have not been obtained following the use of medicinal products containing a lower dose of cyproterone acetate or other treatment options.
- palliative antiandrogen therapy for prostate cancer.

Unfavourable opinion for reimbursement in hirsutism in **postmenopausal women**.

The clinical benefit is now **moderate** (previously it was substantial) in the treatment of hirsutism (only in the defined population, see below) and in palliative antiandrogen therapy for prostate cancer.

Role in the care pathway?

Hirsutism:

The French Endocrinology Society recommends cyproterone acetate, combined with an oestrogen, as a first-line treatment in the event of incapacitating severe hirsutism in premenopausal women.

Spironolactone (off-label), which must be combined with effective contraception, is the second-line treatment in the event of adverse effects, contraindications, patient refusal or a lack of efficacy of cyproterone acetate in premenopausal women.

In postmenopausal women, ANDROCUR (cyproterone acetate) is not recommended and alternative surgical solutions may be envisaged in the rare case when non-tumoural androgenic ovarian hyperactivity persists postmenopause.

Cosmetic measures enabling long-term hair removal may be proposed in combination with antiandrogen therapy: electrolysis or photoepilation.

Role of the medicinal product in the care pathway:

The Committee considers that:

- **in premenopausal women, providing that the recommendations issued are complied with (see special recommendations below), ANDROCUR (cyproterone acetate) retains a role in the treatment of severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life and when satisfactory results have not been obtained following the use of medicinal products containing a lower dose of cyproterone acetate or other treatment options. The Committee has taken into consideration the substantial medical need in the absence of an available alternative for these patients.**
- **in postmenopausal women, in view, firstly, of the increased risk of the development of meningioma demonstrated in this population by the available data (risk that increases with age) and, secondly, of the additional breast cancer risk (postmenopause with oestrogens combined with synthetic progestagens), ANDROCUR (cyproterone acetate) has no role in the treatment of hirsutism. In the rare case of androgenic ovarian hyperactivity, surgical solutions (salpingoophorectomy) may be envisaged.**

Prostate cancer:

According to the 2020 guidelines of the National Comprehensive Cancer Network (NCCN), palliative antiandrogen therapy is aimed at patients with a life expectancy of ≤ 5 years with a high or very high risk of metastases, as well as patients in whom the disease progresses during the no therapy-monitoring phase, with the development of symptoms, or when the increase in PSA (prostate-specific antigen) suggests the imminent development of symptoms. It should be noted that the NCCN guidelines explicitly cite the nonsteroidal antiandrogens nilutamide, flutamide and bicalutamide, but do not mention cyproterone acetate. The European Society for Medical Oncology (ESMO) 2018 guidelines do not mention cyproterone acetate either in the palliative treatment of prostate cancer.

In its 2018 guidelines, the AFU (French Urology Association) highlights that the value of using cyproterone acetate lies in the management of hot flushes related to hormone treatment. Only incapacitating hot flushes should be managed using medicinal treatment.

Role of the medicinal product in the care pathway:

The role of ANDROCUR (cyproterone acetate) is very limited today in view of the alternatives available in palliative antiandrogen therapy for prostate cancer. The risk of meningioma is very limited with ANDROCUR in this indication, possibly due to the shorter exposure duration than in women for the treatment of incapacitating severe hirsutism. However, it should be highlighted that the other nonsteroidal antiandrogens currently used do not expose patients to this risk.

Overall, the Committee considers that cyproterone acetate retains a very limited role in the palliative treatment of prostate cancer, only as a salvage therapy for the management of incapacitating hot flushes related to hormone therapy.

Special recommendations

The Committee reiterates:

- the importance of ensuring patients and healthcare professionals are well informed about the risks of meningiomas, the measures to be taken to prevent them, their detection and their treatment. Annual renewal of the information sheet co-signed by the patient and the doctor must be observed.
- the need for any ANDROCUR 50 mg (cyproterone acetate) prescription to comply with the summary of product characteristics (SPC), particularly as regards investigation for the presence of meningiomas before starting treatment and regularly during treatment. Therefore a brain MRI

should be performed at the start of treatment to verify the absence of meningioma. If treatment is continued for several years, brain imaging by MRI should be performed at most 5 years after the first MRI, then every 2 years if the 5-year MRI is normal.

- the need to use the lowest effective dose of cyproterone acetate to the extent that this is possible, avoiding long-term use at high doses;
- the need to permanently stop treatment if a meningioma is discovered.

COMMITTEE'S CONCLUSIONS

Clinical benefit

Severe hirsutism of non-tumoural origin in women (before menopause)

◗ Hirsutism can lead to a marked deterioration in quality of life, particularly due to its psycho-affective and social consequences.
◗ This proprietary medicinal product is a curative treatment.
◗ Considering:
- old and limited data on the efficacy of ANDROCUR,
- the risk of the development of meningioma, which is lower in young women and increases with age,

the efficacy/adverse effects ratio of ANDROCUR in this indication is moderate.
◗ There are no therapeutic alternatives apart from another proprietary medicinal product containing a very low dose of cyproterone acetate (DIANE 35 (2 mg cyproterone acetate/0.035 mg ethinylestradiol) and generics).
◗ This proprietary medicinal product retains a role in the treatment of severe hirsutism of non-tumoural origin in postmenopausal women (see section 10.1).

Public health impact

Considering:
- the lack of seriousness in terms of threat to patients' life but a very significant impact on their psycho-affective and social life,
- the 5 to 15% prevalence of hirsutism[Erreur ! Signet non défini.] depending on the populations studied and the criteria used, but not specific to severe hirsutism of non-tumoural origin in women,
- the medical need already met by cyproterone acetate,
- the expected but not demonstrated impact on quality of life,
- the absence of any demonstrated impact on the organisation of care,
- the partial response to the identified need,

ANDROCUR 50 mg (cyproterone acetate) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ANDROCUR 50 mg (cyproterone acetate) is moderate in premenopausal women in the indication "severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life" and when satisfactory results have not been obtained following the use of medicinal products containing a lower dose of cyproterone acetate or other treatment options.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in premenopausal women in the indication "severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life and when satisfactory results have not been obtained following the use of medicinal products containing a lower dose of cyproterone acetate or other treatment options" and at the MA dosages.

Severe hirsutism of non-tumoural origin in women after menopause

◗ Hirsutism can lead to a marked deterioration in quality of life, particularly due to its psycho-affective and social consequences.
◗ This proprietary medicinal product is a curative treatment.
◗ The efficacy/adverse effects ratio in this indication in postmenopausal women is poorly established in view of the increased risk:

- of breast cancer post-menopause under treatment with oestrogens combined with synthetic progestagens,
- of meningioma in this population (the risk increases with age).

◗ There are surgical alternatives, with salpingoophorectomy in the rare case of postmenopausal androgenic ovarian hyperactivity.
◗ This medicinal product has no role in the treatment of hirsutism in postmenopausal women, in view, firstly, of the increased risk of the development of meningioma demonstrated in this population by the available data (risk that increases with age) and, secondly, of the additional breast cancer risk (after the menopause with oestrogens combined with synthetic progestagens). In the rare case of postmenopausal androgenic ovarian hyperactivity, surgical solutions with salpingoophorectomy may be envisaged.

Public health impact

Considering:

- the lack of seriousness in terms of threat to patients' life but a very significant impact on their psycho-affective and social life,
- the 5 to 15% prevalence of hirsutism**Erreur ! Signet non défini.** depending on the populations studied and the criteria used, but not specific to severe hirsutism of non-tumoural origin in women,
- the medical need met by salpingoophorectomy in the event of androgenic ovarian hyperactivity,
- the expected but not demonstrated impact on quality of life with hirsutism, which affects psycho-affective and social life,
- the absence of any demonstrated impact on the organisation of care,
- the lack of response to the identified need,

ANDROCUR 50 mg (cyproterone acetate) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ANDROCUR 50 mg (cyproterone acetate) is insufficient to justify its reimbursement by public funding in view of the alternatives available in postmenopausal women in the indication "severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life".

The Committee issues an unfavourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in postmenopausal women in the indication "severe hirsutism of non-tumoural origin in women (idiopathic, polycystic ovarian syndrome), when it has a severe impact on psycho-affective and social life".

Palliative antiandrogen therapy for prostate cancer

◗ Prostate cancer is life-threatening and is the third-ranked cause of cancer-related death**Erreur ! Signet non défini.**.
◗ This is a palliative treatment.
◗ Considering:

- the limited efficacy data,
- the potential risk of the development of meningioma, although this risk is limited in view of the shorter exposure duration in these patients who have a life expectancy of ≤ 5 years,

the efficacy/adverse effects ratio of ANDROCUR is moderate in this indication.

◗ There are therapeutic alternatives with the nonsteroidal antiandrogens cited in chapter **Erreur ! Source du renvoi introuvable.**.
◗ This proprietary medicinal product is a salvage therapy with a restricted role in the management of incapacitating hot flushes related to hormone therapy.

Public health impact

Considering:

- the seriousness of the disease, for which palliative treatment has been initiated,
- its prevalence, with around 5,000 patients having metastatic prostate cancer,
- the partially met medical need,
- the absence of any demonstrated impact on the organisation of care,
- the very partial response to the need, restricted to the management of incapacitating hot flushes related to hormone therapy,

ANDROCUR 50 mg (cyproterone acetate) is unlikely to have an additional impact on public health.

Given all of these elements, the Committee considers that the clinical benefit of ANDROCUR 50 mg (cyproterone acetate) is moderate in the indication of palliative antiandrogen therapy for prostate cancer.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication of palliative antiandrogen therapy for prostate cancer and at the MA dosages.