

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal
Methadone and buprenorphine for the management of opioid dependence
Comments received from Consultees and Commentators on the draft scope

Name of Consultee/Commentator	Comment	Response
APPRAISAL OBJECTIVE		
Schering-Plough	<p>We would suggest modifying the appraisal objective to the following: “To appraise the clinical and cost effectiveness of oral methadone (Physeptone, Hillcross (AAH Pharmaceuticals Ltd) and Martindale Pharmaceuticals Ltd; Metharose, Rosemont Pharmaceuticals Ltd; Methadose, Rosemont Pharmaceuticals Ltd) and sublingual buprenorphine (Subutex, Schering-Plough Ltd) as substitute opiates for short term (detoxification) and longer term (maintenance) use, for the management of opiate misusers and to provide guidance to the NHS in England and Wales.”</p> <p>The two treatment strategies differ significantly and we feel it is appropriate that this is highlighted at the outset.</p>	Comment noted. These aspects will be captured in the economic analysis.
BACKGROUND		
Prison Health, DH	Statistics would benefit from references to published studies	Comment noted. References are not included in the scope document. Some of the figures have been changed to include more up-to-date figures.
Rosemont	Branded products are noted with manufacturers. Generic products are also	Comment noted. Additional

Pharmaceuticals Ltd	available.	manufacturers have been added to the matrix.
	There are lots of facts, figures and estimates given and reference made to a survey without any sources actually quoted.	Comment noted. References are not included in the scope document. Some of the statistics have been changed to include more up-to-date figures.
Royal College of General Practitioners	Pretty standard.	Comment noted. No action required.
Royal College of Nursing	The effect on children should be taken into account in light of 'Hidden Harm' and the effect drug misusing parent/s have on children.	Comment noted. The appraisal will consider the wider implications of this technology. A sensitivity analysis will be carried out to include the wider societal costs and benefits as listed in the 'Economic analysis'.
Schering-Plough	We believe this to be accurate.	Comment noted. No action required.
UK Harm Reduction Alliance	Not very accurate & confusing in places. Opiates alone are not toxic to the liver but this is more an indirect consequence of concurrent alcohol misuse or from BBVs.	Comment noted. Wording has been amended. The scope only provides brief information on the background.
	Anorexia should perhaps read 'loss of appetite'.	Comment noted. Wording has been amended.
	Comes across as stigmatised statement, could identify how much harm associated with illicit sub culture.	Comment noted. Paragraph has been changed.
	Substitute prescribing is one of many harm reduction interventions. Needs more accurate description of HR & interventions.	Comment noted. The scope document only provides brief information on the background,

		however wording has been changed.
	Individual preference is unlikely for the individual user.	Comment noted.
	Maintenance is not defined, in some areas this will be limited period.	Comment noted. The background section has been amended to include a description of maintenance.
West Midlands Health Technology Assessment Collaboration	Paragraph 2 should state clearly that dependence is both psychological and physical.	Comment noted. Wording has been amended.
	Even though technically we are talking about opiates, paragraph 4 should have a sentence that emphasizes that heroin is the primary problem drug. It should also be noted that physical dependence on opioid drugs per se seems to cause relatively few physical problems, but dependence on heroin as an illicit street drug causes huge physical (due to the presence of contaminating inert agents, the spread of blood borne viruses, risk of accidental overdose and death), social and legal problems.	Comment noted. It has been emphasized that heroin is the primary drug problem.
	Estimates suggest that there are between 250,000 and 300,000 opioid dependent drug users in the UK.	Comment noted. Statistics have been amended with up-to-date figures.
	The statement "There are two main strategies.." should read "There are two broad strategies..".	Comment noted. Wording has been amended.
	The final sentence of this paragraph is a little misleading as the psychological, social and medical interventions are the mainstay of the two strategies.	Comment noted. This has been deleted.
	Use of the term "addict" and related should be avoided, the operationally defined "opiate dependence" would be preferred.	Comment noted. Any reference has been amended.
THE TECHNOLOGY/INTERVENTION		

Prison Health, DH	You might add that buprenorphine is a partial agonist and antagonist opioid.	Comment noted. Wording has been amended.
Royal College of Nursing	Methadone has a long half life and therefore should be monitored closely when prescribed. When initially prescribed an admission may be necessary to prevent overdosing	Comment noted. Technologies are appraised within their licences.
Schering-Plough	Yes (In response to the question: Is the description of the technology accurate?)	No action required.
UK Harm Reduction Alliance	Yes (In response to the question: Is the description of the technology accurate?)	No action required.
West Midlands Health Technology Assessment Collaboration	We have no comments on the pre-table paragraph.	No action required.
LICENSING ISSUES		
Rosemont Pharmaceuticals Ltd	The products are available as generics. No licensing issues envisaged.	Comment noted.
POPULATION		
Prison Health, DH	There are approximately 40,000 problematic drug users currently in prison in England and Wales. More than 50,000 men and women and young persons receive treatment for drug dependence per annum	Comment noted. Wording has been amended.
Rosemont Pharmaceuticals Ltd	There are opiate dependent individuals who cannot be stabilised using oral products. Some of these are treated with injectable methadone or even with diamorphine.	Comment noted. The referral from the DH specifies that only oral methadone and sublingual

		buprenorphine are to be appraised.
Royal College of Nursing	Children of drug users and also children using drugs do not appear to have been considered. What are the educational costs?	Comments noted. Methadone is not recommended for use in children and buprenorphine is not recommended for children under 16. Refined target population to "opioid dependent adults" The appraisal will consider the wider implications of this technology. A sensitivity analysis will be carried out to include the wider societal costs and benefits as listed in the 'Economic analysis'.
Schering-Plough	Yes (in response to the questions of: Is the population defined appropriately? Are there groups within this population that should be considered separately?)	No action required. Sub-groups will be examined.
UK Harm Reduction Alliance	Population appears appropriately defined	No action required.
West Midlands Health Technology Assessment Collaboration	"Opioid dependent individuals" should be used instead of "opiate dependent individuals".	Comment noted. The population has been amended to 'opioid dependent adults' in line with the licence indications of the technologies.
COMPARATORS		
Rosemont Pharmaceuticals Ltd	The comparators have to be chosen carefully i.e. oral methadone cannot be compared with injectable methadone because the patient group is different (injectable methadone is a last resort after oral therapy has failed).	Comment noted.

Schering-Plough	Yes. We would wish to clarify that this does include comparison with residential rehabilitation centres, in-patient care and "detox" programmes eg use of Britlofex	Comment noted. These comparators have been taken account of within the 'Other considerations' section (context of care).
West Midlands Health Technology Assessment Collaboration	No comments.	No action required.
OUTCOMES		
Prison Health, DH	They should be expanded to include impact on frequency of injecting drug use, seroconversion rates, Social quality of life (e.g. social indices within the Maudesley Addiction Profile)	Comments noted. The outcomes section has been amended. Details of outcome measures will be expanded upon within the Assessment Group protocol.
Royal College of General Practitioners	I think other outcome measures such as retention in treatment should be included.	Comment noted. The outcomes section has been amended.
	as well as the health care of other members of the users family - especially children as many children of drug users have poor access due to their parents stigma.	Comment noted. The appraisal will consider the wider implications of this technology. A sensitivity analysis will be carried out to include the wider societal costs and benefits as listed in the 'Economic analysis'.
	I think that a specific area of dental health should be included	Comment noted. The outcomes section has been amended. Physical and mental health will be captured under 'drug-related morbidity and mortality'. Details of outcome

		measures will be expanded upon within the Assessment Group protocol.
Royal College of Nursing	The effect on children should be taken into account in light of 'Hidden Harm' and the effect drug misusing parent/s have on children.	Comment noted. The appraisal will consider the wider implications of this technology. A sensitivity analysis will be carried out to include the wider societal costs and benefits as listed in the 'Economic analysis'.
	Another outcome measure might be the numbers who maintain their employment if in treatment.	Comment noted. The outcomes section has been amended to cover these issues. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
Schering-Plough	In addition to the outcomes listed, the following additional points should be included: 1. We would suggest, under mortality, a subsection looking at mortality rates from drug overdose, as this is a key outcome of any substitution therapy.	Comment noted. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
	2. In addition to health related quality of life, we would also suggest adding Health Status. A key outcome of the treatment of opiate addicts is to improve their often poor mental and physical health status. The effect of these treatments on these endpoints is important in considering their clinical and cost effectiveness.	Comment noted. The outcomes section has been amended to cover these issues.
	3. There is a significant risk attached to diversion of opiate substitution therapies. The scope should therefore contain an additional outcome measure to reflect the potential negative impact that diversion has on other societal groups and on the accurate targetting of treatment.	Comment noted. A sensitivity analysis will be undertaken to include the costs/benefits of different service delivery strategies, including dispensing fees.
	4. In addition to relapse as an outcome, it would also be of value to examine the	Comment noted. This has been

	proportion of patients stabilized on substitution therapy who are able to withdraw from it and move to an opioid free state. Although this is the hardest test of a therapy with these often difficult patients, it is the ultimate goal of treatment.	included as an outcome.
	5. The welfare of the patient and their ability to integrate back into everyday life including, where appropriate, employment (plus the impact on their carers/family) is a key goal of treatment and needs to be reflected in the outcome measures.	Comment noted. The outcomes section has been amended to cover these issues. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
	6. "Safety" should be an outcome measure Safety is obviously a key consideration when treating patients and there is evidence that some products have better safety features than others. The scope should include an outcome measure to ensure that this is adequately assessed.	Comment noted. Adverse effects of treatment are considered within the appraisal however safety is not considered as an outcome within the appraisal process.
	7. Primary outcomes for treatment such as retention in treatment and opiate positive/negative urines also need to be included.	Comments noted. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
Substance Misuse management in General Practice	Relapse is a difficult outcome to measure for maintenance treatment. Goals of treatment may be intermediate to that. Relapse to what. Needs clearer definition. Reduced illicit opiate use might be better.	Comments noted. The outcomes section has been amended. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
	Also another outcome may be drug related morbidity.	Comment noted. The outcomes section has been amended.
	Compliance may need closer defining as well	Comment noted. The outcomes section has been amended. Details of outcome measures will be expanded upon within the

		Assessment Groups protocol.
UK Harm Reduction Alliance	Qualitative experiences of service users. needs to include measures of improved quality of life, ie; family life (social services data) & longer term life style improvements.	Comments noted. The outcomes section has been amended to cover these issues. Details of outcome measures will be expanded upon within the Assessment Groups protocol.
West Midlands Health Technology Assessment Collaboration	Effectiveness of addiction treatment is usually measured by its ability to reduce associated problems. Four areas have traditionally been relevant to both patient and society: 1. reduction in drug use; 2. improvement in medical and psychiatric health (and other quality of life indicators); 3. improvements in social function; 4. reductions in threats to public health and safety.	Comments noted. The outcomes section has been amended to cover these issues.
	A key outcome should, therefore, be reduction in the amount of heroin (or illicit drug use).	Comment noted. The outcomes section has been amended to cover this issue.
	Relapse rates are not a useful outcome measure, since substance abuse is a relapse/ remitting condition. In addition, most studies will not have follow up beyond 6-12 months.	Comment noted. The outcomes section has been amended.
	Compliance (and retention in treatment) is an important outcome measure.	Comment noted. The outcomes section has been amended.
	Polydrug use should be included as an outcome measure since many individuals who become opiate-free go on to abuse other substances.	Comment noted. This has been included within the 'Other considerations' section.
ECONOMIC ANALYSIS		
Rosemont Pharmaceuticals Ltd	Don't understand the term "quality-adjusted life year".	Comment noted. This is a standard term used in appraisal economic evaluations. See NICE methods guide, section 5.5 for further

		guidance.
Royal College of General Practitioners	There must be mention of the site of the intervention - e.g community versus specialist care.	Comment noted. This has been covered within the 'Other considerations' section (context of care).
Royal College of Nursing	There is a need to ensure that service users are being offered a free choice of treatment packages. If not then it will lead to inaccurate costings as more and more services move towards a patient centred service.	Comment noted. If the evidence allows the appraisal will consider different service delivery strategies (prescribed dose and context of care).
	Also need to take into account the child care costs. What are the educational costs?	Comment noted. The appraisal will consider the wider implications of this technology. A sensitivity analysis will be carried out to include the wider societal costs and benefits as listed in the 'Economic analysis'.
Schering-Plough	No comments.	No action required.
UK Harm Reduction Alliance	Important aspect but needs longer term view (2 & 5yrs)	Comment noted. Wording has been amended. Economic analysis should examine both the short and longer term benefits.
West Midlands Health Technology Assessment Collaboration	The time horizon should be lifetime.	Comment noted. Wording has been amended.
OTHER CONSIDERATIONS		

Royal College of Nursing	Under the choice of strategy the users often do not have a choice as the choice is made by the prescribing doctor. This needs to be taken into account when looking at costings.	Comment noted.
Schering-Plough	In addition to the comments above we would suggest that the scope directly examines the way services in which these products are used are structured. Different products in this class may be optimally delivered using different service frameworks, and this may further differ whether short term substitution – detoxification – or long term substitution – maintenance – is used. This may be a focus of the Institute’s recommendations to the NHS.	Comment noted. The ‘other considerations’ section does state that the appraisal will consider clinical and cost effectiveness of the context of care. The Institute also currently has two guidelines on drug misuse underway. The scope for the psycho-social management of drug misusers in the community and prison settings is out for consultation between 20 th June – 18 th July. The scope for the detoxification of drug misusers in the community, hospital and prison settings will be out for consultation between 12 th July – 9 August. These can be found on the NICE website.
	Patient choice is also crucial and may be important in helping to retain patients in treatment. Factors that may be relevant include the side effect profile of different products, previous experience of treatment and inherently "positive" attributes associated with any given product.	Comment noted. Retention with treatment has been added as an outcome measure.
UK Harm Reduction Alliance	Subgroups should include women, prison populations, Black and minority ethnic groups.	Comments noted. Subgroups are included within the ‘Other considerations’ section as stated within the remit.
West Midlands Health	Dosage is a key consideration.	Comment noted. Dose is included in the ‘Other considerations’ section as

Technology Assessment Collaboration		stated within the remit.
	Subgroups for consideration should include patient related issues (e.g. level of education, length and severity of dependence etc) and service related issues (e.g. dosage, duration of treatment, treatment setting etc).	Comments noted. Subgroups are included in the 'Other considerations' section as stated within the remit.
ANY ADDITIONAL COMMENTS ON THE DRAFT SCOPE		
Rosemont Pharmaceuticals Ltd	Consider whether to include injectable methadone and prescribed diamorphine in the scope.	Comments noted. The remit from the DH/WAG does not include these products.
Royal College of Nursing	Any study using prisoners as data providers will need to consider what the Number 1 Governor and his/her team's attitude to drug use is. Otherwise the results will be skewed.	Comment noted. The appraisal will consider the use of these technologies in both community and prison settings.
UK Harm Reduction Alliance	These comments apply also to Naltrexone appraisal.	Comments copied to the summary table for naltrexone draft scope.
West Midlands Health Technology Assessment Collaboration	Study design should include randomised controlled trials but may need to include cohort studies to provide long term outcome data.	Comment noted. There is general agreement in the literature that data from well-conducted RCTs are preferable to those from other study designs. However the selection of data sources will often involve trade-offs between methodological rigour and relevance to the question under study.
	The existing level of evidence for methadone is very high (6 Cochrane reviews). There are 2 Cochrane reviews assessing buprenorphine (one published in 2004).	Comment noted.

Comments received from:

Prison Health, DH
Rosemont Pharmaceuticals Limited
Royal College of General Practitioners (RCGP)
Royal College of Nursing (RCN)
Schering-Plough
Substance Misuse management in General Practice
UK Harm Reduction Alliance
West Midlands Health Technology Assessment
Collaboration

Statements of 'no comment' received from:

Action on Addiction
Royal Pharmaceutical Society of Great Britain
The National Pharmaceutical Association
Welsh Assembly Government