Espranor (buprenorphine oral lyophilisate) 2mg and 8mg

Considerations for opioid substitution therapy use in community settings and secure environments

Key messages

- Espranor is a freeze dried wafer (oral lyophilisate) which contains buprenorphine (2mg or 8mg).
- Espranor results in similar clinical outcomes and adverse effects as Subutex but may provide benefits in reducing diversion and timing of supervised doses due to its faster dissolution rate.
- Espranor is not interchangeable with other buprenorphine sublingual formulations at the same dose ("like for like" switch) as the **bioavailabilty is 25-30% higher.** If a switch is necessary, (e.g. if a person moves between care settings from the community in to prison or between prisons and doesn't need re-stabilisation) then clinicians should use their professional judgement regarding a new dose.
- Espranor contains gelatin whereas the other buprenorphine tablets do not. This may need to be considered for certain patients.
- The **initial dose** of Espranor is **2mg compared to 0.8mg – 4mg** for other oral buprenorphine preparations and the maximum single daily dose for Espranor is 18mg **NOT 24mg or 32mg** as with Suboxone and Subutex.
- There is no 0.4mg strength of Espranor, the lowest strength is 2mg – the Espranor SPC suggests that patients may need to be switched to 0.4mg sublingual buprenorphine tablets to enable dose reduction. This should be done accounting for the bioequivalence differences between the buprenorphine products.
- The administration of Espranor is different to other buprenorphine products as it is placed on the tongue (not under it). Median time for disintegration is 2 minutes. Swallowing should be avoided for 2 minutes and food or liquids must not be consumed for 5 minutes after dissolution. Healthcare staff may need to be trained to administer Espranor correctly particularly where buprenorphine is administered at the same time as other medicines.
- Espranor 10mg daily costs **£101.60 for 28 days supply** (the same as Subutex) compared to **£12.28** for generic sublingual buprenorphine 10mg daily.
- Suboxone 10mg daily costs £127 for 28 days supply. If Suboxone 10mg daily was switched to Espranor, this will result in a cost saving.
- Primary care prescribing of generic buprenorphine accounts for 90% of prescribing at a net ingredient cost of £5.47 per prescription. If Espranor prescribing was introduced and reduced the proportion of generic prescribing to 70%, this **would result in a cost rise of £4.7m** with a net ingredient cost per prescription of £35.47.
- In secure environments, the bottom line is that the annual workforce cost saving is unlikely to offset the extra cost of Espranor compared to the current cost of prescribing and administering generic buprenorphine. The cost pressure if Espranor is used in all prisons is estimated to be up to £1.1m. Actual local data could be used to calculate the local overall financial impact in individual secure environments.

Background

What is Espranor?

Espranor is a freeze dried wafer (oral lyophilisate) which contains buprenorphine (2mg or 8mg) and dissolves when placed on the tongue. [1]

Espranor is licensed for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. It is intended for use in adults and adolescents aged 15 years and over who have agreed to be treated for addiction. [2]

Unlike other oral forms of buprenorphine, Espranor contains gelatin. [2] This may need to be considered for certain patients.

The licence applications for Espranor 2mg and 8mg were submitted as hybrid medicines because although the formulation is novel, they contain the same ingredient as Subutex 2mg and 8mg (sublingual buprenorphine tablet), so these were used as the reference medicines.
Three bioavailability (2 pilot and 1 pivotal) studies have been conducted comparing Espranor with Subutex. Two phase II safety studies were conducted in the UK and India. [1]

The plasma concentrations achieved in the bioequivalence studies are within the known safe limits for buprenorphine and Espranor plasma levels achieved during the titration posology fell within the range of all sublingual products available in Europe including Subutex and Suboxone. [1]
Two phase II studies compared safety and effectiveness of Espranor and Subutex. Espranor was as efficacious as Subutex in reducing cravings and preventing withdrawal symptoms at the same dose. No deaths, serious adverse events or safety issues were noted. Administration of Espranor did not result in a higher risk of respiratory depression compared to Subutex. Two Espranor subjects reported 3 events of oral hypoesthesia 5-10 minutes after administration which resolved within 20 minutes, 20-25 minutes and 60 minutes. A higher number of mild treatment emergent adverse effects were reported with Espranor which were mainly associated with withdrawal symptoms (e.g. headache, arthralgia, rhinorrhea) and oral hypoesthesia. [1]

Bioavailability & dose equivalence

Espranor is not interchangeable with other buprenorphine products e.g. Subutex or generic sublingual buprenorphine tablets. This is because the bioavailability of buprenorphine is 25-30% higher with Espranor as it is more completely absorbed compared to sublingual tablets. [1, 2]

Based on the expected plasma concentrations of buprenorphine, the starting and maximum doses of Espranor have been reduced to 2mg and 18mg compared to 0.8mg-4mg and 32mg for Subutex or generic sublingual buprenorphine tablets and 2-4mg and 24mg for Suboxone (buprenorphine + naloxone). The average dose of buprenorphine used in the UK is 10.2mg. The average dose of Espranor is likely to be less due to its increased bioavailability. This means a similar response may be achieved with an overall lower exposure to buprenorphine, however because of individual variability of buprenorphine pharmacokinetics, the dose should always be titrated according to the patients clinical response. [1-5]

Dissolution rate

Espranor oral lyophilisate has been designed to disintegrate quickly when placed on the tongue.
Phase II studies have shown that 96.3% of administrations achieved partial disintegration in ≤ 15 seconds. The median time for complete disintegration is 2 minutes, although one study reports only 58% of administrations were complete within 2 minutes. [1, 6]
In comparison sublingual buprenorphine tablets take 5-10 minutes to dissolve. [3-5]
Where buprenorphine tablets are crushed for administration, the dissolution rate will be less than the solid dose form.

Administration issues
The oral lyophilisate should be removed from the blister pack with dry fingers – any contact with moisture will result in disintegration of the wafer. The oral lyophilisate must be placed whole on the tongue until dispersed. This is different to current buprenorphine tablets which are placed under the tongue. Healthcare professionals need to be clear about this to advise patients and avoid administration errors. Placing Espranor on the tongue makes supervision of dosing easier as it instantly begins to disintegrate making removal from the mouth for the purposes of diversion impossible. If the oral lyophilisate or saliva containing buprenorphine is swallowed, the buprenorphine will be metabolised, excreted and have minimal effect. [2]

Swallowing should be avoided for 2 minutes. Food and drink should not be consumed for 5 minutes after administration. [2] This may require observation of people having supervised consumption, however Espranor may still be beneficial where the solid dose of buprenorphine is administered due to the overall reduced time of administration of Espranor. These factors may have the potential to result in improved compliance and consequently improved treatment outcome. This may also potentially increase capacity in busy community pharmacies.
Secure environment healthcare providers often crush sublingual buprenorphine before administration so it is estimated that the disintegration rate is less than uncrushed buprenorphine. [7] This means that the benefit of Espranor in reducing supervised consumption queues due to its quicker disintegration time (15 seconds – 2 minutes) may not be realised.

Dose tapering
2mg is the lowest available dose with Espranor. The SPC states that patients who may require a lower dose, 1mg or 0.4mg sublingual tablets may be used. This should be done accounting for the bioequivalence differences between the buprenorphine products. However it should be noted that there are no licensed 1mg sublingual buprenorphine tablets available in the UK. [2]

Misuse, abuse, diversion
Buprenorphine is sparingly soluble in water. [1] The SPC states that clinicians should consider the risk of abuse and misuse (e.g. IV administration) particularly at the beginning of treatment. Removal of Espranor from the mouth is virtually impossible due to speed of disintegration. [2] This also reduces the potential for concealment and removal of the dosage form once administered. This could reduce diversion, saving up of doses, or injection of crushed tablets. As Espranor is less likely to be injected, the harms from injecting buprenorphine would be reduced. [8]
Some secure environment healthcare providers already crush sublingual buprenorphine to reduce the risk of diversion and make removal from the mouth virtually impossible.
If Espranor is diverted, buprenorphine is odourless [9] although the oral lyophilisates have a mint flavouring [2] which may or may not be detectable by security dogs.

Place of buprenorphine in opioid substitution therapy
NICE Clinical Guideline 52 (July 2007) on opioid detoxification of drug misuse in over 16 year olds states that methadone or buprenorphine should be offered as the first-line treatment in opioid detoxification. When deciding between these medications, healthcare professionals should take into account:

- whether the service user is receiving maintenance treatment with methadone or buprenorphine; if so, opioid detoxification should normally be started with the same medication
- the preference of the service user. [10]

Continuity of care
When people are transferred between care settings or when a person moves from supervised consumption to non-supervised buprenorphine, care plans will need to take account of the continuation of Espranor versus the change to alternative formulations of buprenorphine given the difference in bioavailability. Collaboration prior to transfer between settings (e.g. community and custodial settings) is advisable so this can be planned as part of the transfer.

How is buprenorphine used in Health & Justice (H&J) pathways?
In H&J settings, the place of buprenorphine within substance misuse opiate substitution therapy can be summarised as follows:

Prescribing choice in H&J

- Methadone is used first line for opioid stabilisation and maintenance with buprenorphine usually used as continuation of community prescribed treatment or switched from methadone prior to release. [10] This equates to an expected maximum of 20% buprenorphine versus 80% methadone use in H&J.
- Suboxone is only used in exceptional cases in H&J where additional safety of naloxone is necessary.

Supply/Administration in H&J
Buprenorphine is given non-in possession (IP) and crushed before use (in line with RPS guidance). This means it takes less time to be absorbed in the mouth than if whole tablets were used. Some prisons expect prisoners to remain observed for several minutes (5-10mins) to minimise the risk of diversion.

Financial considerations

NHS Prices for buprenorphine sublingual tablets and Espranor (Drug Tariff, January 2017)

Product	Strength & pack size	Cost of 28 tablets	Cost of 10mg for 28 days
Buprenorphine generic	2mg x 7	£4.96	£12.28
	8mg x 7	£7.32	
Subutex	2mg x 7	£25.40	£101.60
	8mg x 7	£76.20	
Espranor	2mg x 7	£25.40	£101.60
	8mg x 7	£76.20	
Suboxone	2mg/0.5mg x 28	£25.40	£127

Generic buprenorphine offers the lowest cost compared to Subutex or Espranor: 10mg daily **per month** costs £12.28 compared to £101.60 for Subutex or Espranor; **an 8-fold difference** (costs from January 2017 NHS Drug Tariff). Suboxone is the most expensive preparation.

Current prescribing in primary care
Between April and November 2016 515,220 prescriptions were written for buprenorphine 2mg and 8mg sublingual tablets at a net ingredient cost of £4,324,298. Appendix 1 shows the regional prescribing data. From this data we can conclude that:

- Extrapolating the data for a full year effect for 2017/18 gives an estimated 772,830 prescriptions at a cost of £6,486,447.
- In England prescribing of generic buprenorphine accounts for 90% of prescriptions with a net ingredient cost per generic item of £5.47.
- 10% of buprenorphine is prescribed as Subutex at a net ingredient cost of £35.47 per item.
- If prescribing was changed to Espranor from the generic products resulting in a reduction in generic prescribing from 90% to 70%, this would cause an increased annual cost of prescribing from £6,486,447 to £11,185,264 – an annual cost pressure of £4.7m.
- If prescribing of Suboxone 10mg daily was switched to Espranor, this will result in a cost saving.

Impact in secure environments
Unlike primary care, prescribing in secure environments is not available directly for central analysis. To estimate the impact of a change in prescribing to Espranor, alternative information is used:

- The average dose of both Espranor and other buprenorphine formulations is about 10mg/day. This will be used for cost comparisons.

- The National Drug Treatment Monitoring System (NDTMS) 2015/16 Q4 data suggests that there were 46,141 opiate users in prison. 1 in 3 were on opiate substitution treatment (OST) treatment (15,380) of which 36% (5536) were on this for >3 months.
- Given the lack of actual data on prescribed buprenorphine and methadone, a 20/80 split is used for estimating actual buprenorphine patient numbers and costs. If 20% of 15,380 prisoners on OST receive buprenorphine this equates to 3,076 people. 64% are only on it for 3 months (1,969 people); 36% are on it for > 3 months - worst case is they continue treatment for the whole 12 month period (1,107 people).
- Operational costs for administering buprenorphine:
    - it takes the same time for healthcare staff to ID the prisoner, find and select the dose and record the supply in the patient record – as buprenorphine tablets are currently crushed, the preparation and dissolution time has been estimated and use of Espranor is assumed to be 5 times faster.
    - There are two members of staff in healthcare and one security officer supervising the buprenorphine being administered. 3 x AfC Band 4 staff + 25% on-cost have been used for calculating the reduction in staff costs to administer Espranor.

Using the above information, if all people in secure environments were prescribed Espranor instead of generic buprenorphine, the **annual increase** in prescribing costs is estimated at £1,714,140. Operational **costs saved** would be approximately £620,088 per year.

Bottom line: In secure environments a complete switch to Espranor for buprenorphine prescribing is unlikely to offset the savings in operational costs of non-in possession administration. In the event that all prisons opt to replace generic buprenorphine with Espranor the resulting cost rise accounting for buprenorphine prescriptions and operational costs is estimated as up to £1.1m. Local information can be used to estimate the local overall financial implications for using Espranor in secure environments.

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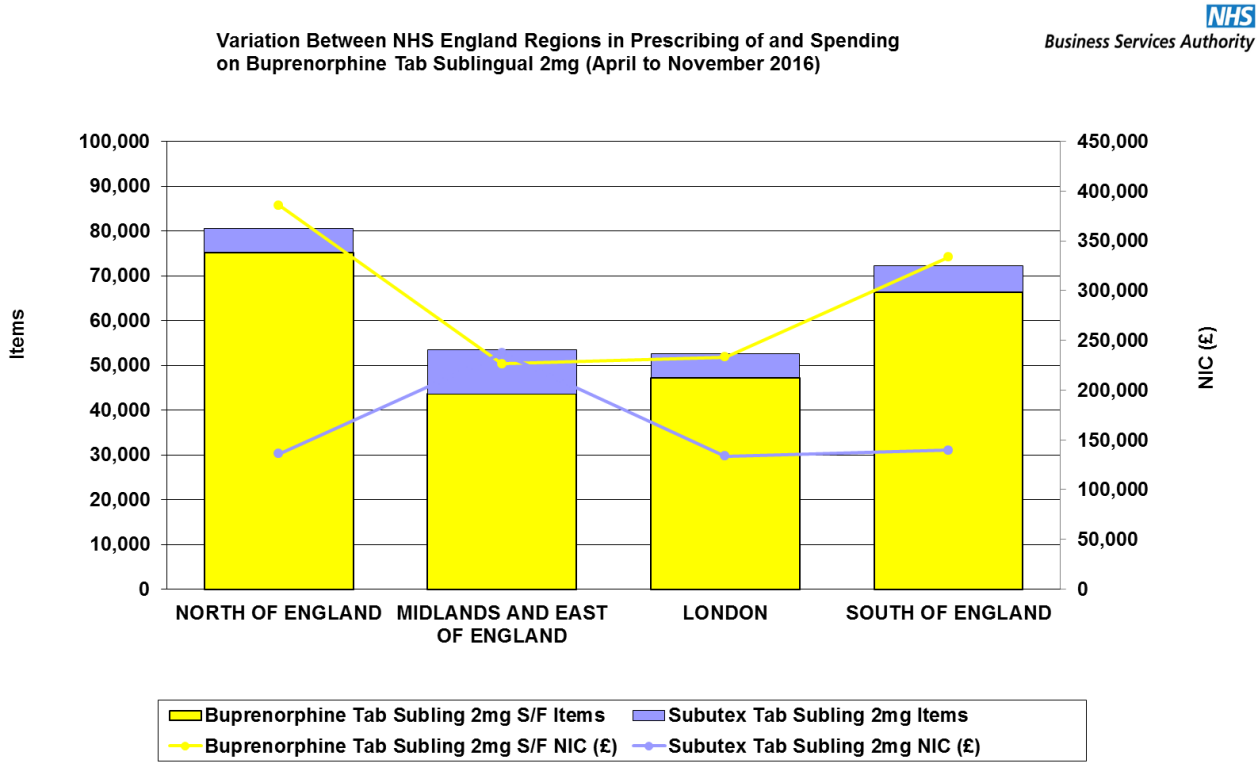
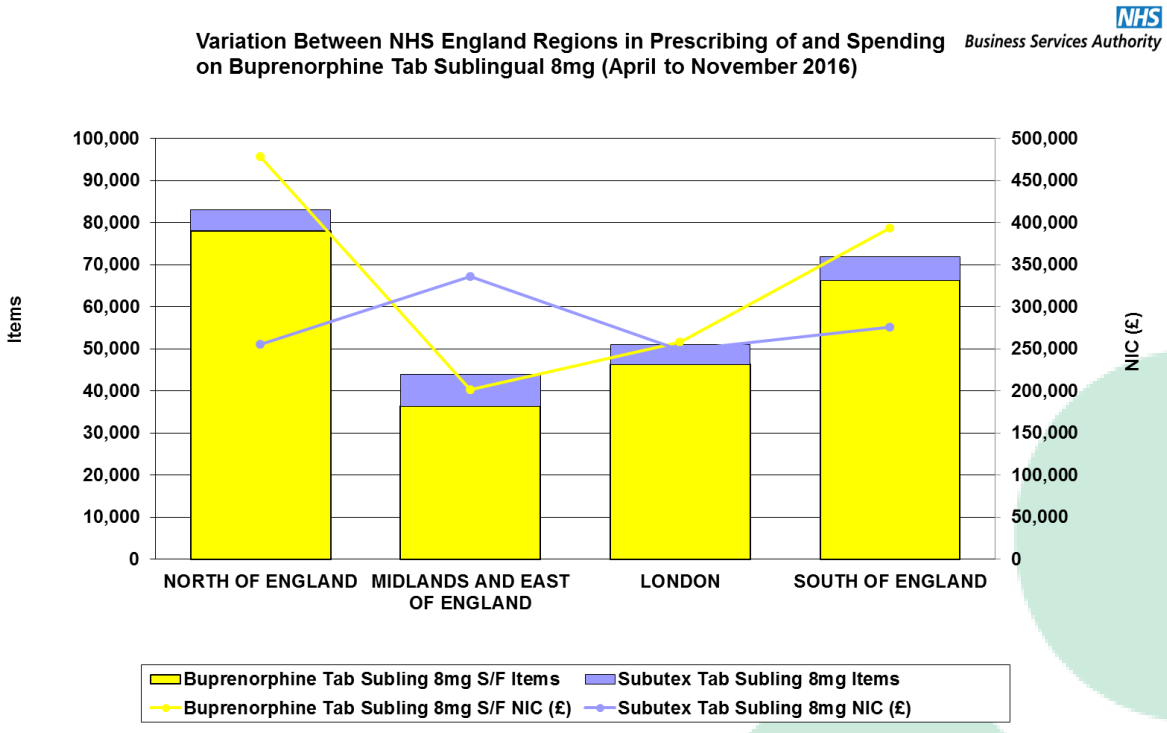
Appendix 1: Prescribing of buprenorphine 2mg and 8mg in NHS England (by region)





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