Questions on supply of nitrosamine-compliant, unlicensed varenicline: Information for services

Background

Following the initial disruption to supply of varenicline (Champix) in June 2021 because of the presence of nitrosamines above the acceptable level of daily intake, Pfizer announced a wholesale and pharmacy recall of Champix in October 2021.

A nitrosamine-compliant, unlicensed varenicline supply is now available in the UK and this briefing gives details of this medication and how it can be obtained.

We asked Thistle Pharma several questions and their answers are reproduced in the following pages.

Varenicline: effectiveness and safety

Varenicline was licensed for use in England in 2006 and is available on prescription only. Compared to placebo varenicline has been shown to more than double long-term abstinence rates. Clinical trials indicate that varenicline is almost twice as effective as bupropion (Zyban) and is more effective than single forms of NRT.

A large randomised controlled train (EAGLES) suggested that varenicline did not significantly increase the risk of neuropsychiatric adverse events compared to placebo or nicotine patch (Niquitin), in patients with or without a history of psychiatric disorder.

Reference: Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet. 2016 Jun 18;387(10037):2507-20. doi: 10.1016/S0140-6736(16)30272-0. Epub 2016 Apr 22. PMID: 27116918.

More information on varenicline, and other stop smoking medications can be found in the NCSCT stop smoking aids quick reference sheet:
https://www.ncsct.co.uk/publication_stop_smoking_medications_quick_reference.php

Information for services

1. **Is direct supply of unlicenced varenicline to patients possible?**
   The varenicline we are providing is an internationally licensed UK/EU nitrosamine-compliant presentation which is unlicensed in the UK. Unlicensed medicines can be prescribed by any UK registered professional authorised to prescribe, and be dispensed directly to patients at a Pharmacy; however, the regulations do not permit an unlicensed medicine to be distributed via a patient group direction (PGD).

   In primary care, most GP prescribing systems provide for an e-prescription to be generated by the prescriber and transmitted to a one-off nominated pharmacy for collection and delivery:

   https://digital.nhs.uk/services/electronic-prescription-service/nominating-a-dispenser

   Dispensed product can be made available directly to patients via free of charge (FOC) postal delivery from a DSP (Distance Selling Pharmacy) e.g., Thistle Pharma's outsourced Pharmacy partner at Flying Scotsman Pharmacy, DN1 3AP ODS Code FXR73 www.weldricks.co.uk. Similarly, any applicable prescription charges can be collected remotely. Where e-prescriptions are not available, physical prescriptions can be addressed to "FREEPOST Thistle Pharma" for remote dispensing and dispatch to patient.

   Prescribing and dispensing of our UK unlicensed varenicline can also be undertaken entirely within a secondary care setting e.g., within an NHS trust with onward dispatch to patient and Thistle Pharma can assist service sites with appropriate Good Distribution Practice courier selection.

   For supply chain or direct to patient solutions, please reach out to us at contactus@thistlepharma.com for signposting.

2. **How is unlicenced varenicline accessed through pharmacy?**
   Thistle Pharma Ltd are an MHRA licensed wholesaler (WDA(H) 43743) and can supply any GPhC registered Pharmacy in receipt of a bona fide prescription.

   At this time, Thistle Pharma has no plans to introduce the product into the broader UK wholesale supply chain to help manage NHS costs, but where groups are associated with a particular provider (e.g., Boots via Alliance Healthcare or Rowlands via Phoenix) arrangements can be made for provision of stock.

   For product supply arrangements please reach out to us at contactus@thistlepharma.com

3. **Can/will GPs/other doctors prescribe it?**
   Where any physician or otherwise qualified prescriber has identified a patient with an unmet need for varenicline and the patient consents, the UK unlicensed presentation can be prescribed and dispensed for them.

   Full guidance with respect to the compliant protocols are available in MHRA Guidance Note 14 (https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials).

   Product descriptors have been created on the Dictionary of medicines and devices (DM&D) and the expectation is that GP system providers will include these descriptors in their system

updates for inventory selection from the prescriber's desktop. The varied descriptors are given below:

Actual Medicinal Product (AMP)	Supplier	Discontinued	Parallel Import	Virtual Medicinal Product (VMP)
Varenicline 1mg tablets and Varenicline 500microgram tablets	Imported (Canada)			Varenicline 1mg tablets and Varenicline 500microgram tablets
Varenicline 1mg tablets	Imported (Canada)			Varenicline 1mg tablets
Varenicline 500microgram tablets	Imported (Canada)			Varenicline 500microgram tablets

Where prescribing system software providers have not automatically included the DM&D descriptors in their system updates, participating prescribers may be required to request the lines inclusion directly with their provider at the next update.

Please reach out to us at contactus@thistlepharma.com with any prescribing queries.

4. **How do local pharmacies get stock of the unlicenced medication to fulfil prescriptions?**
Dispensing doctors and GPhC registered Pharmacies can reach out to Thistle Pharma for signposting at contactus@thistlepharma.com

   Upon exchange of appropriate bona fides, stock can be dispatched for next day delivery.

5. **Is anyone else supplying unlicenced varenicline in the UK?**
In so far as we are aware, Thistle Pharma's unlicensed varenciline is unique and the only MHRA risk-assessed EU/UK nitrosamine compliant product available for UK patients.

6. **Can unlicenced varenicline be supplied as part of a patient group direction (PGD)?**
No.

   Unfortunately, UK legislation does not permit any unlicensed medicines to be supply as part of a PGD.

7. **Can you explain the rules on using / prescribing / direct supply of unlicenced medication to patients in a) community and b) hospital settings?**
Both environments are subject to similar regulation, specifically, GMC with respect to prescribing, GPhC with respect to procurement and dispensing and MHRA with respect to compliant product and behaviours. Detailed guidance is available via MHRA Guidance Note 14 which can be accessed here; https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

   Essentially, from a prescribing perspective, the physician must have

   a) identified a patient clinical need which cannot be satisfied via a licensed alternative
   b) have gained the patient's consent for use of the unlicensed presentation
   c) have familiarity with the clinical characteristics and constraints associated with the drug product being prescribed

From a dispensing perspective, the pharmacist must:

a) ensure the prescription is a bona fide request for an unlicensed presentation and that the above applies
b) procure and dispense appropriate product in line with the prescription
c) maintain a record of supply

The circumstance in a hospital setting is not dissimilar, although the community environment leverages an FP10 prescribing and dispensing process, consequently, applicable primary care prescription charges for the patient will require to be collected.

Please reach out to us at contactus@thistlepharma.com with respect to any regulatory or compliance queries.

8. **What happens when a medic prescribes the medication? How does the patient access it?**
If in a primary care or community setting, the doctor will need to either give the prescription to the patient, transmit an e-prescription to a nominated pharmacy (or Thistle's outsource DSP Pharmacy partner) for direct to patient dispensing.

In secondary care, unless for private patient supply, the prescriptions generated within the Trust should be dispensed by the Hospital Pharmacy.

All Pharmacies can procure directly from Thistle Pharma via contactus@thistlepharma.com

9. **What are the additional costs to when prescribing unlicenced varenicline in a) community and b) hospital settings?**
Our product list price is £59.99 per n56 maintenance pack of 0.5mg or 1mg tablets and £34.99 for an n25 Starter Pack.

From a Drug Tariff perspective our product is classed as a Part VIIIB Non-Tariff Special item. Consequently, in community, FP10 dispensing events will attract an additional £20 "SP" service fee per prescription paid centrally to the Pharmacy to cover relevant supply chain procurement and national dispatch costs. No discount on product cost is permitted.

Within a hospital setting, no £20 "SP" fees are applicable, and a discount can be applied for larger product volumes.

10. **What does the price here include? Is this the cost to services wanting to buy a course, or prescription costs?**
Our list price is for product only and will be the reimbursed value at the point of dispensing as applicable to prescribing budgets. It is our understanding that dispensing Pharmacy "SP" fees are paid centrally and do not impact the GP budget. Although direct to patient dispatch from our DSP partner will be FOC from a patient perspective, individual Pharmacies may levy or waive fees at their own discretion.

Within a secondary care clinic environment with secondary care dispensing provision, only product costs will be applicable with the potential for discount for higher volume users. Dispatch fees for Trust Pharmacies where patients require home delivery would be courier dependent.

11. **Can services purchase the medication from other suppliers?**
If required, but probably not as cost-effectively.

As yet, Thistle Pharma have not released product to the broader wholesale supply chain to try to keep NHS reimbursement costs lower, but if there are preferred points of order, these can be arranged.

12. **What are the additional rules for prescribing unlicenced varenicline (e.g., expectation of GPs, who can advise the patient)?**
Most GPs are familiar with UK "Specials" and there is comprehensive guidance available via MHRA Guidance Note 14 referenced above and from the GMC here:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

The physician should be familiar with the unlicensed drug characteristics (much simpler in this case since varenicline is an established vs unusual "Special" presentation). Given the unlicensed product has no marketing authorisation (licence) the physician takes responsibility for the safety and efficacy of the presentation. Patients should be fully apprised that an unlicensed medicine is being prescribed and the GP should capture their consent in their notes.

13. **How is the unlicenced medication presented? If Thistle Pharma *Starter packs* and *Maintenance packs* are used, what do these look like?**

The starter packs, that we originate in our clean rooms under MS licence permissions, consist of an outer carton with two amber glass bottles. One of these bottles contains 0.5 mg (white) tablets x11 and the other bottle contains 1 mg (blue) tablets x14. The bottles are clearly marked.

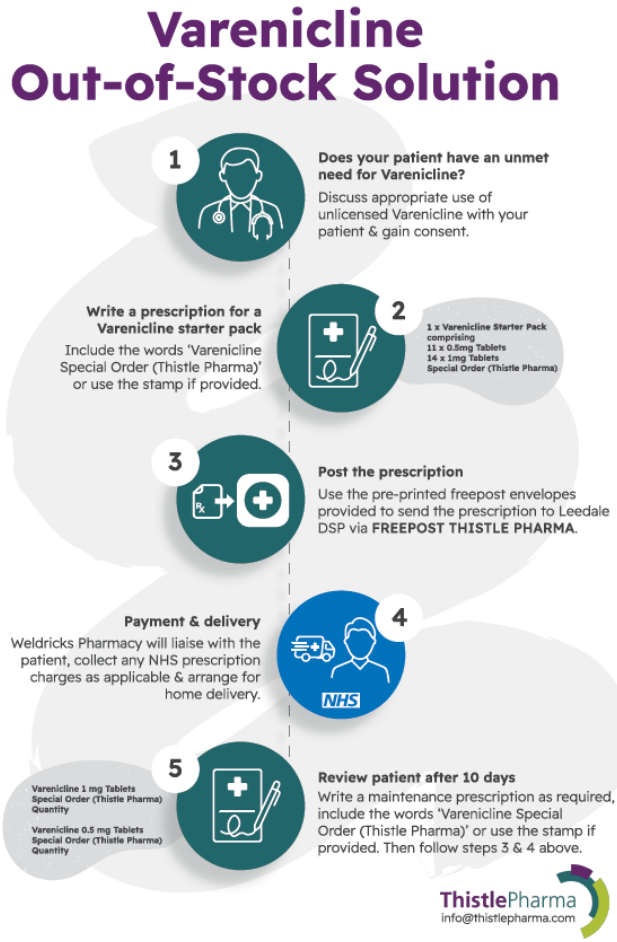
Alternatively, starter pack collateral and packaging can be provided to any GPhC registered Pharmacy for assembly at the point of dispensing under Medicines Act S10 provisions.

Maintenance packs are single bottles of 56 tablets of either 0.5 mg or 1 mg tablets, depending on the patient's needs. These bottles are clearly labelled with their relevant strength and are presented as they would be sold in the country of origin which uses English language labelling.

14. **If a service buys the packs from Thistle, what are the rules for supply to patients?**
A service would need to have access to both prescribing and direct to patient dispensing capabilities. We would need to exchange satisfactory bona fides with the service site for delivery and check compliance re prescribing and GDP distribution.

Please Contactus@thistlepharma.com for signposting to dispensing solutions as required.

15. **Can the packs be posted to patients at home? If so, by the service or by a third party?**
Prescribed product needs to be dispensed by a Pharmacy prior to dispatch to patient. If the service site can arrange prescribing, an electronic prescription could be shared with Thistle's outsource DSP for direct-to-patient dispatch as per question 1. GDP tracked and traced dispatch protocols would be used. An example of a proposed community flow is below.



Secondary care clinic arrangements will require product to be dispensed and dispatched via their Hospital Pharmacy.

For site-specific direct to patient dispensing solutions contactus@thistlepharma.com

16. **How do we know that the product meets UK nitrosamine standards?**
All imported unlicensed medicinal products must comply with certain obligations set out in Schedule 4 of the Human Medicines Regulations 2012, and more specifically, require consent from the MHRA to import the unlicensed medicinal product following a product specific notification.

For unlicensed varenicline, the MHRA reviewed the nitrosamine impurity levels at release and during shelf-life for the batches supplied by Thistle Pharma and agreed that these batches remain well below the UK nitrosamine standard for varenicline (which is 18.5 ppm for n-nitrosovarenicline).

UK/EU Nitrosamine compliance statements can be made available on request via contactus@thistlepharma.com

17. **How do we know that the product is safe (apart from meeting nitrosamine levels)?**
    All imported unlicensed medicinal products must comply with certain obligations set out in Schedule 4 of the Human Medicines Regulations 2012, and more specifically, require consent from the MHRA to import the unlicensed medicinal product following a product specific notification.

    For unlicensed varenicline, the batches were sourced from a large high-quality North American manufacturer that works to Good Manufacturing Practice (GMP) that has a good history of manufacturing safe and efficacious pharmaceuticals.

    The active ingredient in Thistle Pharma's product is identical to Champix®: varenicline.

18. **How do we know that the product is effective?**
    All imported unlicensed medicinal products must comply with certain obligations set out in Schedule 4 of the Human Medicines Regulations 2012, and more specifically, require consent from the MHRA to import the unlicensed medicinal product following a product specific notification.

    For unlicensed varenicline, the batches were sourced from a high-quality manufacturer that works to Good Manufacturing Practice (GMP) that has a good history of manufacturing safe and efficacious pharmaceuticals.

    The active ingredient in Thistle Pharma's product is identical to Champix®: varenicline.

19. **How do we know that the product is cost-effective (e.g., worth the cost)?**
    Our product price needs to cover our MHRA risk-assessment costs, GDP compliant importation from North America, storage, distribution, discoverability campaigns and commercial viability margin. At the same time, our NHS list price has been tempered to be aligned with prior Champix© reimbursement. around which we expect there was considerable cost-efficacy scrutiny to justify the broad prescribing prior to Pfizer withdrawal. A useful link is below:

    https://www.nice.org.uk/guidance/ta123

20. **Is there a website that patients and staff can access?**
    We will provide a specific page at www.thistlepharma.com or services can reach out to our team directly at contactus@thistlepharma.com for further detail

21. **Can a GP refuse to prescribe on the grounds of cost or for other reasons (e.g., because it is unlicensed)?**
    As an unlicensed medicine, prescribers must assure themselves the product is appropriate for their patients. The decision to prescribe is theirs alone.

22. If a 12-week course needs to be extended, can that be done?

As set out in the Champix Summary of Product Characteristics (SmPC), for patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment at 1 mg twice daily may be considered for the maintenance of abstinence.

If the prescribing healthcare professional wishes to extend a patient's course of treatment, they are permitted to do so within their own professional capacity. In all cases it should be noted that Thistle Pharma's varenicline is an unlicensed medicine and that it is the prescriber that is directly responsible regarding the special needs of that patient.