

Commissioning Policy (EMSCGP038V1)

3, 4 Diaminopyridine (phosphate form) (Firdapse®) for treatment of Lambert-Eaton myasthenic syndrome and Congenital Myasthenia Syndromes.

Version 1

1. Definitions

A licensed medicine is a product with a marketing authorisation for one or more therapeutic indications.

An unlicensed medicine is a medicine without a marketing authorisation for any therapeutic indication

Off-label use is use of a licensed medicine but for a therapeutic indication for which it does not have a marketing authorisation

Opportunity cost is the loss of healthcare gain for one group of patients which is forgone when a commissioner decides to invest in a healthcare intervention for another group of patients. If, for example, a commissioner can only afford to fund one of the following: a cancer treatment, a screening programme, or 6 more palliative care beds, then the opportunity cost of choosing the cancer treatment can be seen to be the loss of the benefit that would have been delivered by either the screening programme or the palliative care beds.

Prior Approval refers to the responsible Primary Care Trust's requirement for either an individual patient or a group of patients to access healthcare, including diagnostics, under a Prior Approval Scheme as set out in paragraphs 3.3 to 3.8 of Schedule 3 Part 1 of the Standard NHS Acute Services Contract 2009/10. This is to be differentiated from individual funding requests, in that funding is granted subject to correct notification to the PCT.

Responsible Primary Care Trust (PCT) means the Primary Care Trust which discharges the Secretary of State's functions under the National Health Service Act 2006 for an individual patient.

East Midlands Specialised Commissioning Group (EMSCG) is the means by which Primary Care Trusts (PCTs) in the East Midlands work together to plan, buy and manage services which treat patients with rare conditions.

2. The policy

- 2.1 This policy applies to any patient for whom the EMSCG is the Responsible Commissioner.
- 2.2 Firdapse® will not be routinely commissioned.
- 2.3 Any provision of 3,4 DAP(base form) to patients should comply with the Medicines for Human Use Regulations 1994 (as amended).
- 2.4 The reason that the EMSCG has adopted this policy is that it is satisfied that similar clinical benefits will be provided for LEMS patients by 3,4 DAP(base form) and by 3,4 DAP(phosphate form) (Firdapse®) but that the additional costs of prescribing the licensed drug, 3,4 DAP(phosphate form) (Firdapse®) cannot be justified given the opportunity costs of investing those sums in other areas to deliver healthcare benefits for the local population.

3. Commissioning structure

3, 4 DAP(base form) is commissioned by the EMSCG.

Unlicensed 3,4 DAP(base form) is a tariff exclusion. The EMSCG will fund unlicensed 3,4 DAP using individual prior approval processes.

4. GP prescribing

The EMSCG advises that neither 3,4 DAP(phosphate form) (Firdapse®) nor 3,4 DAP(base form) should be prescribed by general practitioners.

5. Documents which have informed this policy

- East Midlands Specialised Commissioning: CPAG Ethical Framework
- The National Health Service Act 2006, The National Health Service (Wales) Act 2006 and The National Health Service (Consequential Provisions) Act 2006 : Department of Health - Publications
- Department of Health, World Class Commissioning Competencies, December 2007, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_080958
- Department of Health, The NHS Constitution for England, July 2009, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093419
- The National Prescribing Centre, Supporting rational local decision-making about medicines (and treatments), February 2009, http://www.npc.co.uk/policy/resources/handbook_complete.pdf
- NHS Confederation Priority Setting Series, 2008, <http://www.nhsconfed.org/publications/prioritysetting/Pages/Prioritysetting.aspx>

- The supply of unlicensed relevant medicinal products for individual patients, MHRA Guidance Note No.14 Revised January 2008 1 (includes Schedule 1 from the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (as amended), <http://www.mhra.gov.uk/home/groups/is-lic/documents/publication/con007547.pdf>
- European Medicines Agency. Assessment Report for Zenas. 2009, EMEA/793638/2009. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001032/WC500069918.pdf
- Wirtz PW, van Dijk JG, van Doorn PA et al. The epidemiology of the Lambert-Eaton myasthenic syndrome in the Netherlands. *Neurology* 2004;63:397-8
- Paul Kleinschmidt, Lambert-Eaton Myasthenic Syndrome, *emedicine*, <http://emedicine.medscape.com/article/792803-overview> (Accessed November 2010)
- Wirtz PW, Nijhuis MG, Sotodeh M et al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. *Journal of Neurology* 2003;250:698-701
- Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database of Systematic Reviews* 2005, issue 2. Art. No.:CD003279. DOI:10.1002/14651858.CD003279.pub2. <http://www2.cochrane.org/reviews/en/ab003279.html> (Accessed November 2010)
- Wirtz PW, Verschuuren JJ, van Dijk JG et al. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert-Eaton myasthenic syndrome: A randomized, doubleblind, placebo-controlled, crossover study. *Clinical Pharmacology and Therapeutics* 2009;86(1):44-8
- Oh SJ, Claussen GG, Hatanaka Y et al. 3,4-diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. *Muscle and Nerve* 2009; 40(5):795-800 Martindale: The complete drug reference. Pharmaceutical Press. www.medicinescomplete.com (Accessed November 2010)
- Anon. Amifampridine launched for rare autoimmune disease. *Pharmaceutical Journal* 2010;284:281
- 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. J Palace, C M Wiles and J Newsom-Davis *J Neurol Neurosurg Psychiatry* 1991 54: 1069-1072
- Firdapse® appraisal dossier for the North East Treatment Advisory Group. Biomarin Europe. July 2010.
- Data on file. Regional Drug & Therapeutics Centre (Newcastle). June 2010. Personal communication to Giri Shankar. June 2010.
- General Medical Council. Good practice in prescribing medicines – guidance for doctors. September 2008. www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp
- MHRA & CHM. Off-label use or unlicensed medicines: prescribers' responsibilities. *Drug Safety Update* 2009; 2(9):6-7 <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON043809> (Accessed November 2010)
- 3, 4 Diaminopyridine for the treatment of Lambert Eaton Myasthenic Syndrome. East Sussex Health Economy Medicines Committee report. 2010.

- Horsley W. Amifampridine phosphate (Firdapse®) for Lambert-Eaton myasthenic syndrome. NHS North East Treatment Advisory Group July 2010.
- UK Medicines Information. What is the difference between amifampridine and 3, 4-diaminopyridine base for Lambert-Eaton Myasthenic Syndrome in adults? 24 May 2010.

Lead for policy	Malcolm Qualie Head of Health policy East Midlands Specialised Commissioning Team
Version	First
Policy effective from	05/07/2011
Date of next review	As required
Acknowledgements	Dr Giri Shankar, Daphne Austin

Risk Assessment

3,4 DAP(phosphate form) (Firdapse®) November 2010

A. Clinical risk assessment

1. The diseases in which 3,4 DAP base is being currently used

1.1 Lambert Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a chronic progressive debilitating condition of presynaptic neuromuscular transmission. It is caused by insufficient release of a chemical neuro transmitter called acetylcholine from the synaptic vesicles resulting in impaired nerve signal transmission. In 75 to 95% of cases the etiology can be traced to auto-antibodies that are directed against voltage gated calcium channels.

The symptoms of LEMS vary in severity but are characterised by muscle weakness and excessive fatigue, (particularly of the legs and trunk), drooping eyelids and speech impairment. Sensory disturbances such as numbness or tingling are also common. Other features include dry eyes, dry mouth, constipation, and impaired sweating amongst other symptoms. The onset of symptoms is gradual and insidious.

LEMS is strongly associated with cancer, especially small-cell lung cancer (SCLC). It is estimated that about 3% of patients with SCLC have LEMS, and 40 to 60% of patients with LEMS have SCLC and 5% have other cancers. Where LEMS occurs in the absence of cancer it is often associated with an autoimmune disorder.

LEMS is a rare condition with prevalence estimated at 5 per 2 million. It is therefore estimated that there are 150 patients with LEMS in the UK. Annual incidence is estimated at 1 per 2.5 million population.

The mainstay of treatment is oral 3,4-diaminopyridine which has been in clinical use since the early 1980's.

1.2 Congenital Myasthenic Syndromes

Congenital Myasthenic Syndromes (CMS) are a group of disorders all characterised by abnormal neuromuscular transmission but with various underlying genetic defects, a proportion of which remain unidentified. More than 300 different mutations causing CMS on at least eleven genes have been identified. The majority of defects are post-synaptic but can occur pre-synaptically or within the cleft.

Fatigable weakness is the clinical hallmark of the group as a whole, but they are a fairly diverse group and specific phenotypic tendencies for the known genetic subtypes have been identified. Symptoms can include generalised fatigable muscle weakness, ptosis, and ophthalmoplegia and in some patients respiratory and bulbar muscle weakness. Severity is variable between patients even between those with the same genetic subtype. Some are very mildly affected or may be asymptomatic but a proportion has significant disability and risk of death because of respiratory or bulbar involvement.

The syndromes are hereditary and usually patients have symptoms from childhood, if not birth, but it can less commonly present later in adulthood.

CMS is very rare and although the actual prevalence is unknown analysis of referrals to the National Congenital Myasthenia Service in Oxford in 2007 showed an overall UK prevalence of 2.2/million although there is significant geographical variation.

There are a number of established drugs for CMS but the subtypes of the condition respond to these treatments differently. Notably some of the drugs can worsen some of the subtypes.

3, 4-DAP is useful in only some of the subtypes and is most often added as a second line agent when pyridostigmine has failed to work or has proved only partially effective.

2. 3,4 Diaminopyridine (base form) versus 3,4 Diaminopyridine (phosphate form)

3, 4 diaminopyridine (base form) is a non-proprietary drug. It is an unlicensed drug.

3, 4 Diaminopyridine (phosphate form) (Firdapse®) is the phosphate salt formulation of 3, 4 diaminopyridine which has recently been given market authorisation under the European Orphan Drugs legislation. 3, 4 Diaminopyridine (phosphate form) is licensed for use in LEMS patients only and to a maximum daily dose of 60mg.

Legally these are two separate clinical entities. Biomarin hold the intellectual property rights to 3, 4 Diaminopyridine (phosphate form) only.

2.1 The evidence base for 3, 4 Diaminopyridine (phosphate form)

A search of standard medical literature databases did not yield any studies pertaining to the use of 3, 4 Diaminopyridine (phosphate form) in patients with LEMS. A review of the assessment report prepared for the European Medicines Agency (EMA) and published in 2009 identifies that no new studies in LEMS patients were conducted as part of the product license application for 3, 4 Diaminopyridine (phosphate form). Therefore the clinical evidence for the use of 3, 4 Diaminopyridine (phosphate form) in patients with LEMS relies upon the established evidence base for the use of the base form of the drug. Specifically, the two studies included in the systematic review are the principal sources of evidence.

One new study was conducted in 26 healthy male adult volunteers to demonstrate bioequivalence between 3, 4 Diaminopyridine (phosphate form) and the base form. This study could not be identified in the published literature and the results stated are obtained from the EMA report. The DAPSEL study evaluated the relative bioavailability of a single dose of 3, 4 DAP 20 mg administered as either as a salt or base in a cross-over design. The two formulations (salt formulated as a tablet and base in a capsule) demonstrated the pre-specified limits for bioequivalence with respect to cumulative drug levels. The salt formulation demonstrated a greater maximum concentration and time to maximal concentration signifying more rapid absorption, although the actual differences were not large. It is noted in the report that the apparent differences in absorption between equivalent doses of 3, 4 Diaminopyridine (phosphate form) and the base form would be unlikely to affect the overall efficacy although they might have an effect on safety. For this reason the maximum licensed dose of 3, 4 Diaminopyridine (phosphate form) was reduced from 80 to 60 mg daily.

The EMA report also refers to a French patient registry database with details of 82 patients who have been treated with 3, 4 Diaminopyridine (phosphate form) between December 2006 and March 2008 (16 months). Of these patients, at least 28 are known to have LEMS. Efficacy results are not reported. Of the 82 patients, 31 were new to treatment with the remaining 51 assumed to have been transferred from the established treatment to 3, 4 Diaminopyridine (phosphate form). It is reported that 'very few patients have described a lack of efficacy with 3, 4-DAP Phosphate'.

With respect to safety, again the majority of the clinical evidence relates to use of the base form and not specifically 3, 4 Diaminopyridine (phosphate form). In the single-dose DAPSEL study in healthy volunteers 40 adverse events were reported. The majority were perioral parasthesias, a well recognised adverse effect of 3, 4 DAP therapy. All effects were minor except for one case of an increase in liver enzymes which was considered related to the treatment.

There are no reports of 3, 4 Diaminopyridine (phosphate form) being studied in CMS.

2.2 How the drugs compare

There have been no formal comparisons of the two forms of the drug and 3, 4 Diaminopyridine (phosphate form) has not been subject to any clinical trials.

The two forms of the drug are considered to be bioequivalent. There is no evidence to suggest that 3, 4 Diaminopyridine (phosphate form) has better efficacy or is safer than the base form of the drug.

The base form of the drug costs, on average, £1200 per patient per annum. In comparison Firdapse® costs, on average, £44,000 per patient per annum.

3, 4 Diaminopyridine (base form)

- There is 20 years experience with this drug.
- There have been two randomised control trials. A Cochrane review concluded that limited evidence from two randomised controlled trials showed that 3, 4-diaminopyridine improved muscle strength scores and compound muscle action potential amplitudes in patients with LEMS. However, there are insufficient data at present to quantify this treatment effect. There have also been a number of case series reports.
- Currently there are about 200 patients on treatment, most of which are LEMS patients. It has a good safety record. No concerns have been identified.
- The drug is manufactured within the UK under a manufacturing license issued by the Medicines and Healthcare Devices Regulatory Authority (MHRA).
- The drug produced by licensed manufacturing bodies in the UK has a shelf life of 2 years. There is some loss of bioavailability but this has been found to be marginal.

3, 4 Diaminopyridine (phosphate form)

- There is little experience of the drug.
- There have been no studies of clinical effectiveness of this drug. The license was granted to Biomarin on the basis of evidence submitted on the base form of the drug. The drug company have undertaken bioavailability studies of the phosphate form.
- There is no safety information on this drug. The company is setting up a post marketing surveillance database.
- The drug has a maximum daily dose of 60mg. The majority of LEMS patients are on doses exceeding this limit. Biomarin have advised that lower doses will be required for the licensed product.
- The drug cannot be made up to a solution which means liquid forms of the drug cannot be provided to children (the preferred version for this age group). In addition some patients have not tolerated the phosphate form and have had to revert to the base form.

3. Manufacturing of the base form

The base form has been manufactured by companies registered under the Medicines Regulation Act.

The following companies have been supplying the drug to the NHS:

- Durbin
- Small Scale Pharmaceuticals

Manufacturing of sources comply with the requirements cited in David Lock's advice (appendix 3 paragraph 5, (c), (d), (e) & (f)).

The same companies have been manufacturing the drug for the NHS for 20 years. As such, a safe and quality controlled product is available to patients. A certificate of analysis is available from both manufacturers.

The unlicensed form is manufactured in the UK. It is not an imported drug, nor is it classified as a parallel import.

The base form has a shelf life of 2 years without significant loss of bioavailability. Durbin has tested bioavailability at 1 year and found it to be within required tolerances.

4. Costs

The differential cost per patient of Firdapse® is on average an additional £42,800.

The pricing of the phosphate form cannot be explained in terms of:

- Additional benefits in terms of efficacy.
- Additional benefits in terms of safety.

Recouping the costs of drug development normally claimed to be in the order of £500-800 million. The drug was originally developed by a not for profit (the Parisian public healthcare service) organisation. The intellectual property rights were first bought by EUSA Pharma, then Huxley and most recently Biomarin. The terms of agreement were that Biomarin paid Huxley \$15 million up front for the intellectual property rights and an additional \$7.5 million once the drug was given market authorisation. Huxley shareholders will also be eligible to receive an additional \$36 million in milestone payments based on annual and cumulative sales. The third party manufacturer for Biomarin listed in the EMA Summary of Product Characteristics as AGEPS (Agence générale des équipements et produits de santé) based in Paris. This is the manufacturing pharmacy of the Parisian public healthcare service.

The additional costs of moving patients from the unlicensed form to the licensed form of the drug are nationally estimated to be in the order of £9 million. This equates to about 360 patients on dialysis.

The move to Firdapse® would mean other patients sacrificing their healthcare to make up the difference in cost. This is unacceptable given there are no clinical benefits. Firdapse® therefore represents a loss of health benefit.

The economic climate means that most commissioners have to make substantial cost savings. Impact on service delivery is unavoidable over the coming five years.

5. Conclusions

- Unlicensed 3, 4 DAP is safe and clinically effective.
- Firdapse® is not cost-effective.
- Pricing of Firdapse® is not justified and has ethically unacceptable opportunity costs.

- The commissioning position should be that Firdapse® will not be funded.

B. Legal risk assessment

Extensive legal advice has been sought over the issues of use of off label and unlicensed medicines when licensed versions exist.

6. The commissioner's position

A statutory requirement of PCTs is that they must live within budget. They are also expected to invest in services which represent value for money with the view to benefiting as many patients as possible.

The law is clear that PCTs have the right to determine priorities and it would be considered reasonable, having made a careful risk assessment for a PCT to not fund an expensive licensed drug over a cheaper version if this impacts on other patients' health and wellbeing.

7. The clinician's position

The General Medical Code of Conduct strongly encourages doctors to prescribed the most appropriate treatment and wherever possible use a licensed over an unlicensed or off label drug. However the code is not breached if the licensed drug is not made available because it is not funded. Not to fund a drug is a commissioning decision and not a clinical decision (see appendix 1).

8. Provider trust's position

The NHS Litigation Authority has confirmed that it will cover any liabilities related to the prescribing of an unlicensed or off-label drug (see appendix 2).

9. The manufacturers of the unlicensed drug

There is no breach of intellectual property rights.

The MHRA has no authority to close down manufacturing of the unlicensed version.

Under the Medicines Regulation Act manufacturers of the unlicensed drug can provide the drug on a named patient basis provided that the request is unsolicited (see appendix 3)

10. Conclusions

- The unlicensed version can legally be made available to NHS patients.

Appendix 1

Legal advice provided by David Lock, Barrister, regarding the use of generic hydroxycarbamide for sickle cell crisis

July 2009 (Updated November 2010)

Summary of Advice

There is no reason in principle why the NHS should be required to prescribe a more expensive licensed drug when a pharmacologically identical drug is unlicensed for the treatment in question.

There is nothing unlawful (in the sense of creating a criminal offence or a civil wrong) in using an unlicensed drug. Such drugs are used all the time in the NHS, particularly in paediatric medicine where it is very difficult if not impossible to get MHRA approval for the proposed uses.

Where a drug is licensed then the NHS is under a theoretically lower level of litigation risk because the drug company, in effect, takes on the product liability risk involved in prescribing the drug. This protection against litigation risk is not present with an unlicensed drug. However it is important to highlight that this is a “risk” and that, as with all risks, the NHS could decide to accept the risk because the price of the drug means that the price of buying out the risk is too great.

If a doctor has a choice between a licensed and an unlicensed drug then doctors are strongly encouraged by the GMC Code of Conduct to prescribe the licensed drug because, in general, this will represent a lower level of patient risk and a greater chance of effective treatment because of the stringent testing processes that the drug company will have followed prior to being granted a licence. However the Code is silent as how the doctor should prescribe where the licensed product is not available as part of NHS approved treatment. In those circumstances I consider that, for example, an oncologist will not breach the GMC Code if he or she prescribes an unlicensed cancer drug where there is an equivalent licensed product which the PCT has refused to make available as part of NHS treatment. The GMC duty to prescribe licensed products is not absolute because it must be limited to the choices available to the doctor in his or her work setting.

Hence, if doctors are given a choice by the service conditions within which they work, they will be professionally obliged to prescribe the licensed drug (notwithstanding the price differential and that a cheaper pharmacologically identical drug, which is unlicensed, is available for the treatment in question. The key question for the NHS is whether to make that drug available to the doctors as something that the doctor is able to prescribe. That is a commissioning policy decision and not a prescribing decision for which the doctor is held accountable to the GMC.

If a doctor, working for an NHS Trust, was unable (under the terms of his employment contract) to prescribe an expensive licensed drug because there was a cheaper pharmacologically identical drug available for the treatment in question, I am confident that, save in exceptional circumstances, the doctor could not be the subject of a successful complaint to the GMC on the basis that he or she ought to have prescribed the pharmacologically identical licensed alternative.

Equally I find it very difficult to see that the doctor would not be acting negligently in doing so because this is not an option which was open to him as an NHS employed doctor. He may have to have a conversation with the patient about buying the licensed alternative, just as oncologists sometimes discuss patients having private prescriptions for expensive but

unauthorised cancer drugs. However there is no duty on the NHS to provide the “best” treatment for every patient.

The patient would also, in my opinion, have formidable difficulties in suing the commissioner who had made the decision not to make the treatment available on grounds of cost because, as I have explained in previous advices, there is no general duty of care owed by commissioners to patients. If there is no legal duty of that type, the commissioners cannot be sued for alleged breach of that duty.

There has been a suggestion from Nordic Pharma that the NHS may have breached the marketing rules in the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 because the commissioning decisions amount to “promotion” of an unlicensed medicinal product. I have considered the Regulations and advise that there does not appear to be any breach. Commissioners are not, in my view, marketing drugs within the meaning of the Regulations.

I should mention that the restrictions that a PCT can impose on Trusts through the mechanism of the NHS Contract do not apply to GPs who have a much wider freedom to prescribe. In effect, they can ignore the restrictions imposed by a PCT and have the right under the 2004 Contract and the statutory scheme which underpins it to prescribe any drug they consider appropriate. The fact that this will breach their indicative practice budgets is not a good reason for a GP to refuse to prescribe a drug. However I understand from the material I have been provided with that this drug is likely to be prescribed in an acute setting so this may not be a significant problem.

On a practical note, if a decision is to be made not to permit NHS Trusts with whom PCTs contract to prescribe Siklos, I would suggest that discussions are held with the NHSLA to alert them to this issue, as the NHS is thereby taking on a theoretically increased risk due to the lack of a product liability guarantee. However the NHS is not a risk free environment and all risks come at a price. I can see very good reasons why, if the price differential is too high, the PCTs may consider that this is a highly marginal risk which they would be well advised to accept.

In the end whether to commission Siklos is risk based commissioning decision for PCTs. If the drug company with the licensed drug was able to bring the price down sufficiently to persuade the NHS to take the product liability risk then prescribing Siklos would be sufficiently attractive to allow this drug to be commissioned consistent with the PCT duty to break even in each financial year. If the PCTs consider the price differential is too high and there is not sufficient evidence of benefit for patients with the licensed product, then I can see defensible reasons for PCTs taking the decision not to commission this drug.

David Lock
July 2009 (updated November 2010)

Appendix 2

**Personal communication to Dr Daphne Austin from the NHS Litigation Authority
8th June 2010**

“It [The NHSLA] will cover employing NHS bodies for their vicarious liabilities for treatment provided by employees. So if a clinical decision is made to prescribe a certain type of drug (licensed or unlicensed) then we would not look behind that decision and CNST cover will apply for the acts of the prescriber.”

Appendix 3

Legal advice provided by David Lock, Barrister, regarding the treatment of LEMS in adults and in the Medicines for Human Use Regulations 1994

November 2010

In the matter of Symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults

And in the matter of the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 (as amended)

ADVICE

1. Biomarin Europe Limited (“Biomarin”) holds a marketing authorisation for a drug called Firdapse® where the active ingredient is 3, 4 diaminopyridine. The drug is used to treat Lambert-Eaton Myasthenic Syndrome (LEMS) in adults. Unlicensed 3, 4 diaminopyridine has been used for many years to treat Lambert-Eaton Myasthenic Syndrome (LEMS) in adults but that no manufacturer or supplier has obtained a marketing authorisation for the drug. Thus the 2 drugs are used to treat the same clinical condition and have a very similar (if not identical) clinical effect.
2. I have been asked to advise the East Midlands Specialised Commissioning Group as to whether clinicians who made a request to a product manufacturer or supplier to supply 3,4 diaminopyridine (base form) for their patients would be acting unlawfully and to give some views on whether the supplier who responded to that request would be likely to be acting unlawfully.
3. LEMS is a serious but rare disorder of neuromuscular transmission. It is a serious condition which causes a unique set of clinical characteristics, which include proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic changes. Prior to Firdapse® coming onto the market I understand that LEMS was treated with the base form of 3, 4 diaminopyridine, which has an annual cost of £1250 per patient. However the licensed version, Firdapse®, is far more expensive with the maximum annual cost per patient being in the region of about £44,000 per year. I also understand that the only chemical difference between 3,4 diaminopyridine (base form) and Firdapse® is that Firdapse® is a slightly more stable chemical compound due to the addition of a stability molecule but that the drugs are otherwise chemically identical and have roughly equal clinical benefits.
4. Biomarin have written to a number of suppliers of the unlicensed product to say that now that Biomarin have a marketing authorisation for Firdapse®, it would be a breach of the criminal law for them to supply hospitals with 3,4 diaminopyridine (base form). A number of suppliers have moved out of this market but others have refused to stop supplying the drug when requested to do as a “special”, which I understand to be an unsolicited request to satisfy a patient’s special needs.

5. I am asked to advise whether the stance taken by these suppliers is defensible in law and how the NHS should approach the choice between Firdapse® and 3, 4 diaminopyridine (base form). I have been asked to do this against a set of assumed facts involving a hospital doctor or pharmacist who seeks a supply of the drug to treat a particular patient who has LEMS. I will also assume for the purposes of this advice that the patient could theoretically also be prescribed Firdapse® and that this would have similar or equal clinical benefit.
6. The relevant law is set out in the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 (“the Regulations”) which have been amended on multiple occasions since the Regulations were brought into effect on 1 January 1995. These are UK Regulations to bring into UK law the effects of the Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use¹.
7. The Regulations govern how medicines can be marketed by drug companies within the EU. Thus the primary focus of the Regulations (and the Directives which underpin them) is to regulate the commercial marketing activities of drug companies. However the Directive and the Regulations are not focused on restricting the activities of doctors. The scheme of the Regulations (in general terms) is that whilst drug companies are not entitled to promote drug products unless they have a marketing authorisation to do so, doctors and other medical professionals are entitled to take an independent clinical view of which drugs they should provide to their patients and request supplies of unlicensed drugs for their own patients. Thus, in this scheme, the doctors are entitled to take the risks (along with the patients) in prescribing unlicensed drugs.
8. Regulation 3 provides:

“(1) Except in accordance with any exception or exemption set out in the relevant Community provisions and subject to paragraphs 1 and 3 to 5A of Schedule 1—

 - (a) no relevant medicinal product shall be placed on the market; and
 - (b) no such product shall be distributed by way of wholesale dealing, unless a marketing authorization in respect of that product has been granted in accordance with the relevant Community provisions by the licensing authority or the European Commission, and is for the time being in force in accordance with those provisions.

(2) Schedule 1 shall have effect for the purpose of making certain exceptions or exemptions from paragraph (1), and for imposing certain obligations in connection with such exceptions and exemptions”
9. The manufacturers and distributors of 3, 4 diaminopyridine (base form) do not (as I understand matters) seek actively to place this product “on the market” in the sense that they do not actively market the drug. However Regulation 3(1) also prevents the companies from distributing drug “*by way of wholesale dealing*” unless the company has a marketing authorisation. Hence, on the assumed facts, if the drug were to be sold to a hospital pharmacy (even in response to a specific request) then it is likely that this would be “wholesale dealing”. Thus (although this would be a matter for the supplier to consider for themselves) the supplier would be acting unlawfully unless it was able to bring itself within the terms of schedule 1 to the Regulations. Schedule 3 of the Regulations sets out the criminal offences of acting in breach of the terms of inter alia Regulation 3.

¹ [2001] OJ L311/67

10. However there are exemptions to the prohibition in Regulation 3 in Schedule 1 to the Regulations. Paragraph 1 of Schedule 1 provides:
- “Regulation 3(1) shall not apply to a relevant medicinal product supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist, supplementary prescriber, nurse independent prescriber or pharmacist independent prescriber and for use by his individual patients on his direct personal responsibility, in order to fulfil the special needs of those patients, but such supply shall be subject to the conditions specified in paragraph 2”
11. This is the origin of the “special needs” exemption which has been relied on by Biomarin in their letters to manufacturers and distributors of 3, 4 diaminopyridine (base form). The elements which are required to be shown to bring a case within the above paragraph are as follows:
- a. The supply must be of a “relevant medical product”;
 - b. It must be made in response to a bona fide unsolicited order;
 - c. The order must be placed by a doctor, dentist, supplementary prescriber, nurse independent prescriber or pharmacist independent prescriber;
 - d. It must be intended for use by the individual patients of the person who placed the order and is intended to be used on that person’s direct personal responsibility;
 - e. It must fulfil the special needs of those patients.
12. There are a number of further requirements set out in paragraph 2 which I shall consider below. However, on the assumed facts of a request made by an NHS doctor for this drug, it seems to me that:
- a. The supply of 3,4 diaminopyridine (base form) is a supply of a “relevant medical product”;
 - b. It would be supplied in response to a bona fide unsolicited order from an NHS clinician;
 - c. The order will have been placed by a doctor, dentist, supplementary prescriber, nurse independent prescriber or pharmacist independent prescriber;
 - d. The order will be intended for use by the individual patients of the person who placed the order and is intended to be used on that person’s direct personal responsibility.
13. Hence, on the assumed facts, the first set of requirements will all be satisfied. However the paragraph also requires that the drug is “required to fulfil the special needs of those patients”. There is no definition of “special needs” in the Regulations and no real indication as to what is meant by the expression. The origin of this phrase is the Art.5(1) of the Directive which provides:
- “A Member State may, in accordance with legislation in force and to fulfil **special needs**, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility”

14. The special needs exemption was referred to by the European Court in *Ludwigs-Apotheke Munchen Internationale Apotheke v Juers Pharma Import-Export GmbH* (C-143/06)². Unfortunately the judgment in that case does not assist greatly in ascertaining the meaning of the phrase other than a general suggestion that it appears to refer to a patient's individual needs. However the case did establish that whether a patient has or has not got "special needs" is a matter for the judgment of the treating clinician and not the manufacturer or supplier of the drug. Thus "special needs" could be interpreted to mean the identified, individual needs of a particular patient to treat a specific medical condition.
15. LEMS is a rare condition and it seems to me that it would be open to a NHS clinician to reach the view that a patient had a "special need" for 3, 4 diaminopyridine (base form) if that drug could deliver clinical benefits to treat the symptoms of LEMS in that individual patient. However it could be argued that the patient did not have a "need" for the unlicensed drug because a licensed product, Firdapse®, would satisfy that need and accordingly the patient had no need (let alone a special need) for an unlicensed drug. However that argument can only realistically arise if Firdapse® is an alternative that is practically available for a clinician to prescribe.
16. Where an alternative licensed product is available, it is clear that both the GMC Code of Practice and Medicines and Healthcare Regulatory Authority ("MHRA") Guidance provide strong encouragement to doctors to prescribe the licensed product. The MHRA Guidance³ on the ordering of "specials" by clinicians states:
- "2.3 As a rule, an unlicensed medicinal product which is a pharmaceutical equivalent of an available licensed medicinal product should not be placed on the market. A medicinal product should be regarded as a "pharmaceutical equivalent" if:
- it contains the same amount of the same active substance(s), or in the case of liquid dosage forms the same concentration; and
 - it is in the same dosage form; and
 - it meets the same or comparable standards considered in the light of the clinical needs of the patient at the time of use of the product.
- 2.4 A licensed medicinal product obtainable from normal distribution channels in a reasonable time should be considered available for use. If an otherwise suitable licensed product becomes unavailable, it may be necessary for an unlicensed pharmaceutical equivalent to be supplied. This should be seen as a temporary expedient and should not be taken as justification for long term supply. Supply in these circumstances should cease as soon as is practicable, following re-instatement of the suitable licensed product"
17. However this advice needs to be seen within the context of the statutory purpose of the MHRA. The MHRA are, according to their website, "responsible for ensuring that medicines and medical devices work, and are acceptably safe". That purpose will always be achieved by recommending licensed medicines (where there is research and clinical testing to back up the overall effects) are used in preference to unlicensed medicines. The MHRA are not required (as far as I have been able to determine) to make value judgments on the relative cost-effectiveness of licensed medicines against unlicensed medicines. That judgment falls exclusively to PCTs who are making choices within the NHS budget, particularly where there is a vast difference of price between licensed medicines and unlicensed medicines.

² [2008] 1 C.M.L.R. 26

³ See <http://www.mhra.gov.uk/home/groups/is-lic/documents/publication/con007547.pdf>

18. That then raises the question as to whether it would be lawful, given the lower cost of 3,4 diaminopyridine (base form), for NHS clinicians to not be allowed by their Trust employers to prescribe Firdapse®. I understand that NHS Trusts generally do not permit their clinicians to prescribe drugs unless the Trust is able to recover the cost of the drugs from the commissioning PCT (since such treatments fall outside the standard NHS Acute services contract). That must be a reasonable approach (or the Trust would make a significant financial loss on the treatment cycle). This issue must therefore focus on whether the PCT could lawfully refuse to fund the cost of the licensed product, Firdapse® when there is a clinically viable but unlicensed alternative.
19. Without seeking to re-open the whole area of law on priorities in NHS commissioning (where I have advised the clients before on several matters) when the question is put in this way the answer is reasonably clear. PCTs must seek value for money in their commissioning and, if they were to be satisfied of the clinical efficacy of 3,4 diaminopyridine (base form), I consider that they would be entitled to take a lawful decision to commission that unlicensed drug in preference to Firdapse®.
20. It follows that, if Firdapse® is not made available as part of NHS treatment, the only other option would be for the patient to accept a private prescription. The annual cost of Firdapse® is roughly twice the national average salary, and so it seems to me that is unlikely that the majority of patients would be able to pay for Firdapse® themselves (although it may be sensible for clinicians to have that conversation with patients to outline the possibility to them). In those assumed circumstances I consider that the clinician could form the view that the patient has a real “need” for the drug and that the real clinical choice was between 3,4 diaminopyridine (base form) and a less effective form of drug treatment. I can therefore see a strong argument that the clinician could form the view that the patient has a “special need” for the drug.
21. However if a PCT were prepared to commission Firdapse®, and thus a Trust permitted a clinician to prescribe Firdapse®, then it may be difficult for the clinician to say that the patient does have a “need” for the drug since there is a perfectly viable and licensed clinical alternative which the clinician could prescribe. In those circumstances (in my opinion) clinicians may have difficulty in certifying in a bona fide request that the patient does have a special need for the drug.
22. Thus it seems to me that the position of the commissioners is critical. If they refuse to commission the drug (save in exceptional clinical circumstances and in that case probably as a result of an individual request process), the key question is whether it can be lawful for a clinician to make a lawful request to a supplier for an unlicensed product to provide him with the drug on a “special needs” basis. There are legal distinctions between the positions of the commissioning PCT, the Trust which employs the clinician and the individual clinician. If the commissioners are not prepared to permit Firdapse® to be prescribed as part of NHS treatment (and thus in effect are refusing to agree to reimburse the Trust for the cost of supplying the drug) then I can see a strong argument that the Trust would be acting lawfully if it were to refuse to permit the clinician to supply the licensed drug as part of NHS treatment. In general the Trust must be entitled to say to a clinician that, when working as part of the NHS in an acute hospital setting, these are the drugs you are permitted to prescribe as part of NHS treatment and these are the drugs that you are not permitted to prescribe. If that were not the case then the Trust would lose all financial control over its drugs budget.
23. If it is lawful for the Trust to prevent a clinician from being able to prescribe a licensed product as part of NHS treatment (and the patient is unable or unwilling to pay for the drug on a private basis) I can see a strong legal argument to say that the clinician would be entitled to conclude the patient has a “special need” for the unlicensed drug within paragraph 1 of Schedule 1 to the Regulations. In those circumstance the clinician could make a lawful request to the supplier to provide the unlicensed drug within the terms set out in the Schedule to the 1994 Regulations.

24. The criminal offence under the Regulations in this case is by the supplier and not the requesting clinician. However it seems to me that, provided the clinician makes a request in good faith for the drug and states that this is required to treat a patient's special needs, there is probably no need for the supplier to go behind that statement and to ask for further details unless the supplier has specific knowledge that there is no such special need. Given that this is a criminal offence and thus should be interpreted in a narrow way, I consider that the supplier ought to be able to rely on the fact that a doctor or a pharmacist has reached an assessment and have concluded that the drug was needed for the special needs of the clinician's patient. This is supported by paragraph 2.2 of the MHRA Practice Note 14 which states:

“Responsibility for deciding whether an individual patient has “special needs” which a licensed product cannot meet should be a matter for the doctor, dentist or supplementary prescriber responsible for the patient's care”

25. However this Advice is not directed to the interests of the suppliers (who are not my clients) and even if this Advice is shared with them I would recommend them to seek their own legal advice.
26. The request from the clinician must also satisfy the obligations under paragraph 2 of the Schedule which reads as follows:

“The conditions mentioned in paragraph 1 are that—

- (a) the relevant medicinal product is supplied to a doctor, dentist, supplementary prescriber, nurse independent prescriber or pharmacist independent prescriber or for use in a registered pharmacy, a hospital or a health centre under the supervision of a pharmacist, in accordance with paragraph 1;
- (b) no advertisement or representation relating to the relevant medicinal product is issued with a view to it being seen generally by the public in the United Kingdom and that no advertisement relating to that product, by means of any catalogue. . . or circular letter is issued by, at the request or with the consent of, the person selling that product by retail or by way of wholesale dealing or supplying it in circumstances corresponding to retail sale, or the person who manufactures it, and that the sale or supply is in response to a bona fide unsolicited order;
- (c) if manufacture or assembly of the relevant medicinal product is carried out under the supervision of such staff and such precautions are taken as are adequate to ensure that the product is of the character required by and meets the specifications of the doctor, dentist, supplementary prescriber, nurse independent prescriber or pharmacist independent prescriber who requires it;
- (d) written records as to the manufacture or assembly in accordance with sub-paragraph (c) are made and maintained and are available to the licensing authority or the enforcement authority on request by them or either of them;
- (e) if the relevant medicinal product is manufactured or assembled in the United Kingdom, or imported into the United Kingdom from a third country, the product—
- (i) is manufactured, assembled or imported by the holder of a manufacturer's licence which relates specifically to the manufacture, assembly or import of relevant medicinal products to which paragraph 1 applies; or

(ii) has been manufactured, assembled or imported as an investigational medicinal product by the holder of a manufacturing authorization granted by the licensing authority for the purposes of regulation 36 of the Medicines for Human Use (Clinical Trials) Regulations 2004; and

(f) the relevant medicinal product is distributed by way of wholesale dealing by the holder of a wholesale dealer's licence”

27. These are all matters that concern the supplier rather than the NHS. However provided the supplier does not include the drug in its catalogue or take any other active steps to market the product it will satisfy the first part of the tests in the paragraph. The supplier will need to be a registered manufacturer or wholesale supplier of this class of medicines to satisfy the above tests but I understand that this is not likely to be a problem in practice.
28. Thus, in the posed circumstances, I consider that an NHS clinician who was unable to prescribe Firdapse® as part of NHS treatment would be entitled lawfully to request a “special needs” supply of 3,4 diaminopyridine (base form). I also consider that, provided the supplier can satisfy the terms of paragraph 2 of Schedule 1 to the Regulations, the supplier will act lawfully in supplying the drug in response to the request.

David Lock
November 2010