

Recommendations of the Expert Group on the Regulatory Framework for products containing buprenorphine / naloxone and buprenorphine-only for the treatment of opioid dependence

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A. Introduction

In 2006 the European Medicines Agency licensed a new combination buprenorphine / naloxone medicine (Suboxone®) for use as an opioid substitute by physicians experienced in the treatment of opioid dependence/addiction. An expert group was established to consider whether a regulatory framework similar to the Methadone Protocol should also apply to products containing buprenorphine / naloxone or buprenorphine-only (i.e. prescribing by Level I and II medical practitioners, supervised dispensing and with patients registered on a Central Treatment List and having a drug treatment card).

A feasibility study on the use of Suboxone (buprenorphine / naloxone) as an alternative to methadone for the treatment of opioid dependency commenced in June 2009. The feasibility study ran from June 2009 until February 2011 and a report of the independent evaluation of the study carried out by Create Consultancy was finalised in April 2011. The purpose of the feasibility study was to review the use of buprenorphine / naloxone in the Irish context. As part of the study, consultation was undertaken with key groups involved in the feasibility study including service users, prescribers, pharmacists and other dispensers, the Department of Health, the HSE, Drug Treatment Centre Board and others.

These recommendations have been prepared by the Expert Group on the basis of the Report of the Evaluation of the Suboxone Feasibility Study 2011 conducted by Create Consultancy and also, having regard to the following national and international reports:

- The 2010 HSE report ‘The Introduction of the Opioid Treatment Protocol’
- The 2002 NACD report ‘Use of buprenorphine as an intervention in the treatment of opiate dependency syndrome’.
- The 2007 National Centre for Pharmacoeconomics report ‘Economic Evaluation of Suboxone for the management of opiate addiction’.
- The 2007 UK National Institute for Health and Clinical Excellence (NICE) guidelines ‘Methadone and buprenorphine for the management of opioid dependence’.

These recommendations apply to the use of medicinal products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, which have been authorised for use in the treatment of opioid dependence. It is not intended that the content of these Recommendations would apply to the use of buprenorphine products for the treatment of pain and other indications.

In preparing these Recommendations, the Expert Group noted the findings of the ‘Economic Evaluation of Suboxone for the management of opiate addiction’ undertaken by the National Centre for Pharmacoeconomics in 2007, in particular the cost differential between Suboxone and methadone per patient per treatment year and the conclusion that Suboxone cannot be considered cost-effective for patients attending clinics or in the community. However, in preparing these Recommendations, the Expert Group has borne in mind a number of factors including: the desirability from a patient care perspective of providing an alternative treatment to methadone in appropriate circumstances, and the difficulty in demonstrating cost-effectiveness in comparison with methadone in light of the current costs of methadone products.

The Recommendations have been prepared to advise the Minister for Health on the establishment and implementation of a protocol for the use of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, in the treatment of opioid dependence in Ireland. In light of

concerns raised regarding the potential for diversion of buprenorphine-only products for injection by IV drug users, at this time, the Recommendations focus on the use of buprenorphine / naloxone products, with buprenorphine-only products being reserved for use during pregnancy. Importantly, in order to have regard to clinical developments in the treatment of opioid dependence, the use of buprenorphine products, both nationally and internationally, and the changing environment, the Expert Group advise that these Recommendations should be reviewed within 2 years of the date on which they were proffered to the Minister.

B. Terms of Reference of Expert Group on the Regulatory Framework for buprenorphine / naloxone & buprenorphine-only products for the treatment of opiate dependence

The terms of reference of the Expert Group on the Regulatory Framework for products containing buprenorphine / naloxone and buprenorphine-only for the treatment of opiate dependence were as follows:

1. In the context of the product authorisation for Suboxone issued by the EMA, to consider and make a recommendation as to whether the general regulation of relevant professions provides a sufficient regulatory framework for the prescription and dispensing of Suboxone in Ireland.
2. To consider and make recommendations if appropriate as to which if any elements of the methadone protocol should apply to Suboxone, and if so how they could apply in practical terms.
3. To consider and make recommendations if appropriate as to whether and if so how Suboxone should be made available to particular client groups and/or settings in an Irish context, taking into account the work done by the NACD and taking into account the cost of this treatment.
4. To consider and make recommendations if appropriate as to whether and if so in what way buprenorphine should be available in Ireland.
5. To consider any legal advices received in relation to the above matters.

C. Recommendations of the Expert Group:

Term of Reference 1:

The Expert Group considered whether the general regulation of relevant professions provides a sufficient regulatory framework for the prescription and dispensing of buprenorphine products in Ireland. The Group is of the opinion that, in accordance with the Medical Practitioners Act 2007 and Pharmacy Act 2007, the general regulation of relevant professions is sufficient, however regulations and guidelines similar to those which apply to the prescribing and dispensing of methadone for the treatment of opioid dependence should also apply to the prescribing and dispensing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, when used for the treatment of opioid dependence.

General Recommendations:

- 1.1 Regulations and guidelines similar to those which apply to the prescribing and dispensing of methadone for the treatment of opioid dependence should also apply to the prescribing and dispensing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, for the treatment of opioid dependence.

Term of Reference 2:

The Expert Group considered that the elements of the Methadone Protocol Scheme should apply also to the prescribing and dispensing of products containing buprenorphine / naloxone or buprenorphine-only (where appropriate). In this regard, the Group makes the recommendations set out below.

General Recommendations:

- 2.1 Prescribing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, should be in accordance with the terms of the authorised Summary of Product Characteristics for the relevant product.
- 2.2 Initiation of treatment with products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, for opioid dependence should be confined to Consultant Psychiatrists in addiction, junior doctors working under the direction of Consultant Psychiatrists in addiction, suitably trained Level II GPs and medical practitioners employed/engaged as GPs specialising in substance misuse working in HSE addiction clinics.
- 2.3 Prescribing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, should be conducted by Consultant Psychiatrists in addiction, junior doctors working under the direction of Consultant Psychiatrists in addiction, suitably trained Level I and Level II GPs and medical practitioners employed/engaged as GPs specialising in substance misuse working in HSE addiction clinics, and Consultant Physicians in hospital settings in liaison with Consultant Psychiatrists in addiction. All personnel should work and prescribe in accordance with the requirements of the relevant Drugs and Therapeutics Committee to ensure appropriate clinical governance.
- 2.4 Consistent and uniform guidelines should be adopted for the prescribing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, across clinic and community settings. These guidelines should be set within the context of a consistent, coherent and integrated framework of guidelines for the treatment of opioid dependence.

- 2.5 Where practicable, the current methadone prescription form should be adapted to allow for the prescribing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, on the same form.
- 2.6 Supervised dispensing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, should apply in the same circumstances as supervised dispensing of methadone. Supervision of products containing buprenorphine / naloxone should be daily for at least the first full month (at least 6 days a week) and following this where the patient's compliance is assured, the appropriate level of supervision should be determined by the clinician on the basis of an assessment of all of the circumstances relevant to the patient and having regard to the importance from a public health perspective to reduce the potential for diversion of buprenorphine products. In circumstances where the patient is already stabilised on methadone or another opioid substitute, the same level of supervision that applies to methadone may apply after an initial week of stabilisation on buprenorphine / naloxone.
- 2.7 In circumstances where the prescribing and dispensing of products containing buprenorphine-only is appropriate (see Section 4 below) extreme caution is required in supervising the dispensing of buprenorphine-only due to the increased likelihood of diversion of these products and the high risk that the product can be injected by IV drug users.
- 2.8 Consistent and uniform guidelines should be put in place for the dispensing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, across clinics and community settings, including guidelines on the supervised consumption of buprenorphine / naloxone or buprenorphine-only. These guidelines should be set within the context of a consistent, coherent and integrated framework of guidelines for the treatment of opioid dependence.
- 2.9 A coordinated, integrated and multi-disciplinary system of training and professional support should be put in place for prescribers, pharmacists and others involved in the dispensing and supply of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, in all settings and should form part of the overall integrated training in the management of opioid dependence. This should be facilitated through a collaborative approach involving senior clinicians in HSE clinics/DTCB, the College of Psychiatry of Ireland, the Irish College of General Practitioners, the Pharmaceutical Society of Ireland and the Irish Centre for Continuing Pharmaceutical Education.
- 2.10 The system of clinical governance/audit of GPs, which operates under the Methadone Protocol Scheme, should be extended to the prescribing of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate.
- 2.11 A system of clinical governance / audit should be established in respect of pharmacy services in respect of both the dispensing of buprenorphine / naloxone, buprenorphine-only and methadone in clinic and community pharmacy settings and the provision of care and services by pharmacists in those settings.
- 2.12 Patients being treated with products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, for opioid dependence should have their names and relevant information recorded on a designated part of the Central Treatment List. Patients attending community pharmacies should have a drug treatment card which is held by the dispensing pharmacy.
- 2.13 Standard and consistent patient information leaflets must be made available to patients in clinics and community settings on the use of buprenorphine / naloxone for the treatment of opioid dependence.

Term of Reference 3:

The Expert Group's third term of reference required it to consider and make recommendations if appropriate as to how products containing buprenorphine / naloxone should be made available, and whether its use should be limited to particular client groups and/or settings in an Irish context, taking into account the work done by the NACD and taking into account the cost of this treatment. In considering the framework and procedures which should be put in place for the use of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, in Ireland, regard was had to the findings of the Evaluation of the Suboxone Feasibility Study, the Introduction of the Opioid Treatment Protocol Report and international reports referred to in section A above. On the basis of these Reports, the Expert Group makes the following recommendations:

Recommendations relating to the use of Buprenorphine / Naloxone Products:

- 3.1 Methadone is the drug of first choice in the treatment of opioid dependency and therefore should be available to everyone who requires it. If methadone and buprenorphine / naloxone are equally suitable, methadone should be prescribed as the first choice.
- 3.2 The decision about which drug to use should be made, first having explored the appropriateness of methadone and taking into account a number of factors, including:
 - the person's history of opioid dependence,
 - the person's commitment to a particular treatment strategy, and
 - an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person.
- 3.3 In the interests of public health and based on a clinical assessment, buprenorphine / naloxone may be most appropriate for use in the following cohorts of patients or in the following circumstances:
 - 3.3.1 Patients currently receiving treatment with buprenorphine / naloxone who should be maintained on buprenorphine / naloxone.
 - 3.3.2 Patients with a specific medical need for whom methadone is contraindicated or not suitable, such as:
 - patients with prolonged QT intervals,
 - male patients with feminisation syndrome,
 - patients on neuroleptic medications which also affect QT interval
 - patients on high dose methadone treatment, who are also being treated with medicines which inhibit CYP450 enzymes (such as antiretroviral agents eg efavirenz or the anti-infective rifampicin etc.) and therefore are at greater risk of drug interactions or
 - patients diagnosed with HIV in order to facilitate alternative HIV treatment options.
 - 3.3.3 Methadone-naïve patients or patients, including young patients, where detoxification is a primary goal of treatment, provided the prescriber is of the opinion that detoxification is a realistic goal for the patient.
 - 3.3.4 Patients being treated for codeine and other pharmaceutical opioid dependencies.
 - 3.3.5 Patients where, having regard to all of the patient's circumstances, the prescriber is satisfied that there is clear evidence that the patient has been stable, socially, domestically and from a family perspective, for at least a period of six months and particularly where the patient is in stable employment or education and that the patient demonstrates a commitment to compliance with the treatment programme.
- 3.4 Buprenorphine / naloxone may **not** be suitable for the following categories of patients:

- patients who are not stabilised on methadone,
- patients who are poly-drug users,
- patients who are problem benzodiazepine users, and
- patients with a history of non-compliance with treatment regimes.

3.5 Bearing in mind that the greatest risk period for substitute induction death overdose occurs in the first month of induction, consideration may be given to less than daily dosing of buprenorphine / naloxone products, having regard to each individual patient's clinical assessment and needs, and the patient's safety and treatment regimen. In accordance with the product's authorised Summary of Product Characteristics (SmPC), the frequency of buprenorphine / naloxone dosing may be decreased to dosing every other day at twice the individually titrated daily dose. In addition, in some patients, after a satisfactory stabilisation has been achieved, the frequency of the buprenorphine / naloxone dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday, where the Monday and Wednesday dose are twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose with no dose on the intervening days). Where less than daily dosing of buprenorphine / naloxone products is used, in accordance with the product's SmPC the dose given on any one day should not exceed 24mg.

In addition to public health/clinical assessment criteria, the Expert Group recognises that the following are factors which are outside the scope of the Group's considerations, but which are also relevant to the establishment of a buprenorphine / naloxone treatment protocol and which may require further consideration:

- In light of the current financial crisis and the financial pressures on the provision of health services, the Expert Group had to have particular regard to the findings of the Economic Evaluation of Suboxone for the management of opiate addiction undertaken by the National Centre for Pharmacoeconomics in 2007, which found that Suboxone and buprenorphine cannot be considered cost-effective for patients attending clinics or in the community. In addition, the Expert Group recognises the difficulty for any product in demonstrating cost-effectiveness in comparison with methadone, in light of the current costs of methadone products. Consequently these Recommendations aim to provide an alternative treatment to methadone in appropriate circumstances where there is a clinical need.
- HSE discussions regarding buprenorphine / naloxone pricing and the entry of generic products onto the Irish market may have implications for assessment of the cost-effectiveness of the product.
- While the HSE addiction clinics have their own drugs budgets and are in a position to make decisions regarding the funding of the treatment of opioid dependence, consistent criteria for the prescribing of buprenorphine / naloxone should be applied across both clinic and primary care settings to avoid inconsistent approaches to treatment and the transfer of the significant cost of buprenorphine / naloxone treatment to the primary care setting when patients have become stabilised.
- The contractual implications for GPs / community pharmacists with regard to the prescribing and dispensing of buprenorphine / naloxone may require consideration.

In light of these factors, the changing environment and clinical developments in opioid dependence treatment services, the Expert Group advises that these Recommendations be reviewed within 2 years of the date on which they were proffered to the Minister.

Term of Reference 4:

A further term of reference of the Expert Group was to consider and make recommendations if appropriate as to whether and, if so, in what way buprenorphine-only products should be available in Ireland for the treatment of opioid dependence. The Expert Group acknowledges that in some jurisdictions there has been significant evidence of diversion of buprenorphine-only products for injection by IV drug users.

Having regard to the potential for, and health consequences associated with, the diversion of buprenorphine-only products for IV injection, and as the Expert Group is unaware at this time of any buprenorphine-only product being marketed in Ireland for use in the treatment of opioid dependence, the Expert Group make the following recommendations:

Recommendations in relation to the use of Buprenorphine-only Products:

- 4.1 Although buprenorphine-only products are not authorised for use in pregnancy in the treatment of opioid dependence, such products are used across the world in pregnant women who are being treated with products containing buprenorphine / naloxone where the woman has decided not to switch from buprenorphine and where the risks and benefits of such a decision have been clearly outlined to the woman.
- 4.2 In circumstances where the prescribing and dispensing of buprenorphine-only products is appropriate, extreme caution is required in supervising the dispensing of buprenorphine-only due to the increased likelihood of diversion of these products and the high risk that the product can be injected by IV drug users.

Term of Reference 5:

Legal advices obtained have been considered by the Group. If a decision is taken to extend the availability of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, beyond those patients in the feasibility study, appropriate amendments will be required to the 1998 Methadone Regulations.

General Recommendations:

- 5.1 Appropriate amendments should be made to the Misuse of Drugs legislation and the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations 1998 to ensure that a regulatory framework similar to that of methadone applies to the prescribing and supply of products containing buprenorphine / naloxone, or buprenorphine-only where appropriate, for the treatment of opioid dependence.