Section 17.5.3 Antidiarrhoeal (symptomatic) medicines in adults

REVIEW OF THE ROLE OF LOPERAMIDE AND CODEINE IN THE MANAGEMENT OF SYPTOMATIC DIARRHOEA IN ADULTS

JULY 2010

Oshuwa Ibhanesebhor
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16. REFERENCES ............................................................................................................ 20
1. Summary statement of proposal for inclusion, change, or deletion
Loperamide hydrochloride has been proposed as a replacement for Codeine phosphate in the management of symptomatic diarrhoea in the WHO Model List of Essential Medicines.

2. Name of focal point in WHO submitting the application
Not applicable

3. Name of the organisation(s) consulted and/or supporting the application
None.

4. International Nonproprietary Name (INN)
INN: Codeine phosphate
Generic name: Codeine phosphate
Chemical name: Codeine phosphate hemihydrate; codeini phosphas; codeini phosphas hemihydricus; codeini phosphas; methylmorphine phosphate

INN: Loperamide Hydrochloride
Generic name: Loperamide Hydrochloride
Chemical name: Loperamidi hydrochloridum; R-18553. 4-(4-p-chlorophenyl-4-hydroxypiperidino)-NN-dimethyl-2,2-diphenylbutyramide hydrochloride

5. Formulation proposed for inclusion
Loperamide hydrochloride
- Capsules 2 mg
- Tablets 2 mg

6. International availability
Loperamide hydrochloride and Codeine phosphate are available in Europe, Australia, Asia, South America, the United States, and Canada.

7. Category of listing requested
Listing is requested as an individual drug.

8. Information supporting the public health relevance
8.1 Epidemiological information on disease burden
Acute diarrhoea is usually self-limiting and is characterized by a sudden onset of abnormally frequent, watery stools(1). Most acute diarrhoea does not require a doctor visit. However, the associated discomfort, inconvenience, and social embarrassment in relation to faecal incontinence – either real or threatened – makes this an unpleasant condition, even though it usually lasts only a short time (1).

Globally, there are about two billion cases of diarrhoeal disease every year(2).
Diarrhoea can last several days, and can leave the body without the water and salts that are necessary for survival. Most people who die from diarrhoea actually die from severe dehydration and fluid loss (2).

Diarrhoea due to infection is widespread throughout developing countries. In 2004, diarrhoeal disease was the third leading cause of death in low-income countries, causing 6.9% of deaths overall (2).

### Table 8.1 - Estimates for distribution of diarrheal episodes by type according to age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Watery diarrhoea</th>
<th>Persistent diarrhoea</th>
<th>Dysentery</th>
<th>Watery diarrhoea</th>
<th>Persistent diarrhoea</th>
<th>Dysentery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>80</td>
<td>10</td>
<td>10</td>
<td>50</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>5–14</td>
<td>89</td>
<td>1</td>
<td>10</td>
<td>75</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>15–44</td>
<td>90</td>
<td>0</td>
<td>10</td>
<td>80</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>45–59</td>
<td>90</td>
<td>0</td>
<td>10</td>
<td>80</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>≥ 60</td>
<td>85</td>
<td>0</td>
<td>15</td>
<td>85</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>


### 8.2 Assessment of current use

Codeine phosphate is indicated for the treatment of acute diarrhoea in adults.

Loperamide hydrochloride is indicated for the treatment of acute and chronic diarrhoea in adults.

### 8.3 Target population

Adults with symptomatic diarrhoea

### 9. Treatment details

#### 9.1 Dosage regimen and duration

**Codeine Phosphate**

Dose: Acute diarrhoea, 30 mg 3–4 times daily (range 15–60 mg)

**Loperamide**

Dose: Acute diarrhoea, 4 mg initially followed by 2 mg after each loose stool for up to 5 days; usual dose 6–8 mg daily; max. 16 mg daily;

Chronic diarrhoea, initially, 4–8 mg daily in divided doses, subsequently adjusted according to response and given in 2 divided doses for maintenance; max. 16 mg daily;

### 9.2 Reference to WHO and other clinical guidelines

**WHO's current guideline:**

Antimotility drugs like loperamide and codeine are opiate drugs which inhibit intestinal motility. They may reduce the frequency of stool passage in adults.
Loperamide and Codeine do not prevent dehydration or improve nutritional status, which should be the main objective of treatment. Also, they could have dangerous, and sometimes fatal side-effects. Though commonly used, they have no practical benefit.

Moreover, they can cause severe paralytic ileus, which can be fatal, and they may prolong infection by delaying elimination of the causative organisms. Sedation may occur at usual therapeutic doses and fatal central nervous system toxicity has been reported for some agents. (10)

World Gastroenterology Organisation practice guideline:
Loperamide is the agent of choice for adults (4–6 mg/day) — Should be used mostly for mild to moderate traveller’s diarrhoea (without clinical signs of invasive diarrhoea). — Inhibits intestinal peristalsis and has mild antisecretory properties. — Should be avoided in bloody or suspected inflammatory diarrhoea (febrile patients). — Significant abdominal pain also suggests inflammatory diarrhoea (this is a contraindication for loperamide use)(11)

9.3 Need for special diagnostic or treatment facilities and skills
None

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence

10.1.1 Search strategy
www.cochrane.org, MedlinePlus, The Cochrane library, Bmj and ClinicalTrials.gov were searched for relevant trials assessing the use of loperamide or/and codeine in the treatment of symptomatic diarrhoea in adults.

Search terms used to identify studies included: Codeine, Loperamide and Diarrhoea.

Reference list from identified studies were checked for relevant studies which could have been missed during the database search.

The literature search identified six randomised trials.

10.1.2 Systematic reviews identified
There were no systematic reviews identified comparing the use of loperamide and/or codeine in the management of symptomatic diarrhoea in adults
10.1.3 Reasons for selection/exclusion of particular data

Randomised trials comparing codeine and/or loperamide in the symptomatic management of diarrhoea in adults was searched for. Trials that included the use of codeine or loperamide in the symptomatic management in adults were included. Trials that included children or HIV positive patients were excluded.

Table 10.1.3 lists the included trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>DuPont HL, Flores Sanchez J, Ericsson CD, Mendiola Gomez J, DuPont MW, Cruz Luna A, Mathewson JJ.</td>
<td>An open-label, parallel efficacy comparison of loperamide hydrochloride (Imodium A-D) and bismuth subsalicylate (Pepto-Bismol) in adult students with acute diarrhoea (three or more unformed stools in the preceding 24 hours plus at least one additional symptom of enteric infection).</td>
</tr>
<tr>
<td>Palmer KR, Corbett CL, Holdsworth CD.</td>
<td>Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhoea</td>
</tr>
<tr>
<td>Johnson PC, Ericsson CD, DuPont HL, Morgan DR, Bitsura JA, Wood LV.</td>
<td>Loperamide hydrochloride was compared with bismuth subsalicylate for the treatment of acute nondysenteric travellers’ diarrhoea</td>
</tr>
<tr>
<td>Barbezat GO, Clain JE, Halter F</td>
<td>A double-blind trial of loperamide in the treatment of chronic nonspecific diarrhoea</td>
</tr>
<tr>
<td>Herbert L. Dupont, M.D., Charles D Ericsson, M.D., Margaret W. Dupont, M.A., Alejandro Cruz Luna, M.D., John J. Mathewson, Ph.D.</td>
<td>The efficacy of loperamide hydrochloride (Imodium® A-D) was compared with nonfibrous activated attapulgite (Diasorb®) in a randomized, parallel, open-label study of adult patients with acute diarrhoea.</td>
</tr>
<tr>
<td>Hwang-Huei Wang, Ming-Jium Shieh, Kuan-Fu Liao</td>
<td>A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhoea in adults</td>
</tr>
<tr>
<td>F P L Van Loon, M L Bennish, P Speelman, and C Butler</td>
<td>Double blind trial comparison of loperamide with a placebo for treating acute watery diarrhoea in expatriates in Bangladesh</td>
</tr>
</tbody>
</table>

10.2 Summary of available data

10.2.1 Appraisal of quality

Table 10.2.1 provides an assessment of the quality of the included trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Done</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DuPont HL, Flores Sanchez J, Ericsson CD, Mendiola Gomez J, DuPont MW, Cruz Luna A, Mathewson JJ.</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>No</td>
<td>open label</td>
</tr>
<tr>
<td>blinding</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>concealment of treatment allocation</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>inclusion of all randomised participants in analysis (ITT)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>description of withdrawals</td>
<td>Yes</td>
<td>reasons for discontinuation of treatment are provided</td>
</tr>
<tr>
<td>objective outcomes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Palmer KR, Corbett CL, Holdsworth CD.</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>randomisation</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Trials</td>
<td>Done</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>blinding</td>
<td>No</td>
<td>identical capsules used</td>
</tr>
<tr>
<td>concealment of treatment allocation</td>
<td>No</td>
<td>not mentioned</td>
</tr>
<tr>
<td>inclusion of all randomised participants in analysis (ITT)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>description of withdrawals</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>objective outcomes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Johnson PC, Ericsson CD, DuPont HL, Morgan DR, Bitsura JA, Wood LV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td>randomisation</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>blinding</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>concealment of treatment allocation</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>inclusion of all randomised participants in analysis (ITT)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>description of withdrawals</td>
<td>No withdrawals</td>
<td></td>
</tr>
<tr>
<td>objective outcomes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

| Barbezat GO, Clain JE, Halter F                                       |      |                                              |
| Number of subjects                                                    | 40   |                                              |
| randomisation                                                         | Yes  |                                              |
| blinding                                                              | Yes  | Double blinded                               |
| concealment of treatment allocation                                   | No   | Not stated                                   |
| inclusion of all randomised participants in analysis (ITT)            | Yes  |                                              |
| description of withdrawals                                            | Yes  |                                              |
| objective outcomes                                                    | No   |                                              |

| Herbert L. Dupont, M.D., Charles D Ericsson, M.D., Margaret W. Dupont, M.A., Alexandro Cruz Luna, M.D., John J. Mathewson, Ph.D. |      |                                              |
| Number of subjects                                                    | 194  |                                              |
| randomisation                                                         | No   |                                              |
| blinding                                                              | No   |                                              |
| concealment of treatment allocation                                   | No   |                                              |
| inclusion of all randomised participants in analysis (ITT)            | No   |                                              |
| description of withdrawals                                            | Yes  | reasons for discontinuation of treatment are provided |
| objective outcomes                                                    | Yes  |                                              |

| Hwang-Huei Wang, Ming-Jium Shieh, Kuan-Fu Liao                        |      |                                              |
| Number of subjects                                                    | 62   |                                              |
| randomisation                                                         | Yes  |                                              |
| blinding                                                              | Yes  | Single blind                                |
| concealment of treatment allocation                                   | No   | Not stated                                   |
| inclusion of all randomised participants in analysis (ITT)            | Yes  |                                              |
| description of withdrawals                                            | Yes  | reasons for discontinuation of treatment are provided |
| objective outcomes                                                    | Yes  |                                              |

| F P L Van Loon, M L Bennish, P Speelman, and C Butler                 |      |                                              |
| Number of subjects                                                    | 50   |                                              |
| randomisation                                                         | Yes  |                                              |
| blinding                                                              | Yes  |                                              |
| concealment of treatment allocation                                   | No   |                                              |
| inclusion of all randomised participants in analysis (ITT)            | Yes  |                                              |
| description of withdrawals                                            | Yes  | reasons for discontinuation of treatment are provided |
| objective outcomes                                                    | Yes  |                                              |
10.2.2 Outcome measures

Table 10.2.2 provides the primary outcome measures used in the included trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DuPont HL, Flores Sanchez J, Ericsson CD, Mendiola Gomez J, DuPont MW, Cruz Luna A, Mathewson JJ. 1990</td>
<td>Relative efficacy (1) the number of unformed stools passed during 12-hour intervals (2) the time in hours from the initial dose to the time of passage of the last unformed stool after which only formed stools or no stools were subsequently reported (3) the time in hours beginning 30 minutes or more from the initial dose to the occurrence of the first unformed stools.</td>
</tr>
<tr>
<td>Palmer KR, Corbett CL, Holdsworth CD. 1980</td>
<td>Stool frequency, consistency, urgency and incontinence</td>
</tr>
<tr>
<td>Johnson PC, Ericsson CD, DuPont HL, Morgan DR, Bitsura JA, Wood LV. 1986</td>
<td>Number of unformed stools over the previous 24 hours symptoms or etiologic agent isolated.</td>
</tr>
<tr>
<td>Barbezat GO, Clain JE, Halter F 1979</td>
<td>Number and character of stools</td>
</tr>
<tr>
<td>Herbert L. Dupont, M.D., Charles D Ericsson, M.D., Margaret W. Dupont, M.A., Alejandro Cruz Luna, M.D., John J. Mathewson, Ph.D. 1990</td>
<td>Relative efficacy (1) the number of unformed stools passed (2) the time in hours beginning 30 minutes or more from the initial dose to the occurrence of the first unformed stool (3) the time that elapsed from the start of therapy to the occurrence of the last unformed stool after which only formed stools or no stools were subsequently reported (4) enteric symptom severity (5) subjective ratings of overall relief (6) the number of doses required to obtain relief.</td>
</tr>
<tr>
<td>Hwang-Huei Wang, Ming-Jium Shieh, Kuan-Fu Liao 2005</td>
<td>Duration of diarrhoea after beginning the treatment</td>
</tr>
<tr>
<td>F P L Van Loon, M L Bennish, P Speelman, and C Butler 1989</td>
<td>Number and character of bowel movements</td>
</tr>
</tbody>
</table>

10.2.3 Summary of results

Table 10.2.3 provides a summary of results of the trials.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Results</th>
</tr>
</thead>
</table>
| DuPont HL, Flores Sanchez J, Ericsson CD, Mendiola Gomez J, DuPont MW, Cruz Luna A, Mathewson JJ. 1990 | • Patients who received loperamide had an average of 1.51 unformed stools in the first 12 hour interval following the start of therapy as compared with an average of 2.06 unformed stools passed in those given atapulgite  
  • Difference between treatments were also apparent during the second 12 hour interval after the start of therapy, with fewer stools passed for the loperamide group  
  • During the third and fourth 12 hour intervals, the difference between the two treatment groups equalized as the mean number of unformed stools passed in each group substantially decreased. |
| Palmer KR, Corbett CL, Holdsworth CD. 1980                            | • There was no significant difference between either the number of capsules taken per day or the stool frequency in each of the treatment periods  
  • Treatment with diphenoxylate was associated with a significantly smaller percentage of solid stools than either loperamide or codeine  
  • There was no significant difference between codeine phosphate and loperamide in either control of symptoms or side effects. |
<p>| Johnson PC, Ericsson CD, DuPont HL, Morgan DR,                        | • The benefit of loperamide and bismuth subsalicylate was                                                                                                                                                   |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Bitsura JA, Wood LV. 1986                                            | most marked during the first day of illness  
  - The difference between loperamide and bismuth subsalicylate was significant (P < 0.0004) for the zero to four hour treatment interval  
  - During the second day of treatment, there were fewer unformed stools passed in the loperamide group  
  - Fewer unformed stools were passed in the loperamide group than the bismuth subsalicylate group for all etiologic groups and during all time intervals |
| Barbezat GO, Clain JE, Halter F 1979                                  | In week 1 there was a difference was highly statistically significant (P < 0.001) in favour of loperamide |
| Herbert L. Dupont, M.D., Charles D Ericsson, M.D., Margaret W. Dupont, M.A., Alejandro Cruz Luna, M.D., John J. Mathewson, Ph.D. 1990 | Patients taking loperamide passed significantly fewer unformed stools than did subjects taking bismuth subsalicylate during the first and second 12 hour observation periods  
  - The last to last unformed stool was 9.9 hours for loperamide and 17.3 hours for bismuth subsalicylate. The difference was significant (p < 0.0004)  
  - Relief from diarrhoea was maintained significantly (p < 0.0001) longer in subjects given loperamide  
  - On the first day of treatment, 47.7% of the subjects who were assigned loperamide required only the initial dose, whereas a single dose of medication was sufficient for only 14.1% of the bismuth subsalicylate treated patients (p < 0.0001) |
| Hwang-Huei Wang, Ming-Jium Shieh, Kuan-Fu Liao 2005                  | The clinical success rates were 95.7% and 92% for racecadotril and loperamide respectively  
  - Patients on racecadotril had a median duration of diarrhoea of 19.5 h compared with a median of 13 h for patients on loperamide |
| F P L Van Loon, M L Bennish, P Speelman, and C Butler 1989            | Loperamide patients had significantly fewer stools on study day 1 and 2 than did placebo treated patients |

### 10.3 Summary of available estimates of comparative effectiveness

**Studies comparing loperamide to placebo**

Two studies were included which compared Loperamide with a placebo (6,9). Both studies showed that Loperamide was more effective when compared to placebo in controlling diarrhoea. Also the side effects of Loperamide were not significant.

**Studies comparing loperamide to bismuth subsalicylate**

Two studies were included which compared Loperamide with Bismuth Subsalicylate (3,5). Both studies showed that Loperamide was superior to Bismuth Subsalicylate in reducing the frequency of bowel movements and in improving stool consistency.

**Study comparing loperamide to racecadotril**

One study was included which compared loperamide to racecadotril (8). This study showed that the efficacy, tolerability and safety of racecadotril are comparable to those of loperamide in treating acute diarrhoea in adults but racecadotril treatment is less associated with the adverse event of constipation.

**Study comparing loperamide to attapulgite**

There was one study comparing loperamide to attapulgite (7). Significant difference was seen in the number of unformed stools passed, the time to last unformed stool, and the time to first unformed stool in favour of loperamide.
Study comparing loperamide, codeine and diphenoxylate
One study was included which compared loperamide, codeine and diphenoxylate (4). This study showed that there was little difference between loperamide and codeine phosphate in either control of symptoms or side effects. Both are significantly superior to diphenoxylate in terms of improving stool consistency, relieving urgency, and incidence of side effects.

No study was found which showed that loperamide was more effective when compared to codeine phosphate or vice versa. Both seem to have equal efficacy. I would however recommend that codeine phosphate is replaced with loperamide because even though they are both opioids, dependence with codeine phosphate is more likely compared to loperamide.

11. Summary of comparative evidence on safety:

11.1 Estimate of total patient exposure to date
Millions of people have been exposure to both loperamide and codeine. Both drugs have been around since the 1970s.

11.2 Description of adverse effects/reactions

Loperamide
To document the safety profile from the widespread over the counter use of loperamide for diarrhoea worldwide, a detailed analysis of 4738 post marketing case reports in the Johnson&Johnson Pharmaceutical Research & Development (PRD) Benefit Risk Management (BRM) Safety Databases that are associated with over the counter use of loperamide over a period of 5 years (2004 – 2009) was carried out. Results from this analysis suggest that loperamide is substantially safe when used as directed. All adverse experiences for over the counter loperamide are very rare or isolated events, and similar in nature and frequency to the established overall safety profile of loperamide in prescription use.(12)

In clinical trials, constipation and dizziness have been reported with greater frequency in loperamide hydrochloride treated patients than placebo treated patients. (14)

The following adverse events have also been reported with use of loperamide hydrochloride:
Immune system disorders
Very rare: isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.

Psychiatric system disorders
Very rare: drowsiness

Nervous System disorders
Very rare: Loss of consciousness, depressed level of consciousness, dizziness

Gastrointestinal Disorders
Very rare: abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon, flatulence, and dyspepsia.

Skin and subcutaneous tissue disorders
Very rare: rash, urticaria and pruritus.
Isolated occurrences of angioedema, and bullous eruptions including Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis.

Renal and urinary disorders
Very rare: isolated reports of urinary retention.
A number of the adverse events reported during the clinical investigations and post-marketing experience with loperamide are frequent symptoms of the underlying diarrhoeal syndrome (abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects. (14)

Dependence
Physical dependence to loperamide in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high dose produced symptoms of physical dependence of the morphine type. (12)

Potential for abuse
In adults with a functioning blood brain barrier, it is unlikely that even very high doses of loperamide would be sufficient to produce an opiate euphoric effect. Contact with specialists in drug abuse in the UK (Drugscope and the National Poisons Information Centre), do not suggest that there is any significant usage of loperamide alone, by any route, as a drug of abuse. In the absence of evidence, either from formal drug interaction studies or elicit experimentation, that loperamide can be used with other easily obtained substances to achieve a CNS euphoric effect, it seems unlikely that ‘abuse’ of loperamide will become a problem. (12)

Preclinical data and clinical data have consistently proven that loperamide does not have abuse potential. This lack of abuse potential is the result of its poor oral bioavailability, its inability to cross the blood brain barrier, and therefore its lack of central opiate effects even at very high doses. (12)

Originally marketed as a prescription drug product, loperamide has since been marketed as a non-prescription product for many years in many countries. Post marketing surveillance data have established that loperamide does not lead to abuse in actual use. Based on its lack of abuse potential, the World health Organisation indicated that atropine should not be added to loperamide (mandatory for other opioid-like antidiarrhoeals such as diphenoxylate). (12)

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. (15)

Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped. Very rare occurrence of pancreatitis. (15)
11.3 Identification of variation in safety due to health systems and patient factors

**Loperamide** is contraindicated:

- In patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- In children less than 4 years of age.
- When inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon, in particular:
  - When ileus or constipation are present or when abdominal distension develops, particularly in severely dehydrated children,
  - In patients with acute ulcerative colitis,
  - In patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella, and Campylobacter,
  - In patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

Loperamide should not be used alone in acute dysentery, which is characterised by blood in stools and elevated body temperatures. The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in young children and in frail and elderly patients with acute diarrhoea.

Loperamide must be used with caution when the hepatic function necessary for the drug’s metabolism is defective (e.g. in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity.

Patients with AIDS treated with Loperamide for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.(14)

**Codeine** is contraindicated in the following conditions:

- Acute asthma
- Respiratory depression
- Acute alcoholism
- Head injuries
- Raised intra-cranial pressure
- Following biliary tract surgery(15)
11.4 Summary of comparative safety against comparators

Oral Rehydration Salts solution is the recommended first step in the management of common episodes of diarrhoea to provide rehydration.

Central nervous effects were greatest with diphenoxylate(4). Itching was higher with racecadotril(8)

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

12.1 range of costs of the proposed medicine

Loperamide

Capsules, 2 mg, net price 30-cap pack = from £1.07 to £1.23 1000 cap pack $9.93
Tablets, 2 mg, net price 30-tab pack = £2.15 100 tab pack $1.59 to $4.23 1000 tab pack
$1.59 to $23.44

Codeine

Tablets 15 mg, net price 28-tab pack = from £1.14 to £1.25; 30 tab $0.94 100 tab pack
$11.09
30 mg, 28-tab pack = from £1.22 to £1.51; 100 tab pack $8.06 to $9.15 1000 tab pack
$29.82 to $35.29
60 mg, 28-tab pack = from £1.84 to £2.06.

12.2 comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

There are no published cost-effectiveness analyses of loperamide or codeine used in the treatment of diarrhoea in adults

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Table 13 Classification status of loperamide in various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>First Registered</th>
<th>Reclassified as a Pharmacy Only Medicine</th>
<th>Reclassified as a GSL Medicine</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1979</td>
<td>1987</td>
<td>Application submitted Jan 2010</td>
</tr>
<tr>
<td>Belgium</td>
<td>1973</td>
<td>1979</td>
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</tr>
<tr>
<td>Canada</td>
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</tr>
<tr>
<td>USA</td>
<td>1977</td>
<td>1988</td>
<td>1988</td>
</tr>
</tbody>
</table>
**Codeine** is usually either a controlled drug or prescription only drug in most countries depending on the strength of the formulation


**Loperamide**
- British Pharmacopoeia: Yes
- International Pharmacopoeia: Yes
- United States Pharmacopoeia: Yes

**Codeine**
- British Pharmacopoeia: Yes
- International Pharmacopoeia: Yes
- United States Pharmacopoeia: Yes

15. **Proposed (new/adapted) text for the WHO Model Formulary**

**CODEINE PHOSPHATE**

Codeine is a centrally acting analgesic which produces its effect by its action at opioid-binding sites (μ-receptors) within the CNS. It is a full agonist.(15)

**Indications:**
- Mild to moderate pain; diarrhoea; cough suppression

**Cautions:**
- Opioids should be used with caution in patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders.

A reduced dose is recommended in elderly or debilitated patients, in hypothyroidism, and in adrenocortical insufficiency.

Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence.

**Variation in metabolism:**
- The capacity to metabolise codeine can vary considerably and lead to either reduced therapeutic effect or marked increase in side-effects

**Contra-indications:**
- Opioid analgesics should be avoided in patients with acute respiratory depression and when there is a risk of paralytic ileus. They are also contra-indicated in conditions associated with raised intracranial pressure and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment). Comatose patients should not be treated with opioid analgesics.

**Hepatic impairment:**
- Opioid analgesics may precipitate coma in patients with hepatic impairment; avoid use or reduce dose.
Renal impairment:
The effects of opioid analgesia are increased and prolonged and there is increased cerebral sensitivity when patients with renal impairment are treated with opioid analgesics; avoid use or reduce dose.

Pregnancy:
Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

Breast-feeding:
Amount usually too small to be harmful; however mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant

Dose:
Acute diarrhoea, 30 mg 3–4 times daily (range 15–60 mg)

Side-effects:
Opioid analgesics share many side-effects, although qualitative and quantitative differences exist. The most common side-effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth, and biliary spasm; larger doses produce muscle rigidity, hypotension, and respiratory depression.

Other common side-effects of opioid analgesics include bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion, drowsiness, sleep disturbances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus.

Driving:
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

Interactions:
Alcohol:
enhanced hypotensive and sedative effects when opioid analgesics given with alcohol

Anaesthetics, General (intravenous)
opioid analgesics possibly enhance effects of intravenous general anaesthetics

Anaesthetics, General (volatile liquids)
opioid analgesics possibly enhance effects of volatile liquid general anaesthetics

Antidepressants, Tricyclic
sedative effects possibly increased when opioid analgesics given with tricyclics

Antihistamines, Sedating
sedative effects possibly increased when opioid analgesics given with sedating antihistamines
Antipsychotics
Enhanced hypotensive and sedative effects when opioid analgesics given with antipsychotics. Increased risk of toxicity with myelosuppressive drugs

Anxiolytics and Hypnotics
increased sedative effect when opioid analgesics given with anxiolytics and hypnotics

Barbiturates
CNS effects of opioid analgesics possibly increased by barbiturates

Cimetidine
metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Ciprofloxacin
avoidance of premedication with opioid analgesics advised by manufacturer of ciprofloxacin (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis

Domperidone
opioid analgesics antagonise effects of domperidone on gastro-intestinal activity

Monoamine oxidase inhibitors (MAOIs)
possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs —avoid concomitant use and for 2 weeks after stopping MAOIs

Metoclopramide
opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity

Moclobemide
possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with moclobemide

Selegiline
Avoidance of opioid analgesics advised by manufacturer of selegiline. Selegiline is a MAO-B inhibitor

Sodium Oxybate
opioid analgesics enhance effects of sodium oxybate (avoid concomitant use)

**LOPERAMIDE HYDROCHLORIDE**
Loperamide hydrochloride is a synthetic opioid which inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter.(14)

**Indications:**
Symptomatic treatment of acute diarrhoea; adjunct to rehydration in acute diarrhoea in adults and children over 4 years; chronic diarrhoea in adults only
Contra-indications:
Conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis

Hepatic impairment:
Risk of accumulation—manufacturer advises caution

Pregnancy:
Manufacturers advice avoid—no information available

Breast-feeding:
Amount probably too small to be harmful

Side-effects:
Abdominal cramps, dizziness, drowsiness, and skin reactions including urticaria; paralytic ileus and abdominal bloating also reported

Dose:
Acute diarrhoea, 4 mg initially followed by 2 mg after each loose stool for up to 5 days; usual dose 6–8 mg daily; max. 16 mg daily;

Chronic diarrhoea in adults, initially, 4–8 mg daily in divided doses, subsequently adjusted according to response and given in 2 divided doses for maintenance; max. 16 mg daily;

Interactions:
Desmopressin
loperamide increases plasma concentration of oral desmopressin
16. REFERENCES

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