

Debate & Analysis

Special unlicensed medicines:

what we do and do not know about them

INTRODUCTION

A special unlicensed medicine is one that is manufactured without a marketing authorisation (MA) from the Medicines and Healthcare products Regulatory Agency (MHRA). An MA (or product licence) is granted by the MHRA only once a medicinal product has been proven to be safe and effective. Prescribed products that do not hold an MA include those prepared on an individual basis by 'special order' manufacturers (for example liquid preparations), products classed as 'food supplements' (such as vitamin D preparations), and medicines that are licensed abroad but which do not hold a UK MA.¹

CURRENT GUIDELINES

The MHRA recommends that unlicensed medicines should only be used when existing licensed medicinal products are not appropriate to meet patient needs² and this is also echoed in guidance from the General Medical Council.³ An example of this situation often arises in paediatric medicine due to smaller or unusual doses being required, which cannot normally be administered using standard solid oral dosage forms. Other examples include patients with difficulty swallowing solid oral dosage forms and patients needing to receive medicines through enteral feeding tubes. Medicines that have received marketing authorisations in countries other than the UK are another example of unlicensed medicines that may be employed where licensed preparations have been unsuccessful or unsuitable.⁴ Midodrine tablets for example, which are licensed in the US but not in the UK, may be used for the treatment of orthostatic hypotension where treatment with fludrocortisone has been unsuccessful, or use of a steroid is unsuitable for the patient. There is also significant prescribing of products classed as 'food supplements' that do not hold a marketing authorisation.⁵

IMPLICATIONS FOR PRESCRIBERS

Prescribing and dispensing of unlicensed medicines comes with additional professional responsibilities for both the prescriber and the dispensing pharmacist.⁶ Without a marketing authorisation, there is no MA holder to take responsibility for any adverse reactions associated with the medicine's use and this means any liability rests with the prescriber.⁷ However, a prescriber will not

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usually know the source of the medicine, as this is decided by the pharmacist.⁶ Furthermore, the pharmacist does not usually have sufficient information to know why an unlicensed preparation has been prescribed when undertaking any clinical checks. Some unlicensed medicines may be initiated by secondary care consultants, but the prescribing of them continues in general practice through the use of protocols and information. For example, a recommendation to prescribe melatonin solution for a child with a sleep-wake disorder using a shared care guideline, such as those used by NHS Gateshead CCG.⁸ It is not yet established how patients and professionals perceive and understand the potential risks associated with the use of unlicensed medicines in such circumstances.

Without marketing authorisations, unlicensed products do not benefit from the data generated as part of the licensing application process.⁹ There is no clinical trial data to demonstrate safety and efficacy of the formulation and there are no stability studies to support a clear expiry date.^{9,10} As a result, unlicensed medicines often have recommended expiry and storage conditions based only on the experience of their manufacturers.¹⁰ Frequently unlicensed medicines come with no detailed patient information, which would also ordinarily be produced as part of the application for an MA.⁹

In 2012, the National Patient Safety Agency (NPSA) issued a safety alert around the use of buccal midazolam¹¹ and highlighted 132 medication incidents which had been reported through the National Reporting and Learning Service. Incidents were found in relation to prescribing, dispensing, and administration of buccal midazolam and included three incidents that resulted in severe patient harm and five in moderate harm. One of the NPSA recommendations to minimise the potential risk was to limit the prescribing of midazolam to licensed formulations where possible.¹¹ Although

a licensed preparation of midazolam, oromucosal, solution has been available since October 2011,¹² unlicensed midazolam 10 mg/mL remains on Part VIII B of the Drug Tariff, implying that it is still acceptable to the NHS that prescribers use an unlicensed formulation.

It is not known if healthcare professionals recognise the limitations and risks of using unlicensed medicines, whether they employ any strategies to minimise any potential risks, and how they balance these risks against patient need. The quality of any information the patient may receive when they are prescribed an unlicensed medicine is also unknown.

HEALTH ECONOMIC IMPACT

Another significant aspect of the use of unlicensed medicines is cost. Based on data from the top 500 special order items in England and Wales from Quarter 1 2014/2015, the average cost of an unlicensed medicine item was £104.47.¹³ Among the cheapest items are colecalciferol 20 000 unit capsules with an average price per item of £14.42 (43 717 items), and among the most expensive are sodium benzoate tablets with an average cost of £807.19 per item (43 items).¹³ It should be noted however that an 'item' in these data include prescriptions for all quantities prescribed, therefore treatment durations for each prescription will affect the average cost incurred. The overall average net ingredient cost per prescription item for all medicines in 2013 was £8.37,¹⁴ making the average cost of unlicensed medicines over twelve times more expensive than licensed preparations. While the introduction of Part VIII B of the Drug Tariff in November 2011 seems to have caused an overall decrease in total spend on special unlicensed medicines¹⁵ in primary care (no data are available for their use in secondary care), they remain a significant cost burden to the NHS. However, it remains to be seen if healthcare professionals view this spend as justified.

Increasingly, there has been a drive to take frequently-used unlicensed formulations and create new licensed products. Where new products have been introduced, the range of unlicensed preparations for that product has been removed from the Drug Tariff list, in anticipation that patients receiving other strengths of unlicensed products could be converted to the newly-available licensed preparations. However, this does not seem to be the case. In May 2012, the unlicensed liquid preparations for ramipril were removed from Part VIII B of the Drug Tariff due to the introduction of the licensed ramipril 2.5 mg/5 mL oral solution. However, in the financial period Quarter 1 2014/2015, prescribing data report that there were still 355 dispensed unlicensed items for ramipril, costing the NHS £77 139.75 when an appropriate licensed oral liquid formulation was available.

In addition, the top 10 unlicensed medicines in the prescribing data still include drugs for which there are licensed formulations available including melatonin, omeprazole, and midazolam (Table 1).¹³ It is still unclear why unlicensed medicines continue to be prescribed despite an increasing number of licensed alternatives.

SUNDERLAND MODEL OF PHARMACIST PRACTICE SUPPORT

An example of pharmacist intervention is in Sunderland, where clinical pharmacists provide support to general practices. This is delivered through a contract with a pharmacist support service paid for by Sunderland Clinical Commissioning Group, however some practices also opt to pay for additional pharmacist support themselves and there are examples in other regions where pharmacists are employed directly by the practice, such as in Cambridge.¹⁶ As part of their work plan in Sunderland,

pharmacists will use NHS prescribing data to identify patients prescribed unlicensed medicines and review their therapy. Requests for unlicensed medicines, for example, from hospital consultants or where care homes require liquid forms of medication, are referred to a pharmacist who can review and recommend appropriate switches. Practice pharmacists also liaise with hospital and community pharmacists to ensure patients are prescribed the most appropriate product to meet their clinical needs.

The potential role of pharmacists and their role in supporting appropriate use of medicines was highlighted as part of the NHS England Clinical Pharmacists in General Practice Pilot¹⁷ and included the example of 'sorting out secondary care referrals for "specials"' as one of the potential roles for practice pharmacists.

WHERE DO WE GO FROM HERE?

Despite the issues associated with the use of unlicensed medicines, little information is available on the views of healthcare professionals on their use in practice. Further research is required to explore the views of prescribers, pharmacists and patients on the use of unlicensed medicines across primary and secondary care. A review of any existing systems or strategies currently employed is required to address some of the issues associated with unlicensed medicines and to enable healthcare providers to understand and control their usage.

CONCLUSION

Currently, unlicensed medicines are being prescribed and used when there are licensed alternatives available and these unlicensed medicines are often more expensive than their licensed counterparts. There are guidelines on the use of unlicensed medicines from both the medicines

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regulator and the GMC,^{2,3} which highlight the liability of prescribers who choose to supply unlicensed medicines.

What is not currently understood are the contexts in which unlicensed medicines are used, how prescribers use unlicensed medicines, what patients know about unlicensed medicines, and how pharmacists interact with unlicensed medicine requests as part of their supply function. Without this full understanding, it is difficult to propose systems and processes to ensure that unlicensed medicines are used appropriately and safely by patients, professionals, and the wider NHS.

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Table 1. Commonly-prescribed unlicensed medicines¹³

Medicine	Type of unlicensed medicine	Number of items Quarter 1 2015/2016
Colecalciferol 20 000 unit capsules ^a	Food supplement	17 213
Melatonin 1 mg/1 mL oral solution ^a	Special order ^a product	10 142
Melatonin 3 mg capsules	Non-UK Food supplement	8002
Diltiazem 2% cream	'Special order' product	4967
Omeprazole 10 mg/5 mL oral suspension	'Special order' product	4751
Midazolam oromucosal solution 10 mg/1 mL	'Special order' product	4993
Magnesium glycerophosphate 97.2 mg tablets	Food supplement	4303
Midodrine 5 mg tablets	Non-UK import	3243
Metolazone 2.5 mg tablets	Discontinued product	2653
Acetylcysteine 600 mg capsules	Food supplement	1812

^aLicensed product now available

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