

## **Buprenorphine (final decision)**

### ***I. Introduction***

Buprenorphine (INN) was placed in 1989, by a decision of the UN Commission of Narcotic Drugs, in Schedule III of the Convention on Psychotropic Substances (1971 Convention). The decision followed the recommendation of the 25<sup>th</sup> meeting of the Expert Committee on Drug Dependence (ECDD). In 2000, during its 32<sup>nd</sup> meeting, ECDD considered the question of buprenorphine scheduling and recommended critical review of the substance, taking into account relevant request of the International Narcotics Control Board (INCB) made already in 1995, as well as the perceived lack of rationale for the control of this substance under the 1971 Convention rather than the 1961 Single Convention (1961 Convention).

In its 33<sup>rd</sup> meeting ECDD commenced the critical review of the scheduling of buprenorphine. The Committee considered that buprenorphine met both the requirements for scheduling in the 1961 Convention and for its present scheduling in the 1971 Convention. The Committee considered that taking up a decision was hindered by the lack of an authoritative guidance for a choice between the two possibilities. For that reason the Committee did not discuss which Schedule of the 1961 Convention would be more appropriate in the case of transfer. The Committee recommended that WHO develop in consultation with UN bodies, guiding principles for making a choice of the more appropriate convention when a substance under review meets the criteria for the both conventions. The Committee concluded that the final decision on buprenorphine should be taken at a future meeting, so the Committee did not finish its critical review process.

After the meeting, WHO Secretariat developed additional guidelines, with assistance of representatives of the International Narcotics Control Board (INCB) and United Nations Drug Control Programme (UNDCP). The draft of Supplementary Guidelines was presented to the Executive Board for approval. The Executive Board discussed the draft additional guidelines in its 114<sup>th</sup> and 115<sup>th</sup> meetings. For many members of the Board the main point of disagreement was the question of the influence that transfer of substances between conventions will have on implementation of conventions by national law. It was feared that such transfer would, as a consequence, give rise to rescheduling at the national level, which would have an unintended effect of restricting access to drugs used to treat drug dependence. In its decision taken up during the 115<sup>th</sup> meeting the Executive Board agreed to maintain the revised Guidelines for the WHO review of dependence-producing psychoactive substances for international control approved in decision EB105(3), and asked the Secretariat and the ECDD to continue their work on the issue.

As the result the Expert Committee has to find guidance for its decision from the conventions, from the existing guidelines as are already established by WHO's Executive Board, and from general legal principles.

Although the greater part of this critical review took place during the 33<sup>rd</sup> meeting of the ECDD, the Committee should now take also into consideration information received by WHO Secretariat after the Committees' last meeting.

## **II. New information acquired by the Secretariat since 2002**

### ***a. Change in role of buprenorphine***

Buprenorphine (and other medicines used in agonist pharmacotherapy of opioid dependence, like methadone) is generally recognized now as an effective and cost effective treatment for opioid dependence. In addition, scientific evidence has accumulated that buprenorphine maintenance is supportive against the transmission of HIV among injecting drug users (IDU's) and it is regarded now as a very important part of HIV prevention programmes. It is also supportive to increase compliance with antiretroviral therapy (ART). Buprenorphine maintenance treatment programmes provide opportunities for expanded HIV prevention among injecting drug users and a platform for implementation of directly observed antiretroviral therapy for people with opioid dependence who have also HIV/AIDS, as well as therapy for opportunistic infections such as tuberculosis for such people.

It should be mentioned that at present, apart from sub-Saharan Africa, an estimated one third of all new HIV infections are related to injecting drug use and HIV prevalence rates of as high as 60-80% are seen in many drug injecting populations. However, only 5% of all IDU's are reached with treatment programs. Therefore, it is extremely important for international public health to increase the access to agonist pharmacotherapy, and especially in order to halt the HIV epidemic.

In response to the resolution of the UN Economic and Social Council 2004/40, the Management of Substance Abuse Team under WHO Department of Mental Health and Substance Abuse, has started the process of developing Guidelines for psychosocially assisted pharmacological treatment of persons dependent from opioids, in consultation with UNODC. These guidelines are to be published at end of 2006.

It can be expected that these guidelines will not only give guidance on the rational use of buprenorphine in the treatment of dependence according to the state of the art of medicine, but also will contribute to the prevention of misuse and abuse of buprenorphine.

Buprenorphine maintenance treatment (BMT) is currently available in 29 countries: Australia, Austria, Belgium, China (Hong Kong), Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, India, Indonesia, Israel, Italy, Lithuania, Luxembourg, Malaysia, Netherlands, Norway, Portugal, Singapore, Slovak Republic, Slovenia, South Africa, Sweden, Switzerland, Ukraine, United Kingdom and the United States of America. Several of those countries started with very large treatment programs. Among countries that will start treatment programs is also Iran.

In March 2005, WHO included methadone and buprenorphine in the 14<sup>th</sup> edition of the Essential Medicines List for use in agonist therapy, which means that access to buprenorphine became a human right <sup>1</sup>

The availability of buprenorphine was strongly advocated in 2005 in the United States, by resolutions of the College on Problems of Drug Dependence (a WHO Collaborating Centre), the American Academy of Addiction Psychiatry, the American Psychiatric Association and the American Society of Addiction Medicine. (As these resolutions are identical, only one is attached as an **annex** to this document). The message of these resolutions is that a change in scheduling would form a serious barrier for the accessibility to treatment.

Recently, after the agenda for the 34th ECDD was published, also many other organizations expressed their concern, inter alia the International Harm Reduction Association (IHRA). The governments of Australia and the United States of America wrote letters (**annexes**).

Moreover, the mandatory the importation quota for buprenorphine if scheduled under the Single convention could limit its availability in some countries.

### ***b. abuse and diversion reports***

The INCB reported the diversion and smuggling of buprenorphine injections in South East Asia, mainly in India, Bangladesh and Nepal since 1994, originating from Indian domestic sources. More recently seizures of buprenorphine preparations of Indian origin were reported from Armenia, Azerbaijan and the Russian Federation, Pakistan (large seizures in 2004) and from India (bound towards the United Arab Emirates and Iran).

An Indian national survey in 2004 on the use of the substance showed the increasing popularity of abuse of buprenorphine in injectable form, which is a major concern, particularly in relation to growing rates of HIV infection associated with injecting drug use. The number of countries reporting abuse of the substance has grown. Abuse of and/or seizures of buprenorphine have been reported by countries in Europe (Denmark, Finland, France, Norway, Portugal, Spain), Western Asia (Iran) and South East Asia (Japan). Finnish authorities report that buprenorphine seized in Finland has partly been diverted from domestic distribution channels in that country but that the major part of abused buprenorphine, in the form of the preparation Subutex, is smuggled from France or is illicitly obtained by Finnish drug users in Latvia.

As far as reports on seizures of buprenorphine are concerned, please note that under the 1971 Convention, Governments have no obligation to report to INCB on their seizures of psychotropic substances. Therefore, information on seizures of buprenorphine is not complete.

According to the INCB Annual Report 2005, there has been significant diversion of preparations prescribed to opiate users registered in substitution treatment programmes in France, which has considerable experience in dispensing buprenorphine for the treatment of persons dependent on opioids,. In some countries, such as Finland, buprenorphine has become the most important illicitly used substitute for opiate users; in some illicit markets, it has almost totally replaced heroin. The INCB notes that in several countries buprenorphine continues to be diverted from

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<sup>1</sup> Committee On Economic, Social And Cultural Rights, Twenty-Second Session, The Right To The Highest Attainable Standard Of Health (General Comments), Geneva, May 2000, E/C.12/2000/4, point 12.

licit distribution channels and that opiate users are used as couriers, traveling from one country to another to obtain medical prescriptions for the substance.

Seizures reported to UNODC include seizures by Bangladesh, Finland (37,300 tablets), Mauritius and Sweden for 2003 and Bangladesh, Finland (32,970 tablets), Georgia, Mauritius, Pakistan (111,700 injections) and Portugal for 2004.

Abuse of buprenorphine is however not a new phenomenon. For example, before 1990 buprenorphine was registered as a psychotropic substance in the former Soviet Union and was used for treatment of withdrawal symptoms. However, due to increase in its abuse and the subsequent registration of buprenorphine addicts, buprenorphine was transferred to the list of narcotic drugs in the Russian Federation. Due to this fact, access to agonist therapy is very difficult at the moment in Russia. Many other countries control buprenorphine either entirely or partly as a narcotic drug providing thereby more stringent control measures than for other psychotropic substances.

In its Annual Report 2005 the INCB recommends WHO the following (par 652, recommendation 43):

Buprenorphine, a potent opioid included in Schedule III of the 1971 Convention continues to be diverted from domestic distribution channels in several countries. The Board reiterates its request to WHO to examine information on the misuse and diversion of buprenorphine when reviewing the control status of the substance and to consider reviewing the control status of other mixed agonist-antagonist analgesics.

### ***c. Effects of rescheduling as reported by the member states in answer to the WHO Questionnaire***

56 Countries answered the questions on buprenorphine asked in the questionnaire sent out by WHO in October 2005 to all the Member states. Of these, 42 answered that there would be no impediment for access if the substance would be scheduled in Schedule I of the Single Convention. For a number of countries, the reason for this was, that the substance was not marketed in their country. However, 14 countries answered that such a re-scheduling would mean an impediment for access. Inter alia, they gave the following remarks as explanation:

- a special regimen has to be established (special prescription form, only a limited number of medical professionals would be allowed to prescribe, distribution restrictions) One country was not sure: one agency said that it would strongly impede access, while another agency said that it would not impede at all) (5 countries)
- Two countries said that it would make access difficult, for instance "it will interfere with proper use".
- Two countries are worried about access in other countries and the impact on global public health
- One country said that it would make a barrier for access, but only to illicit use and not for licit use.
- One country was said that bringing the substance under control would mean that it would become more attractive to divert the substance to illicit markets, where profits are higher, thus causing a shortage for proper medical use.

Also, France remarked that a rescheduling would not only limit access for opioid agonist treatment of dependence, but access for pain relief as well.

### **III. Legal considerations concerning transfer of substances between Conventions**

#### ***a. Applicable regulations and other formal guidance***

The Single Convention on Narcotic Drugs (1961 Convention) controls substances listed in its schedules. The criteria for scheduling are mentioned in its article 3. The United Nations Convention on Psychotropic Substances (1971 Convention) controls other substances, also listed in its schedules. The scheduling criteria are given in its article 2.

Official commentaries to the both Conventions were published on behalf of the United Nations' Secretary-General.

For further guidance the Guidelines for the WHO review of dependence-producing psychoactive substances for international control were given by WHO's Executive Board.<sup>2</sup>

Of these documents, both conventions and guidelines are binding, unless they are, in specific situations, contradictory to any other international rule of law of higher rank.

Both commentaries have the status of authoritative documents, which should be followed wherever possible, but which are not formally binding.

#### ***b. Content of applicable regulations and choice between conventions***

As could be expected, the 1961 Convention does not give any indication how to decide between the two conventions, as at the time it was agreed on, the other convention did not exist yet.<sup>3</sup> Neither does the 1971 Convention provide a mechanism for a choice between the conventions in respect of individual substances.

The official commentary to 1971 Convention recognized the possibility that a substance can be brought under the 1961 Convention, even if it already is under the control of the 1971 Convention. It says even that there is no legal obstacle to place a substance already under control of the 1971 Convention under the 1961 Convention, no matter whether those substances are deleted from the former one or not.<sup>4</sup> However, it should be mentioned that such a double control would be very confusing, due to the different control measures. Therefore the WHO guidelines recommend that it is advisable that a substance should not be under more than one convention.<sup>5</sup>

WHO guidelines give guidance for the newly scheduling of drugs, and for the scheduling of drugs already on the 1988 convention. They also give guidance for the choice between the conventions in case of substances that are not yet scheduled at all. In that case, it first should be examined if a substance meets the criteria for scheduling under the 1961 Convention. Only after that, it should be examined whether a

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<sup>2</sup> EB 105/2000/REC/1, Annex 9, with appendices.

<sup>3</sup> The Single Convention was amended by its 1972 protocol, but this protocol does not affect the scheduling of substances.

<sup>4</sup> numbers 16 and 17 on page 40.

<sup>5</sup> Guidelines, point 35.

substance meets the criteria for the 1971 Convention.<sup>6</sup> However, the guidelines do not give guidance for the transfer of a substance from the 1961 to the 1971 convention or vice versa.

A transfer of a substance between Conventions would demand from the UN Commission of Narcotic Drugs to take up a simultaneous decision on deletion of a substance from one convention and adding it to an appropriate schedule of another convention. In the 1971 Convention a procedure for a deletion from its schedules is included in article 2 para. 6 and requires a new assessment by WHO. A similar provision is included in the 1961 Convention article 3 para. 6(b). No provision is included, however, on any decision of this kind to be taken simultaneously.

Because the WHO guidelines do not apply to the removal of a substance from the 1971 to the 1961 convention, no other rules apply than the texts of the conventions and the general principles of law, among them rules of conflict between treaties.

In the case of such a conflict there is the general legal rule of *Lex posterior supra lex anterior*, which means that in case of two conflicting regulations the newer regulation (whether being it a law or a treaty) prevails, except if explicitly stated in the newer regulation. The priority of a newer treaty can be explained by the fact that its authors were aware, or at least could be aware, of the existence of an earlier treaty.

As the ECDD concluded in its 33<sup>rd</sup> meeting, buprenorphine meets the criteria for both of the conventions. Because of that, the answer to the question which convention prevails is decisive. As it is the *Lex posterior* rule that decides that the newest convention prevails, from a legal point of view the scheduling of buprenorphine should be continued under the 1971 Convention. It was confirmed by the WHO Office of the Legal Council (LEG) that this rule applies in this situation.

#### **IV. Sublingual tablets of buprenorphine**

Given the great importance for public health of buprenorphine, the Secretariat brings to the attention of the Committee that the 1971 convention has a provision for preparations of substances in Schedule II, III or IV to exempt them from certain control measures.<sup>7</sup> The convention allows that in the case a preparation "is compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem, the preparation may be exempted from certain of the measures of control provided in this Convention in accordance with paragraph 3."

As the INCB reports on illicit trade and abuse of buprenorphine show, these are limited to buprenorphine injections. Sublingual tablets are of lesser interest for abuse and diversion, as they do not have a physiological effect as immediate as injections have.

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<sup>6</sup> Guidelines, points 33 and 37

<sup>7</sup> article 3, paragraph 2

The Committee could consider therefore to indicate in its report the option that is offered by article 3 para. 2 of the 1971 Convention for countries that carry out large scale programmes of psychosocially assisted pharmacological treatment of persons dependent on opioids that involve buprenorphine to explore this approach of exempting sublingual tablets from certain control measures, in order to increase the ease of access for medicinal purposes. However, before a country would decide to exempt these tablets it should assess the recoverability of the substance from the specific preparation and the liability for its diversion in the country specific situation.

As far as sublingual preparations with low recoverability are not available, pharmaceutical producers should be encouraged to develop them.

In addition countries could consider to exempt combination sublingual tablets with buprenorphine and naloxone from certain control measures, as the buprenorphine is also difficult to extract from these tablets.

## **V. Proposed ECDD conclusions**

The criteria for scheduling in both of the conventions comply in the case of buprenorphine. However, there is a considerable body of opinion, including that of the members of WHO Executive Board, that the transfer from the 1971 Convention to the 1961 Convention would, as a consequence, give rise to rescheduling at the national level, which would have an unintended effect of restricting access to drugs used to treat drug dependence. Moreover, there exist also complications in formulating a legal basis for removing buprenorphine from the 1971 convention to the 1961 convention once it was scheduled under the 1971 convention, as long as it meets the criteria for the latter.

There is still considerable and even increasing abuse of buprenorphine by injection. However, as buprenorphine was included in the list of essential drugs, and its great usefulness in patient treatment was thus confirmed, it meets the criteria for schedule III of the Convention on Psychotropic Substances (1971) and should therefore remain, as it already is, under this Schedule.

The risk of abuse of sublingual tablets is lower, although still significant. But the sublingual preparations are of the utmost importance for public health. Therefore, the Committee may indicate in its report that countries should consider to exempt the sublingual tablets of buprenorphine and buprenorphine/naloxone from certain control measures after assessing the recoverability of the substance from the specific preparation and the liability for its diversion in the specific situation in the country.

Annexes:

resolution of CPDD (doc 2006/6.2a)

Letter from the US Ministry of HHS (doc 2006/6.2b)

WHO's answer to the US Ministry of HHS (doc 2006/6.2c - pages 1-4)

Letter from the Australian department of Health and Ageing (doc 2006/6.2d)