HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

METHADONE AP-HP 1mg, gelatin-coated capsule
Box of 7 (CIP: 379 146-2)

METHADONE AP-HP 5mg, gelatin-coated capsule
Box of 7 (CIP: 379 147-9)

METHADONE AP-HP 10mg, gelatin-coated capsule
Box of 7 (CIP: 379 148-5)

METHADONE AP-HP 20mg, gelatin-coated capsule
Box of 7 (CIP: 379 149-1)

METHADONE AP-HP 40mg, gelatin-coated capsule
Box of 7 (CIP: 380 508-1)

Applicant BOUCHARA - RECORDATI

Methadone (hydrochloride)

Treatment is restricted to adults and adolescents over 15 who agree to receive it. Conditions of prescription and supply:

1) Narcotic: prescription-only medicine under the terms laid down in the Decree of 31 March 1999. Up to fourteen days supply at a time may be prescribed. Up to seven days supply at a time may be handed over by the pharmacist. The prescribing doctor must indicate on the prescription the length of time that the amount to be supplied is intended to last. However, the prescribing doctor may overrule the principle of splitting the amount to be supplied by adding the words "to be supplied in a single batch" to the prescription if the patient's particular circumstances justify this.
Where the drug is to be supplied by a dispensary, the prescription may, if necessary, specify that it should be given to the patient by the dispensing pharmacist every day.

2) Drug subject to initial prescription for six months by doctors working in specialist drug dependency units (DDU) or in hospital departments specialising in drug dependency.
Unrestricted renewal. Medicinal product requiring specific monitoring during treatment

Date of marketing authorisation: 20 September 2007 (national procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Methadone hydrochloride

1.2. Indication
"Replacement treatment for individuals heavily dependent on opiates in the context of medical, social and psychological management. Patients who have been taking the syrup form for at least a year and who have been stabilised, particularly in respect of their medication and addictive behaviour, may be transferred to this form."

1.3. Dosage
The gelatin-coated capsule form is not designed for starting treatment with methadone

Transfer from the syrup form to the gelatin capsule form
The initial dosage for the gelatin-coated capsule form must correspond to the maintenance dose reached with the syrup form.
The patient must take the capsule for the first time the day after his or her last dose of the syrup form, at the usual time.
The normal dosage is 60 to 100 mg/day, though some patients may require higher doses.
Any subsequent dose changes will, as for the syrup form, be made in the light of a clinical reassessment of the patient, taking account of other medical circumstances.
The treatment will be administered once a day (see section headed Conditions of prescription and supply).
Conditions for stopping treatment
If it is decided that an attempt to stop the replacement treatment should be made, the dose must be reduced very slowly, leaving an interval of at least a week between each reduction (1 to 5 mg) in the dose. Particular caution is advised throughout this period, and patients must be closely monitored in order to detect any clinical symptoms pointing to withdrawal syndrome (this must immediately be compensated for by returning to the previous dose level) and any resumption of addictive behaviour that would be incompatible with treatment using the gelatin capsule form (see section headed Conditions of prescription and supply).
(Refer to SPC)

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification 2007:
N : nervous system
N07 : other medicines for the nervous system
N07B : medicines used in addictive disorders
N07BC : medicines used in opiate dependency
N07BC02 : methadone

2.2. Medicines in the same therapeutic category
Buprenorphine : SUBUTEX, BUPRENORPHINE ARROW
Methadone : METHADONE HYDROCHLORIDE AP-HP, syrup

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The marketing authorisation for METHADONE AP-HP capsules is based on a bioequivalence study versus the syrup form conducted on 26 opiate-dependent adult volunteers.
This study showed that the 20 mg capsules (three capsules once a day together) were bioequivalent to the 60 mg/15 ml syrup. The results were then transposed to the other dosages.

3.2. Safety

No serious adverse events were observed in the bioequivalence study.
The capsule form did not cause any new adverse events that had not been seen with the syrup form.

According to the SPC, the most frequent adverse events occurring in opiate-dependent patients taking methadone in the maintenance phase are abundant sweating, nausea and constipation.

3.3. Conclusion

The study showed METHADONE AP-HP 20 mg capsules (three capsules once a day together) were bioequivalent to METHADONE syrup 60 mg/15 ml, but did not precisely quantify the size of the effect observed.

The marketing authorisation indication states that METHADONE AP-HP gelatin capsules must be used as replacement treatment for patients who are heavily dependent on opiates in the context of medical, social and psychological management. Patients who have been taking the syrup form for at least a year and who have been stabilised may be transferred to this form.

The study presented in the file is insufficient to confirm the efficacy of METHADONE AP-HP gelatin capsules in this indication.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Opiate dependency is a serious condition that can endanger an individual's vital prognosis, either because of the risks of overdose or because of the risks associated with the way the opiates are taken (HIV and hepatitis C infection in the case of addicts who inject).

The efficacy/safety ratio of METHADONE AP-HP is high. This medicine must be administered in the context of global medical, social and psychological management.

Therapeutic alternatives to this proprietary drug exist.

Public health benefit:

The public health burden represented by opiate dependency and the harmful consequences of IV injection of these illegal drugs or abuse of replacement treatments is moderate.

Improvement in the overall management (medical, psychological and social management) of drug addiction is a public health need in the context of established priorities (2007 - 2011 governmental plan on the management and prevention of addiction; 2004 - 2008 governmental plan to combat illegal drugs, tobacco and alcohol; public health legislation; etc.).

The data available (bioequivalence study) do not show whether there is any direct or indirect public health impact (i.e. as far as the patient and society are concerned) from using the gelatin-coated capsule form of methadone as opposed to the syrup form.

However, although there is no evidence to back them up, various arguments can be put forward suggesting that this form has a positive direct impact, in particular:

- the gelatin-coated capsule form of methadone is more convenient to take and so is likely to improve patients' quality of life and increase therapy compliance by making the continuation of methadone treatment more acceptable to individuals who have been taking the syrup form for at least a year;
- the fact that gelatin-coated capsules can be administered in doses varying by 1 mg could meet the need for dosage levels allowing optimum dose adjustment towards the end of treatment for individuals who are having the medication gradually withdrawn. This is not currently possible with the dosages of the syrup form that are currently available.

These theoretical advantages for the patient should be set against the identified risks which cannot rule out a negative indirect public health impact, particularly the risks of accidental intoxication in naïve individuals (children) and abuse (trafficking and injections).

In the final analysis, the impact of METHADONE AP-HP gelatin-coated capsules will depend on all the measures aimed at supporting the prescription, supply and use of this proprietary drug and on the measures set out in the risk management plan.

Furthermore, as METHADONE AP-HP gelatin-coated capsules are indicated as transfer product in patients who have been taking the syrup form for at least a year and who have stabilised, this medicinal product does not seem able to meet the objective of political and medical circles to widen access to methadone treatments.

Consequently, although METHADONE AP-HP gelatin-coated capsules offer a potential benefit in respect of the identified need, this medicinal product is not expected to offer any public health benefit in view of the lack of sufficient data.

The actual benefit of METHADONE AP-HP gelatin-coated capsules in this indication is substantial.

4.2. Improvement in actual benefit

METHADONE AP-HP offers no improvement in actual benefit compared to the syrup form (IAB V).

This proprietary product is an additional therapeutic option that is useful in the replacement therapy of individuals heavily dependent on opiates.

4.3. Therapeutic use

Replacement therapy for individuals who are dependent on opiates involves the use of buprenorphine and methadone[1]. It must be administered in the context of global medical, social and psychological management.

Before treatment is started, the doctor must take account of the type of opiate dependency, the length of time that has passed since the individual last took opiates, and the level of opiate dependency.

Abuse of opiate replacement medicinal products is still an issue. The clinical practice guidelines published by ANAES in 2004[2] state that it is essential to avoid IV injection of any tablet or gelatin-coated capsule in view of the major risks associated with IV injection of a medicinal product that has not been designed for this administration route (bolus, infections, local complications, etc.). Any opiate replacement medication supplied in a solid form (tablets, gelatin-coated capsules) must have the optimum formulation to prevent injection (combination with an antagonist, gelling agents, etc.).
The principal recommendations in these guidelines, which are designed to try to prevent and reduce this practice, are for improvements in the diagnosis and monitoring of patients and in the prescription and supply of replacement medicinal products.

METHADONE AP-HP capsules are indicated in replacement therapy for individuals heavily dependent on opiates in the context of medical management.
The marketing authorisation for METHADONE AP-HP gelatin-coated capsules states that it must be used only as a medication to which individuals can be transferred once they have been taking the syrup form for at least a year and have been stabilised, particularly with regard to their medication and addictive behaviour.

As no data is available on use in adolescence (individuals aged between fifteen and eighteen), METHADONE AP-HP gelatin-coated capsules must be used with caution in this age group.

4.4. Target population

The target population for METHADONE AP-HP gelatin-coated capsules is constituted by adult and adolescent patients aged over fifteen who are dependent on opiates, who have been taking the syrup form for at least a year and who have been stabilised, particularly with regard to their medication and addictive behaviour.

Of the 150,000 to 180,000 users of heroin, between 80,000 and 100,000 are currently receiving replacement therapy. About half of these are receiving regular treatment with buprenorphine or methadone, amounting to 40,000 to 50,000 patients.

In the current state of knowledge, there is no clear consensus as to the criteria which should be used to transfer patients (only those who have been taking the syrup form for at least a year and who are stabilised with regard to their medication and addictive behaviour) to METHADONE AP-HP gelatin-coated capsules. It is therefore not possible to give a precise figure for the population eligible to be prescribed METHADONE AP-HP gelatin-coated capsules.

1 Therapeutic strategy for opiate-dependent individuals: role of replacement treatments. Consensus conference, ANAES, June 2004
2 Reducing abuse of opiate replacement medication. Clinical practice guidelines. ANAES, June 2004

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in the indication specified in the marketing authorisation.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 65%