TRANSPARENCY COMMITTEE

The legally binding text is the original French version

OPINION

19 July 2006

ANDROCUR 100 mg, scored tablet
3 blister packs 20 tablets : 340 417-5

Applicant: Schering SA

cyproterone acetate

List I

For this indication, treatment must be decided by a multidisciplinary team including for example a psychiatrist, a psychotherapist and an endocrinologist.

Date of Marketing Authorisation: February 26, 1996, amended on July 21, 2005 (extension of indication: “control of libido …”).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “control of libido in sexual deviation in combination with psychotherapy”
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Cyproterone acetate (CPA)

1.2. Background
First medicinal product for this indication

1.3. Indications
− Palliative treatment for prostate cancer.
− Control of libido in sexual deviation in combination with psychotherapy

1.4. Dosage
In prostate cancer: 200 to 300 mg, 2 to 3 tablets daily continuously.
Control of libido in sexual deviation:
This treatment should be combined with psychotherapy.
The recommended starting dose of Androcur is 100 mg. The dose may be increased to 200 mg daily and up to 300 mg daily for a short period. Research on the minimum effective dose (which may be 50 mg daily) should be carried out as soon as possible.
When discontinuing treatment, the dose should be reduced gradually over several weeks.
Treatment for this indication must be decided by a multidisciplinary team including a psychiatrist, a psychotherapist and an endocrinologist.
In adolescents, bone maturation should be assessed before treatment is initiated. Androcur should not be given to adolescents whose bone maturation is incomplete.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

G : Genito urinary system and sex hormones
G03 : Sex hormones and modulators of the genital system
G03H : Antiandrogens
G03HA : Antiandrogens, plain
G03HA01 : Cyproterone

2.1 Medicines in the same therapeutic category
None.
2.2 Medicines with a similar therapeutic aim

None.

3 ANALYSIS OF AVAILABLE DATA

The company submitted the results of 3 comparative\textsuperscript{1,2,3} and 3 observational\textsuperscript{4,5,6} studies.

3.1. Cooper study (1981)

The aim of this study was to compare CPA with placebo in 9 patients with sexual behaviour disorders with social and legal consequences.

The trial was scheduled over 5 periods of 4 weeks. Each patient was his own control and received successively:

1. no treatment
2. 50 mg CPA twice daily
3. no treatment
4. placebo twice daily
5. no treatment.

Contrary to the SPC recommendations, the dose remained the same during the study.

Endpoints
- a sexual interest score: visual analogue scale from 0 to 100,
- a sexual activity score: number of orgasms and ejaculations during the last 7 days
- number of spontaneous daily erections,
- planned masturbation sessions: visual analogue scale from 0 to 100,
- serum testosterone.

Results

<table>
<thead>
<tr>
<th>Mean score in the last week of each period (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
</tr>
<tr>
<td>No treatment</td>
</tr>
<tr>
<td>Sexual interest score</td>
</tr>
<tr>
<td>Sexual activity score</td>
</tr>
<tr>
<td>number of spontaneous daily erections</td>
</tr>
<tr>
<td>Arousal and pleasure during planned masturbation</td>
</tr>
<tr>
<td>Serum testosterone (unit not specified in publication)</td>
</tr>
</tbody>
</table>

Statistical analysis was not possible because of the small number of patients and the lack of randomisation of the drugs. A reduction in end-point values was recorded after CPA treatment.

\textsuperscript{1} Cooper A. J Psychiatry 1981; 22; 5:458-465
\textsuperscript{2} Cooper A. J Can J Psych 1992; 37:687-693
\textsuperscript{3} Bradford JMW. Arch Sex Behav 1993; 2; 5:383-402
\textsuperscript{4} Bradford JMW. Arch Sex. Behav 1993; 22; 6: 629-641
\textsuperscript{5} Laschet U. Neurol Psychol Pharmacol 1971;2;99-104
\textsuperscript{6} Mothes B. Symposium Schering 1971
3.2. **Cooper study (1992)**

The aim of this study was to compare CPA and medroxyprogesterone acetate (MPA) in paedophiles. MPA has never received a Marketing Authorisation (MA) for this indication and is no longer used in France.

This was a randomised double blind study, scheduled over 7 periods of 4 weeks:

1. placebo
2. CPA or MPA (100 mg/day)
3. CPA or MPA (200 mg/day)
4. placebo
5. MPA or CPA (100 mg/day)
6. MPA or CPA (200 mg/day)
7. placebo.

Each patient was his own control.

**Endpoints**
- frequency of sexual thoughts, masturbation, morning erections and level of sexual frustration
- observation of sexual behaviour: exhibitionism, masturbation…
- phallometry
- laboratory values (serum testosterone, FSH, LH)

Treatment was administered to 7 patients. This small number precluded statistical analysis. Both drugs resulted in a similar reduction in the number of sexual thoughts and fantasies, masturbations, morning erections, and episodes of sexual frustration. Testosterone, FSH and LH levels decreased during the active drug treatment periods, but returned to initial values at the end of the 3rd placebo period.

3.3. **Bradford study (1993)**

The aim of this study was to show the efficacy of CPA, compared to placebo in improving sexual behaviour, and reducing arousal, for the treatment of sexual deviation.

This was a 13-month randomised, double blind, crossover study:

1. a 1-month observation period without treatment (baseline)
2. a 3-month period during which patients were randomised to either 200 mg CPA daily or placebo
3. periods of 3-month each, during which patients alternatively received either CPA (50 mg to 200 mg) daily or placebo.

The posology of CPA was adjusted every month.

**Endpoints**
- reduction in sex hormone levels (testosterone, LH, FSH and prolactin),
- sexual arousal evaluated through the measurement of penis circumference in mm and through self-assessment
- psychopathological scores
- sexual desire scores.

A total of 19 sexual delinquents were included in the trial.
Results

Effects of ANDROCUR on endocrine functions, sexual arousal, physiopathology and sexual desire (n=19)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>Placebo Mean (SD After treatment)</th>
<th>CPA Mean (SD After treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>24.81 (7.93)</td>
<td>23.52 (6.44)</td>
<td>12.37 (6.9)*</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>12.24 (4.81)</td>
<td>12.18 (5.15)</td>
<td>10.78 (5.22)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>10.78 (6.25)</td>
<td>11.42 (7.17)</td>
<td>7.83 (5.37)*</td>
</tr>
<tr>
<td><strong>Sexual arousal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slide - Change in penis circumference (mm)</td>
<td>11.01 (8.77)</td>
<td>11.07 (9.71)</td>
<td>7.33 (9.54)</td>
</tr>
<tr>
<td>Fantasy - Change in penis circumference (mm)</td>
<td>6.66 (7.23)</td>
<td>11.25 (8.67)</td>
<td>5.21 (7.84)</td>
</tr>
<tr>
<td>Slide - Self-assessment</td>
<td>3.29 (1.36)</td>
<td>2.53 (1.81)</td>
<td>2.35 (1.62)</td>
</tr>
<tr>
<td>Fantasy - Self-assessment</td>
<td>2.65 (1.47)</td>
<td>2.41 (1.42)</td>
<td>2.09 (1.68)</td>
</tr>
<tr>
<td><strong>Psychopathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric scale (BPRS)(^*)</td>
<td>11.44 (5.24)</td>
<td>7.33 (5.91)</td>
<td>5.22 (4.59)*</td>
</tr>
<tr>
<td>Buss-Durkee Hostility Inventory</td>
<td>35.67 (10.43)</td>
<td>37.50 (9.98)</td>
<td>35.39 (9.11)</td>
</tr>
<tr>
<td><strong>Sexual desire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual interest score</td>
<td>3.65 (1.09)</td>
<td>2.94 (1.11)</td>
<td>2.78 (1.17)</td>
</tr>
<tr>
<td>Sexual activity score</td>
<td>5.65 (4.69)</td>
<td>6.58 (8.25)</td>
<td>3.59 (4.19)*</td>
</tr>
</tbody>
</table>

\(^*\)BPRS: Brief Psychiatric Rating Scale
\(^\d\)p<0.05 active drug vs placebo at end of treatment

A statistical analysis was performed despite the small number of patients and showed that there was a significant difference in serum testosterone and FSH levels, BPRS and sexual activity score between placebo and CPA at the end of treatment.


The aim was to show the efficacy of CPA in reducing sexual desire in paedophiles, for the treatment of sexual deviation.

This was a noncomparative study in patients receiving 50 to 200 mg CPA daily for 9–12 weeks.

**Endpoints**

- change in serum testosterone levels
- assessment of sexual behaviour by studying penile tumescence after listening to recordings.

Twenty patients were included.

**Results**

Serum testosterone level fell during treatment. The higher was the baseline value, the greater was the decrease.

The efficacy of CPA on sexual behaviour was uncertain; sexual behaviour varied according to the type of recording listened to. In addition, the study design (noncomparative, small patient number) was inadequate to provide conclusive evidence on efficacy.
3.5. Lashet study (1971)

This was a follow-up study of 110 patients with sexual disorders receiving oral or parenteral CPA in a psychoendocrinology centre in Germany. Treatment duration was 6 to 50 months; half of the patients were sexual aggressors.

**Results**

A reduction in sexuality was observed in 80% of patients at the 100 mg/day dose. The noncomparative design precluded any conclusions on CPA efficacy.

3.6. Mothes study (1971)

This was a follow-up study of 352 patients treated for sexual deviation with CPA (100 to 300 mg/day) over a maximum period of 3 years.

The noncomparative study design precluded any conclusions on CPA efficacy.

3.7. Adverse Events/Safety

Lashet reported increased fatigue, sleep disorders, depressive moods, weight gain, and reduced growth of body hair. Gynaecomastia was reported in 20% of patients after 6 to 8 months of treatment.

According to the AFSSAPS\(^7\) public assessment report (April 2005), dyspnoea, thromboembolism and osteoporosis have been reported. No hepatic toxicity has been observed in this indication.

Overall, the safety profile of Androcur in this extended indication was not different from what was previously known.

3.8. Conclusion

The company submitted the results of 3 studies in patients with sexual behaviour disorders, comparing CPA with placebo and/or medroxyprogesterone acetate (a drug which does not have a Marketing Authorisation (MA) for this indication). The quantity of efficacy of CPA in this extension of indication is difficult to assess as it is based on old studies of questionable design (low numbers, patients acting as their own controls, unsuitable endpoints,…) conducted under conditions that do not correspond exactly to the MA wording which stipulates that a psychotherapy should be combined with the drug. These studies show a reduction in sexual interest and activity scores and a reduction in serum testosterone level.

The Committee regretted that no data had been submitted on the combination of CPA with psychotherapy, as described in the SPC.

The tolerability of Androcur in this extended indication was not different from what was previously reported.

---

\(^7\) AFSSAPS: French health products safety agency
4.1. Actual Benefit

- Uncontrolled libido in paraphilia in combination with psychotherapy may have legal and social consequences and may be life-threatening to the victim of an assault.
- Androcur is a symptomatic treatment
- The efficacy/safety ratio of Androcur is difficult to evaluate, given the available data.
- Androcur is a first-line drug, in combination with psychotherapy.
- There are no alternative drugs.

Public Health Benefit:

- The seriousness of paraphilic acts is essentially related to the potential impact (psychological, physical, social and economic) on the victims, which is probably underestimated. It is also related to the psychological distress of the offenders. The public health burden is, at the least, moderate.
- Therapeutic management of libido in potential sexual offenders is an uncovered public health need which constitutes a priority in the “National Campaign to limit the impact of violence, risk-related behaviour and addictive behaviour, on health”.
- There are insufficient data to estimate the impact of Androcur, particularly in controlling libido leading to a sexual offence. Nevertheless, in the absence of any recognised effective alternatives and in view of the accumulated clinical experience with Androcur, an impact on morbidity as well as a partial response to the identified public health need are expected.
- The risk that paraphilic patients who have committed a sexual offence may not comply with treatment cannot be ignored. In addition, the impact of long-term Androcur treatment on bone mineral density (osteoporosis) is not known and it is uncertain whether clinical results can be extrapolated to real life.
- In view of these observations, a small public health benefit is expected from Androcur. This should be confirmed by a follow-up study of treated patients.

In the present state of knowledge, the actual benefit of Androcur in this extension of indication is substantial.

4.2. Improvement in Actual Benefit

Androcur provides a minor improvement in actual benefit (IAB level IV) in controlling the libido of patients with sexual deviation, when combined with psychotherapy.

4.3. Therapeutic use

According to the consensus conference on “Psychopathology and current treatment of perpetrators of sexually aggressive crimes”\(^8\), published by the French Psychiatry Federation, patient management is based on two approaches:

\(^8\) “Psychopathologie et traitements actuels des auteurs d'agression sexuelle”, report published in 2001 by the Fédération Française de Psychiatrie
- Psychotherapy, particularly cognitive behavioural therapy, group psychotherapy or family and systemic therapy.
- Drug therapy with different types of drugs:
  - Antiandrogens, including CPA and GnRH analogues which do not have a Marketing Authorisation (MA) for this indication.
  - Psychotropics (antipsychotics, mood stabilisers and serotonin selective re-uptake inhibitors) are only indicated when psychiatric illness is associated with the disorder.

Surgical management, being irreversible, is almost never used in France. Past procedures were:
- destroying certain areas of the hypothalamus and disconnect the frontal lobes of the cerebral cortex to reduce gonadotrophin production.
- surgical castration (orchidectomy).

According to the consensus conference guidelines, antiandrogen therapy may create a favourable environment for psychotherapy. However, long-term undesirable effects cannot be excluded (especially reduced bone mineral density). It is prescribed in patients with a high risk of committing a sexual assault (rapist or paedophile) when other treatments are ineffective or when psychotherapy is unsuitable because of the patient’s intellectual level.

4.4. Target population

There are no epidemiological data in France on numbers of non-delinquent patients with paraphilia who need treatment. In 2003, 8109 persons were convicted and detained for sexual offences. There are no statistics on the percentage of offenders who are the subject of a treatment order. In addition, convicted sex offenders may receive antiandrogen therapy after release.

In the absence of epidemiological data, experts consider that the likely target population would be between 500 and 2000 patients.

4.5. Transparency Committee Recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services in the new indication in the marketing authorisation “Control of libido in sexual deviation in combination with psychotherapy”.

4.5.1 Packaging: appropriate for the prescription conditions.

Because the pharmaceutical form of Androcur (tablets to be taken daily) is associated with a risk of non-compliance, particularly in sexual delinquents, the Committee considered that the development of a monthly treatment is warranted.

In view of the current situation, the Transparency Committee requests, with the public authorities’ initiative, to conduct a trial in patients treated with Androcur for “control of libido in sexual deviation” which would describe the following under real life conditions:
- profile of treated patients (age, type of sexual deviation, comorbidities)
- treatment methods (dose, duration, compliance, reasons for treatment discontinuation)
- sexual offences committed and/or recidivism
- reason for starting treatment (treatment order or at the patient’s request).

---