This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.
Assessment against Ethical Framework

Evidence of Clinical Effectiveness

- The cost impact of recommending fentanyl over immediate release morphine or oxycodone cannot be justified.
- Therefore, NICE does not offer fentanyl IR as first line for breakthrough pain.
- NICE published an evidence update on opioids in palliative care (Evidence Update 58, May 2014) which identified a 2013 Cochrane review assessing opioid analgesics for managing breakthrough pain in patients with cancer. Meta-analysis of data from only 2 of the studies (considered to be relevant to NICE CG 140) for pain intensity difference at 15 minutes reported a statistically significant difference favouring transmucosal fentanyl compared with morphine tablets (mean difference=0.37, 95% CI 0.00 to 0.73, p=0.048; 2 studies, n=154).
- Both the statistical and clinical significance of this finding have been questioned. Statistical significance is not clear cut, with the lower boundary of the confidence interval touching 0.00 (i.e. the point of no difference).
- In August 2015, acting on feedback, the Cochrane Editorial Unit withdrew this Cochrane review on the basis that it was misleading.
- Two further randomized controlled trials comparing immediate release fentanyl to an active comparator (oral morphine) for breakthrough cancer pain have been identified, however methodological limitations (including lack of proper randomization) mean that further studies addressing this question are needed.

Safety:

- The National Patient Safety Agency (NPSA) produced a Rapid Response Report on opioid medicines in 2008 to ensure that all health professionals involved in the prescribing, dispensing or administration of opioids were aware that they have the responsibility to check that an intended opioid dose is safe and appropriate for that patient.
- Fentanyl is metabolised by CYP3A4. Hepatic metabolism is reduced by grapefruit juice and a number of medications including macrolide antibiotics, azole antifungals and some protease inhibitors.
- As with all opioids, risk of addiction and misuse should be borne in mind.
- The availability of a number of different formulations of immediate release fentanyl products with similar strengths but different dosage instructions and pharmacokinetic profiles creates potential for prescribing and dispensing errors.

Cost of treatment and cost-effectiveness

- There is a significant cost difference between fentanyl IR and similar drug preparations such as morphine and oxycodone, see below table. The fentanyl IR formulation to use as first line will also depend on the following factors:
- Nasal products generally work quicker and are shorter lasting (less oral absorption) than the sublingual/buccal route. They may be preferred in the presence of severe dry mouth, mucositis or nose bleeds.

Cost Comparison Table - Fentanyl IR, Oxycodone IR and Morphine IR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per dose unit</th>
<th>Cost of 28 days treatment with three doses/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstral® sublingual tablets (all strengths)</td>
<td>£4.99</td>
<td>£419.16</td>
</tr>
<tr>
<td>Effentora® buccal tablets (all strengths)</td>
<td>£4.99</td>
<td>£419.16</td>
</tr>
<tr>
<td>Actiq® lozenges (all strengths)</td>
<td>£7.01</td>
<td>£588.84</td>
</tr>
<tr>
<td>Breakyl® buccal film (all strengths)</td>
<td>£4.99</td>
<td>£419.16</td>
</tr>
<tr>
<td>Instanyl® nasal spray (all strengths)</td>
<td>£5.95</td>
<td>£499.80</td>
</tr>
<tr>
<td>PecFent® nasal spray (all strengths)</td>
<td>£4.56</td>
<td>£383.04</td>
</tr>
<tr>
<td>Morphine sulphate tablets 10mg</td>
<td>£0.09</td>
<td>£7.56</td>
</tr>
<tr>
<td>Morphine sulphate tablets 20mg</td>
<td>£0.19</td>
<td>£15.96</td>
</tr>
<tr>
<td>Morphine sulphate oral solution 10mg/5ml 10mg dose</td>
<td>£0.09</td>
<td>£7.56</td>
</tr>
<tr>
<td>Morphine sulphate oral solution 10mg/5ml 20mg dose</td>
<td>£0.18</td>
<td>£15.12</td>
</tr>
<tr>
<td>Oxycodone 5mg capsules</td>
<td>£0.20</td>
<td>£16.80</td>
</tr>
<tr>
<td>Oxycodone 10mg capsules</td>
<td>£0.41</td>
<td>£33.60</td>
</tr>
<tr>
<td>Oxycodone oral solution 5mg/5ml5mg dose</td>
<td>£0.19</td>
<td>£15.96</td>
</tr>
<tr>
<td>Oxycodone oral solution 5mg/5ml10mg dose</td>
<td>£0.39</td>
<td>£32.63</td>
</tr>
</tbody>
</table>

The needs of the population

The needs of the population appear to be low as there are alternative treatments (morphine IR and oxycodone IR) which are effective and lower cost. There may be a small cohort that may benefit from treatment with fentanyl IR.
The needs of the community
The needs of the community are small as fentanyl IR is not required in the vast majority of patients with breakthrough pain. The impact on the health economy appears to be high as fentanyl IR has a higher cost than other alternative pharmacological therapies. Therefore the cost benefit ratio is likely to be high.

Policy Drivers
NHS England Recommendations - Items which should not routinely be prescribed in primary care:
Guidance for CCGs.
Recommendations
1. Advise CCGs that prescribers in primary care should not initiate immediate release fentanyl for any new patient.
2. Advise CCGs to support prescribers in de-prescribing immediate release fentanyl in all patients and, where appropriate, ensure the availability of relevant services to facilitate this change.
3. Advise CCGs that if, in exceptional circumstances, there is a clinical need for immediate release fentanyl to be prescribed in primary care, this should be undertaken in a cooperation arrangement with a multi-disciplinary team and/or other healthcare professional.

Exceptions and further recommendations:
These recommendations do not apply to patients undergoing palliative care treatment and where the recommendation to use immediate release fentanyl in line with NICE guidance (see below), has been made by a multi-disciplinary team and/or other healthcare professional with a recognised specialism in palliative care.

Category:
Items which are clinically effective but where more cost-effective products are available, including products that have been subject to excessive price inflation.

NICE CG 140: Palliative Care for Adults: Strong opioids for pain relief.
- Offer oral immediate release morphine for the first line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.
- Do not offer fast-acting Fentanyl as first line rescue medication (a NICE Do Not Do Recommendation).
- If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

Equity
No impact anticipated

Implementability
Significant cost of prescribing in primary and secondary care. Review of existing patients in primary care will require support. Prescribing guidance documentation will be developed with the support of palliative care specialists.

References:
- PRESQIPP: https://www.prescqipp.info/component/jdownloads/send/51-Fentanyl/2626-bulletin132-Fentanyl-drop-list
- Palliative care dosing guidance: http://www.palliativecareguidelines.scot.nhs.uk/guidelines/medicine-information-sheets/Fentanyl-patches.aspx

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.